Associazione Italiana di Oncologia Medica

BREAST NEOPLASMS

Guidelines

2018 edition

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How to read

Key clinical recommendations are presented in tables and are accompanied by the certainty of evidence and the strength of the recommendation.

The header line of the table is **green** or **orange** if the certainty of evidence was assessed using the old version of SIGN (Scottish Intercollegiate Guidelines Network) level of evidence or GRADE quality assessment, respectively, (see the specific chapter in the methodological handbook).

SIGN Quality of Evidence (1)	Clinical recommendation (3)	Strength of clinical recommendation (2)
B	In advanced cancer patients with pain from various causes, NSAIDs and paracetamol could be administered for limited periods of time, closely monitoring potential side effects.	**Conditional Positive**

(1) SIGN Quality of Evidence: BEFORE THE RECOMMENDATION

With the old version of SIGN level of evidence, the quality of evidence depended on both the study design and how it was conducted: The *Level of Evidence* was reported <u>within the text</u> alongside the description only for those <u>studies that were deemed relevant</u> for or against a specific intervention.

SIGN Levels of Evidence

1	*Systematic reviews and meta-analyses of RCTs or individual RCTs*
1 ++	*Very low bias risk.*
1 +	*Low bias risk.*
1 -	*High bias risk -> Study results are unreliable.*
2	*Systematic reviews and meta-analyses of epidemiological case-control or cohort studies or individual case-control or cohort studies.*
2 ++	*Very low bias risk, very low probability of confounding factors, high probability of causal relationship between intervention and effect.*
2 +	*Low bias risk, low probability of confounding factors, moderate probability of causal relationship between intervention and effect.*
2 -	*High bias risk -> study results are unreliable, there is a high risk that the relationship between intervention and effect is not causal.*
3	*Non-analytical study designs, such as case reports and case series.*
4	*Expert opinion.*

The *SIGN Global Quality of Evidence* was then reported using letters (A, B, C, D) that summarized the study design, together with an indication of the direct applicability of the evidence.

Each letter indicated the **"confidence"** in the entire body of evidence assessed in support of the recommendation; they did **<u>NOT</u>** reflect the clinical significance of the recommendation and were **<u>NOT</u>** synonymous with the strength of the clinical recommendation.

SIGN Global Quality of Evidence

A	At least one meta-analysis or systematic review or RCT rated 1++ and directly applicable to the target population *or*
	The available body of evidence mainly consists of studies rated 1+ directly applicable to the target population and with consistent results in terms of effect direction and size
B	The body of evidence includes studies rated 2++ with results directly applicable to the target population and with consistent results in terms of effect direction and size
	Evidence from studies rated 1++ or 1+
C	The body of evidence includes studies rated 2+ with results directly applicable to the target population and with consistent results in terms of effect direction and size.
	Evidence from studies rated 2++
D	Level 3 or 4 evidence
	Evidence from studies rated 2+

Since 2016, the AIOM guidelines (GLs) no longer use the SIGN level of evidence, because the latter has decided to integrate GRADE, which decline the assessment of the certainty of evidence into four levels: VERY LOW, LOW, MODERATE, and HIGH.
For recommendations formulated from 2016 onwards, the table of recommendations undergoes minor changes and is more similar to the one resulting from the entire GRADE process.

Global quality of evidence	Recommendation	Strength of clinical recommendation
HIGH	In patients with pN+ tumor or resective surgery without adequate lymphadenectomy (<D2) or also R1, an adjuvant radiochemotherapy should be considered as first option (68,73).	**Strong Positive**

(2) STRENGTH OF A CLINICAL RECOMMENDATION

The strength of a clinical recommendation is graded based on clinical importance according to 4 levels:

Strength of clinical recommendation	Terminology	Meaning
Strong Positive	"In patients with (selection criteria), intervention xxx **should** be considered as a first option"	The intervention under examination should be considered as the first therapeutic option (evidence that benefits exceed harms)
Conditional Positive	"In patients with (selection criteria), intervention xxx **could be** considered as a first option compared to yyy"	The intervention under examination can be considered as a first therapeutic option, while being aware of the existence of acceptable alternatives (uncertainty about benefits exceeding harms).
Conditional Negative	"In patients with (selection criteria), intervention xxx **should not** be	The intervention under examination should not be considered as a first therapeutic option; it could however be used in highly

Strength of clinical recommendation	Terminology	Meaning
	considered as a first option compared to yyy"	selected cases and after fully informing the patient (uncertainty about harms exceeding benefits).
Strong Negative	"In patients with (selection criteria), intervention xxx **should not** be considered	The intervention under examination must not be taken into consideration under any circumstances (evidence that harms exceed benefits)

(3) THE CLINICAL RECOMMENDATION

It should express the clinical importance of an intervention/procedure. It should be formulated on the basis of the P.I.C.O.* (population, intervention, comparison, outcome). In some instances, it may contain specifications for subgroups, identified by the symbol √.

A complete description of the methodologies applied to AIOM GLs and how to formulate the clinical question can be found at www.aiom.it
SIGN= Scottish Intercollegiate Guidelines Network
GRADE= Grading of Recommendations Assessment, Development and Evaluation
Complete information on the GRADE process and the appendices along with the *flow* of study selection are provided at the end of the document.

TABLE OF CONTENTS

Flow charts

Drugs authorized and reimbursed by the Italian Medicines Agency (AIFA) are considered in the recommendations and in the diagnosis & therapy flow charts. Non-negotiated Class C drugs (Cnn) are specifically described as such.

Figure 1 - DUCTAL CARCINOMA IN SITU (DCIS): treatment
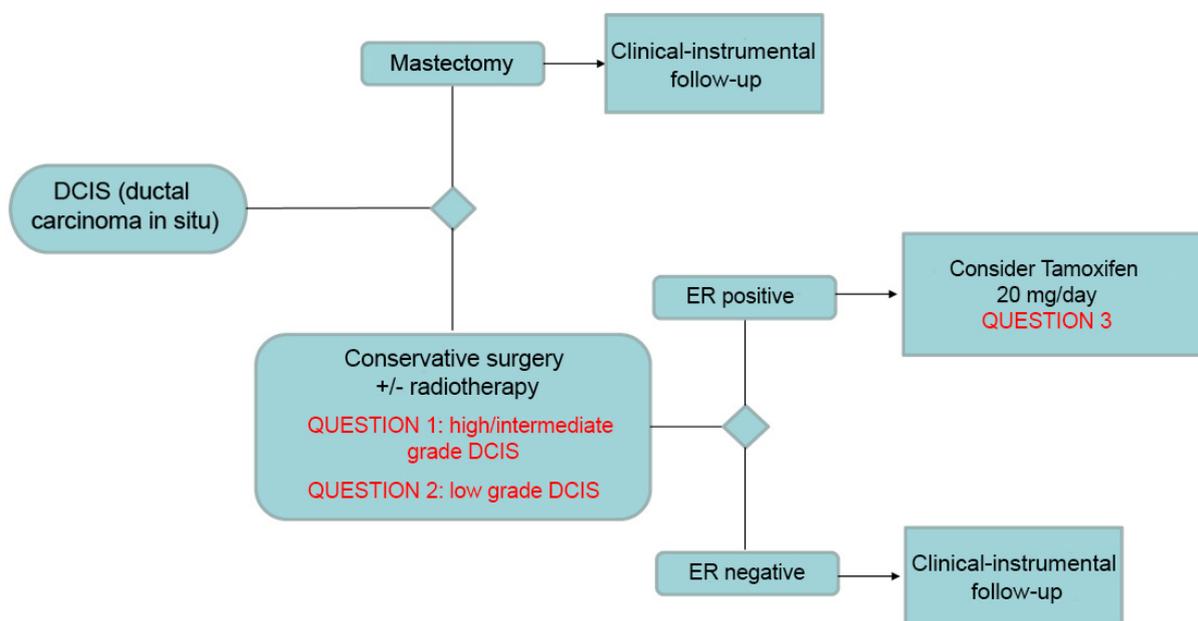
Figure 2 - OPERABLE INFILTRATING BREAST CANCER: Local-regional treatments
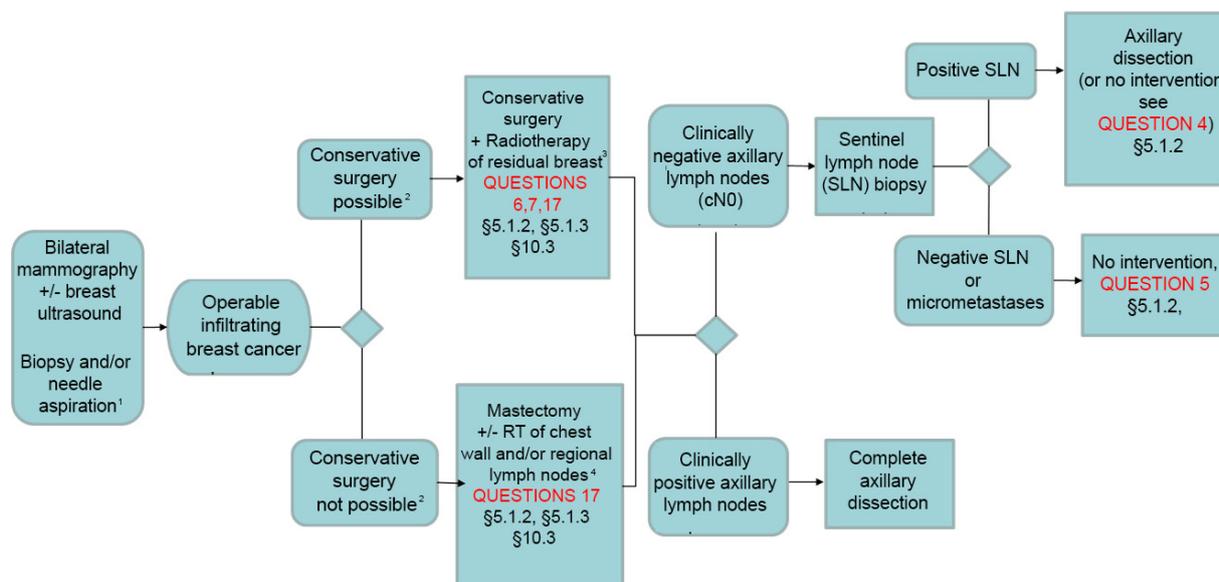
Note 1 - Biopsy is preferable to needle aspiration, as it allows histological definition and molecular characterization.

Note 2 - Based on: localization, multifocality, T size, breast size, patient preference, RT contraindications. If indicated for neoadjuvant therapy, see Figure 9.

Note 3 - Standard radiotherapy 50 Gy/25 fractions or hypofractionated 42.5 Gy/16 fractions or other iso-equivalent fractionation; +/- 10-16 Gy boost; +/- RT of regional lymph nodes (see sections 5.1.2, 5.1.3).

Note 4 - Chest wall radiotherapy if: T>5 cm or primitive T with skin invasion and/or pectoral muscle and/or thoracic wall; 4 or more metastatic axillary lymph nodes. Radiotherapy on regional lymph nodes if: pT3 or pT4, PT1 or pT2 with at least 4 positive axillary lymph nodes, pT1-4 with 1-3 positive lymph nodes (see sections 5.1.2 and 5.1.3).

Figure 3 – RESECTED NON-METASTATIC INFILTRATING BREAST CANCER: Treatment based on predictive factors
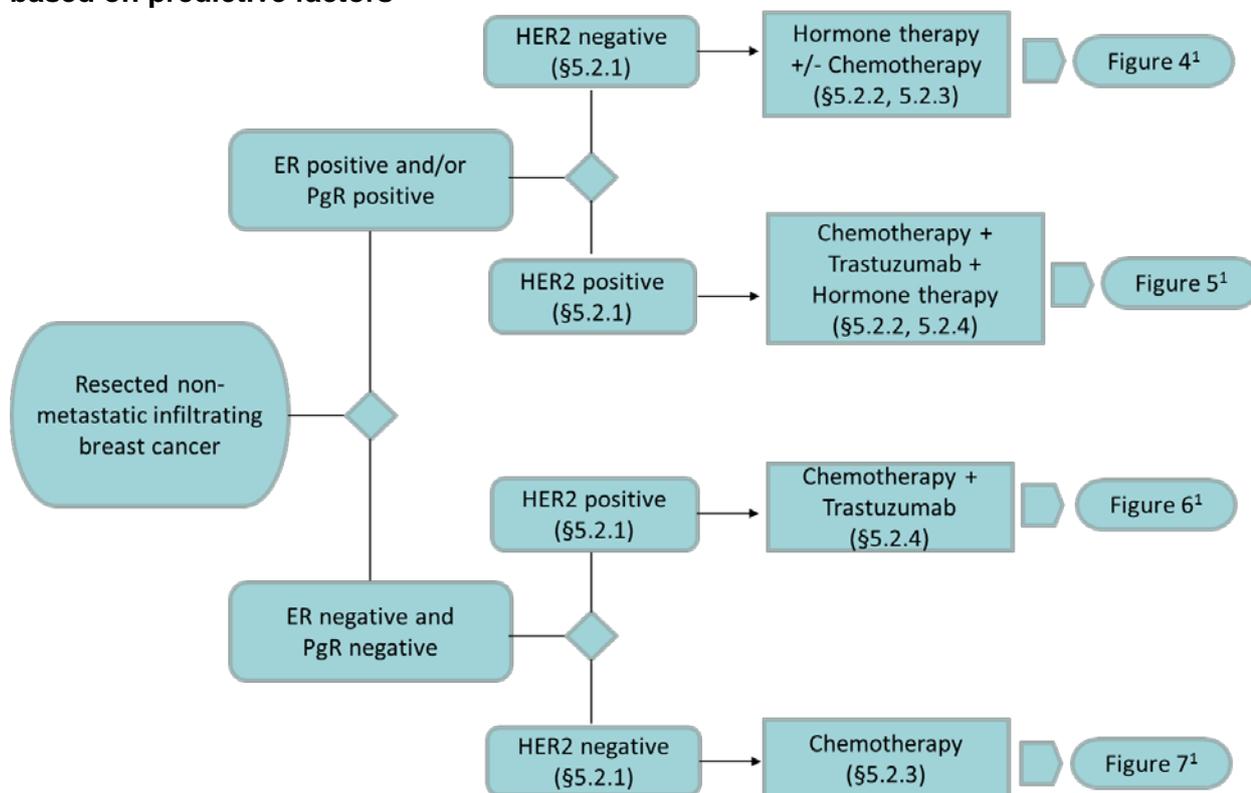
Note 1 - See Figures 5,6,7,8 for detailed information by stage

Figure 4 – RESECTED ER and/or PgR positive, HER2 negative NON-METASTATIC infiltrating breast cancer: Adjuvant systemic therapy
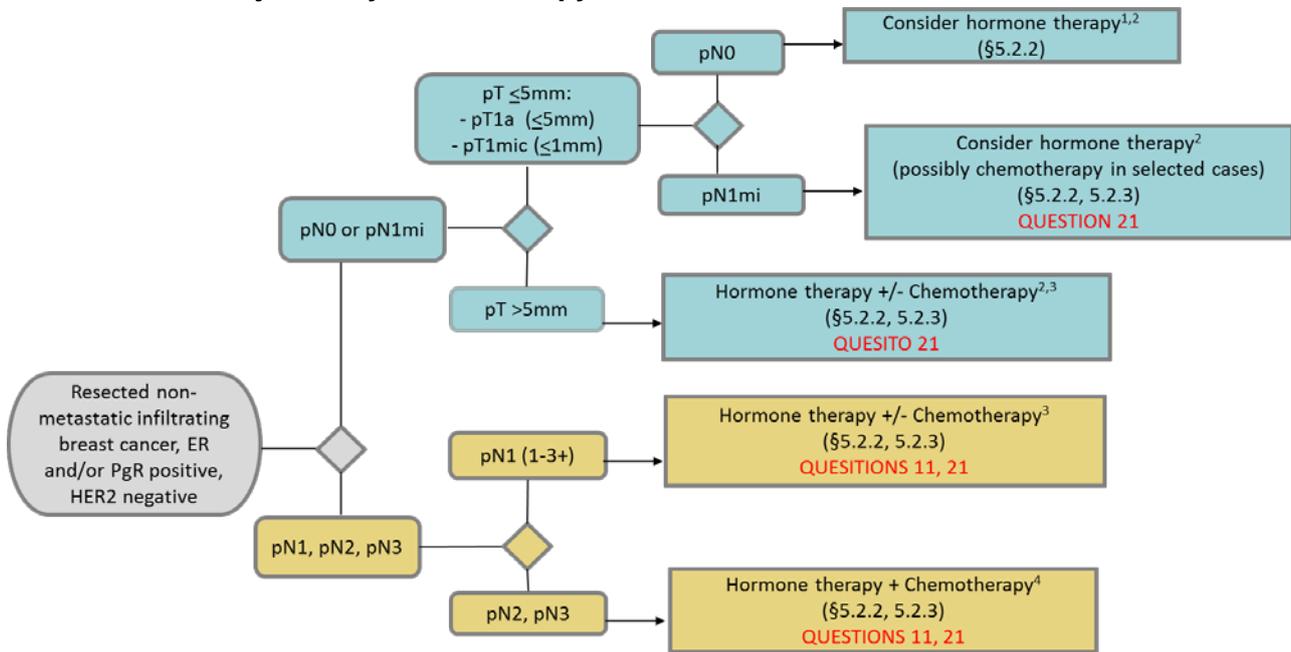
Note 1 - It may be decided not to administer any adjuvant treatment in pT1mi and pT1a tumors if pN0, based on factors such as: biological parameters (G1/G2, low Ki-67 levels, high ER levels), histology, advanced age, presence of comorbidities (see section 5.2.1).

Note 2 - Tubular, mucinous and papillary histotypes, which have a better prognosis than ductal histotypes, may also not be given any treatment if pN0 and pT ≤ 10 mm (see section 5.2.1).

Note 3 - Risk factors to be considered in order to add chemotherapy to hormone therapy include: stage (pT, pN), biological parameters (G3, high Ki-67 levels, low ER and/or PgR levels), histology (ductal vs. lobular). The age and comorbidity of the patient must be taken into consideration. If available, the risk category based on gene expression profiles can be used as a prognostic factor to be integrated into the therapeutic decision (see section 5.2.1).

Note 4 - pN2-pN3 tumors should generally be treated with chemotherapy in addition to hormone therapy regardless of G, Ki-67, ER and PgR levels. Chemotherapy in addition to hormone therapy should also be considered in lobular histology, when associated with a high risk of recurrence based on T (pT3/pT4) and N (pN2/pN3).

**Figure 5 – RESECTED ER and/or PgR positive, HER2 POSITIVE NON-METASTATIC
infiltrating breast cancer: Adjuvant systemic therapy**
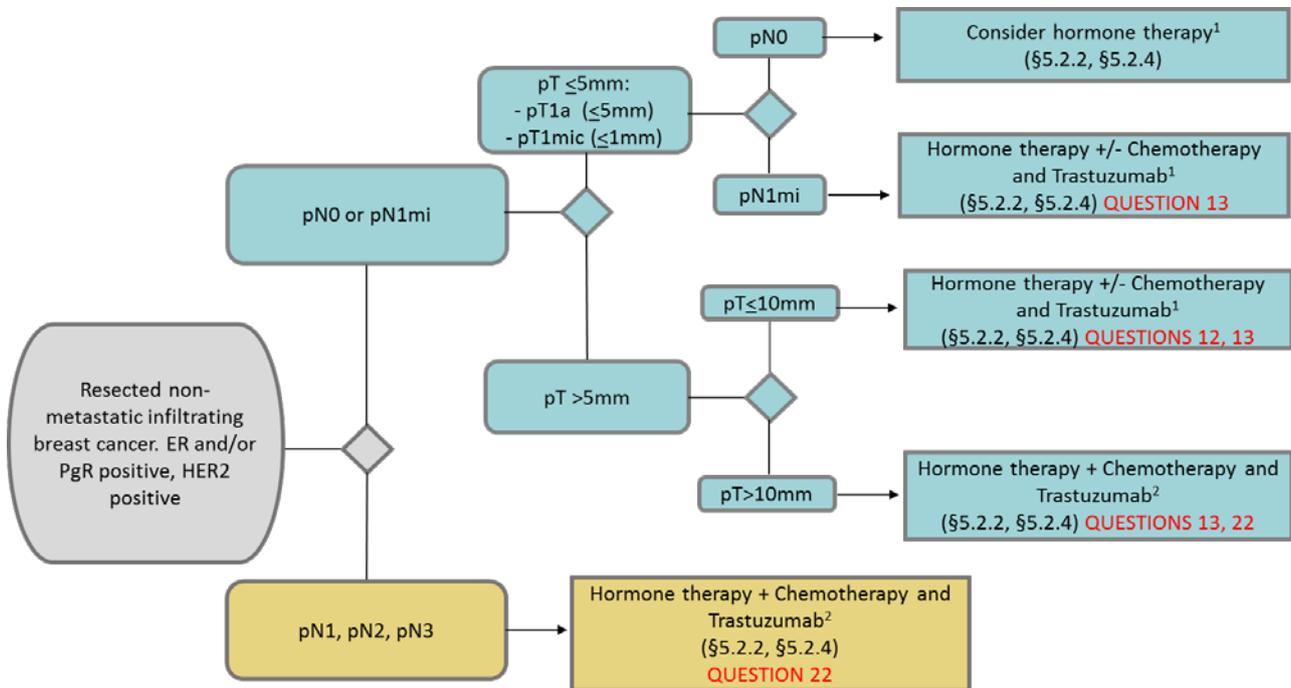
Note 1 - In small tumors (pT1a and pT1b) and pN0/N1mi, there are currently no prospective data available from randomized studies on the benefit of adjuvant trastuzumab. The addition of chemotherapy and trastuzumab to hormone therapy may be considered, based on G, Ki-67, age, and comorbidities of the patient (§5.2.4). There is a lack of perspective data on the possibility of combining trastuzumab with adjuvant hormone therapy alone.
Note 2 - In tumors with T size greater than 1 cm or with positive axillary lymph nodes (not N1mi), trastuzumab and chemotherapy are indicated in addition to adjuvant hormone therapy.

**Figure 6 – RESECTED ER and PgR NEGATIVE, HER2 POSITIVE NON-METASTATIC
infiltrating breast cancer: Adjuvant systemic therapy**
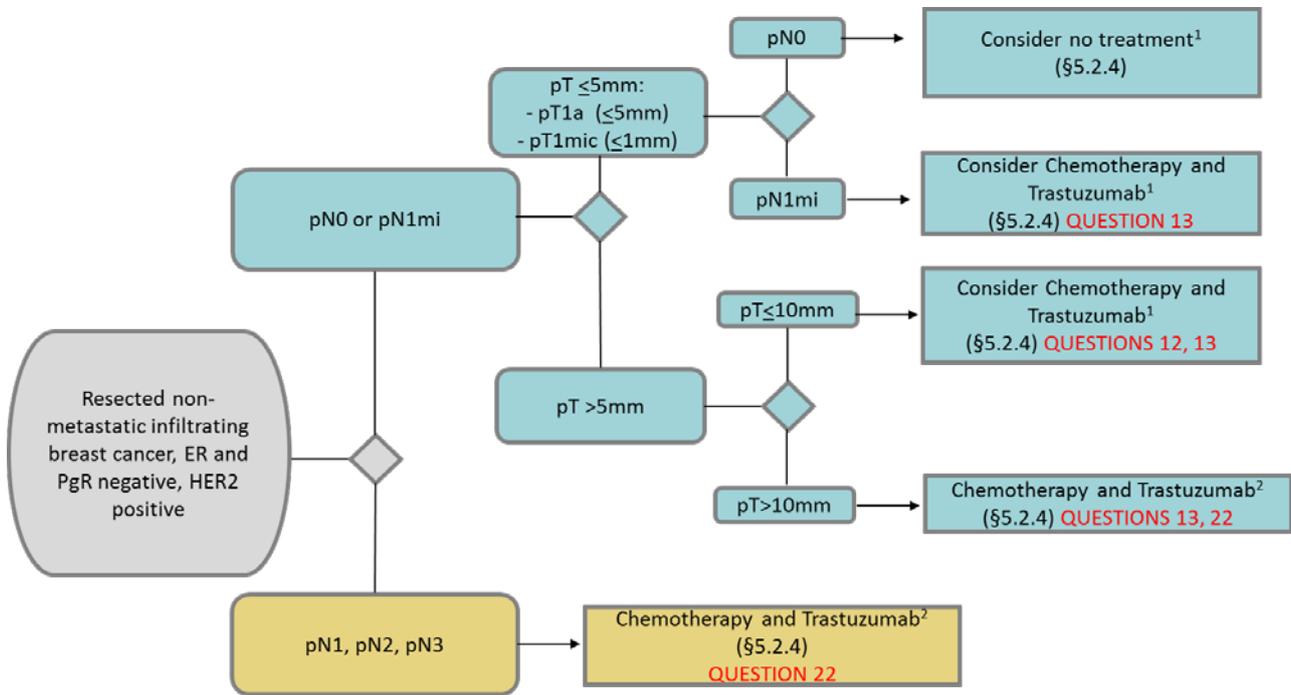
Note 1 - In small tumors (pT1a and pT1b) and pN0/N1mi, there are currently no prospective data available from randomized studies on the benefit of adjuvant trastuzumab. Chemotherapy and trastuzumab may be considered based on G, Ki-67, age, and comorbidities of the patient. §5.2.4
Note 2 - In tumors with T size greater than 1 cm or with positive axillary lymph nodes (not N1mi), trastuzumab and chemotherapy are indicated.

**Figure 7 – RESECTED ER and PgR NEGATIVE, HER2 NEGATIVE NON-METASTATIC
infiltrating breast cancer: Adjuvant systemic therapy**
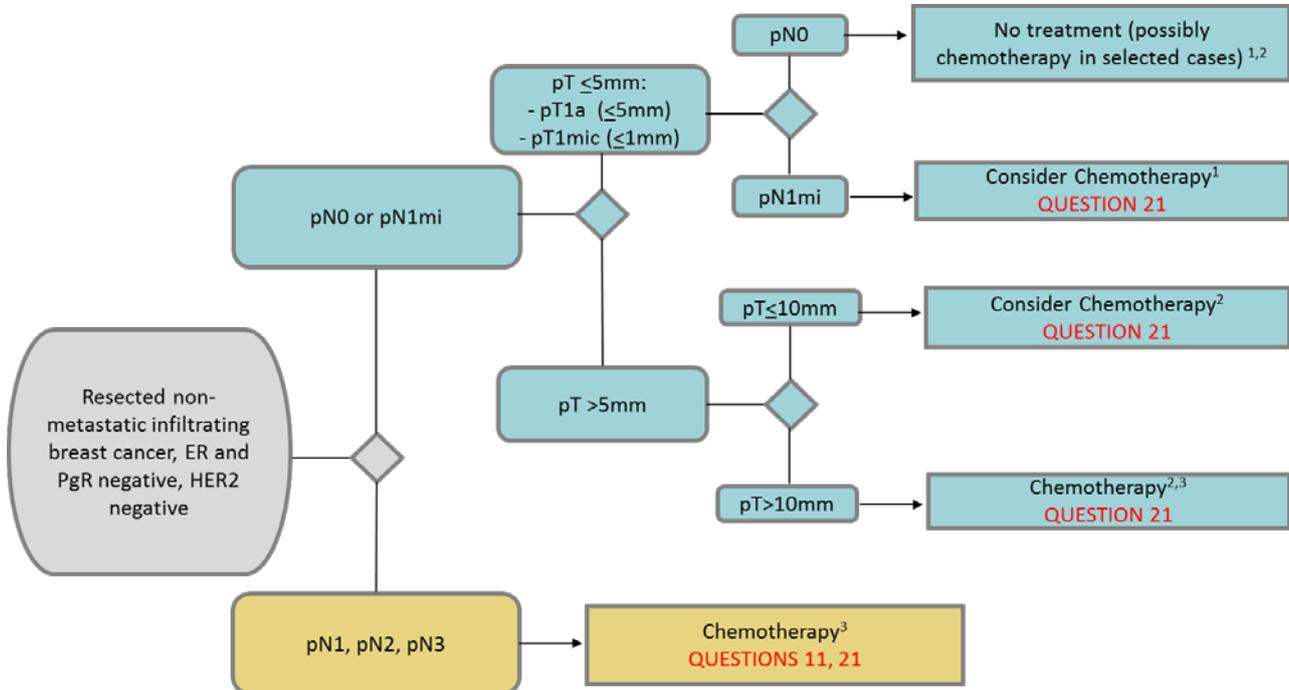
Note 1 - In pT1a tumors, adjuvant chemotherapy may be considered if G3 or Ki67 is elevated.
Note 2 - Some histological types of "triple negative" tumors, such as medullary carcinoma and adenoid cystic carcinoma, have a favorable prognosis and may not require systemic adjuvant treatments if N0 and in the absence of additional risk factors. §5.2.1
Note 3 - Adjuvant chemotherapy is indicated for tumors larger than 1 centimeter in diameter or for pN1, pn2, pN3 tumors.

**Figure 8 – RESECTED ER AND/OR PGR POSITIVE NON-METASTATIC INFILTRATING
BREAST CANCER: Adjuvant hormone therapy**
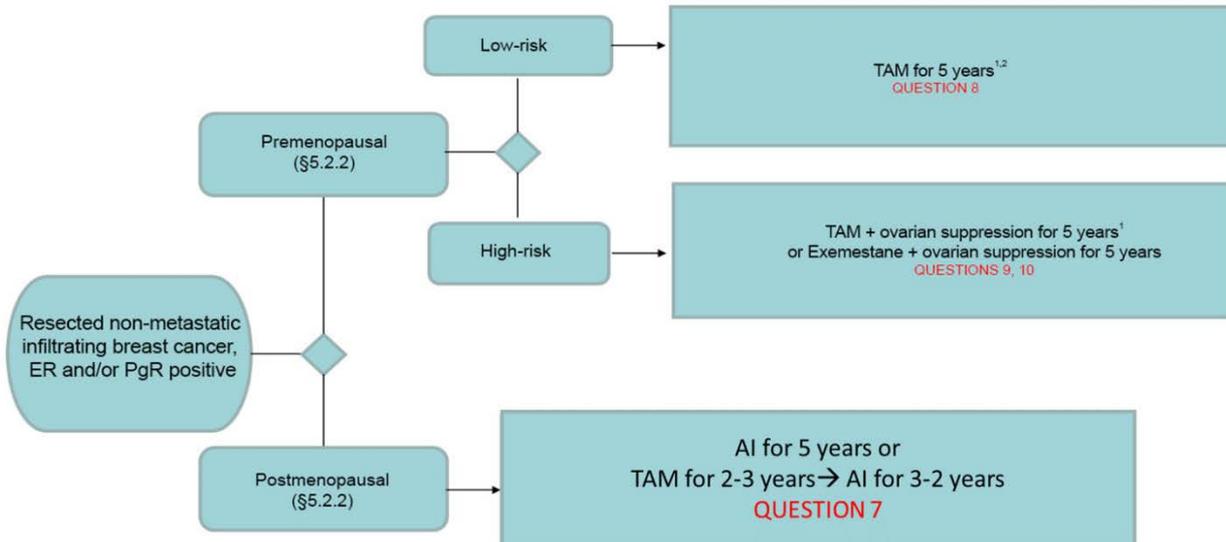
Note 1 - After 5 years of tamoxifen, the continuation of tamoxifen for a further 5 years may be considered in women with resected infiltrating breast cancer with ER-positive and/or PgR-positive who are still premenopausal or perimenopausal, based on the results of ATLAS and aTToM studies; however, the benefit/harm ratio and the risk of recurrence for the individual patient must be assessed (§5.2.2).

Note 2 - In women who are premenopausal when diagnosed with infiltrating breast cancer, are treated with tamoxifen for 5 years, and enter menopause during the adjuvant treatment with chemotherapy or tamoxifen, treatment with letrozole after 5 years of tamoxifen could be considered, assessing the benefit/harm ratio and the risk of recurrence for the individual patient (§5.2.2).

Note 3 - In postmenopausal women with ER-positive and/or PgR-positive infiltrating breast cancer, the extension of aromatase inhibitor therapy after the fifth year could be considered, subject to a risk/benefit assessment (§5.2.2).

Figure 9 - NON-METASTATIC INFILTRATING BREAST CARCINOMA: Neoadjuvant Therapy
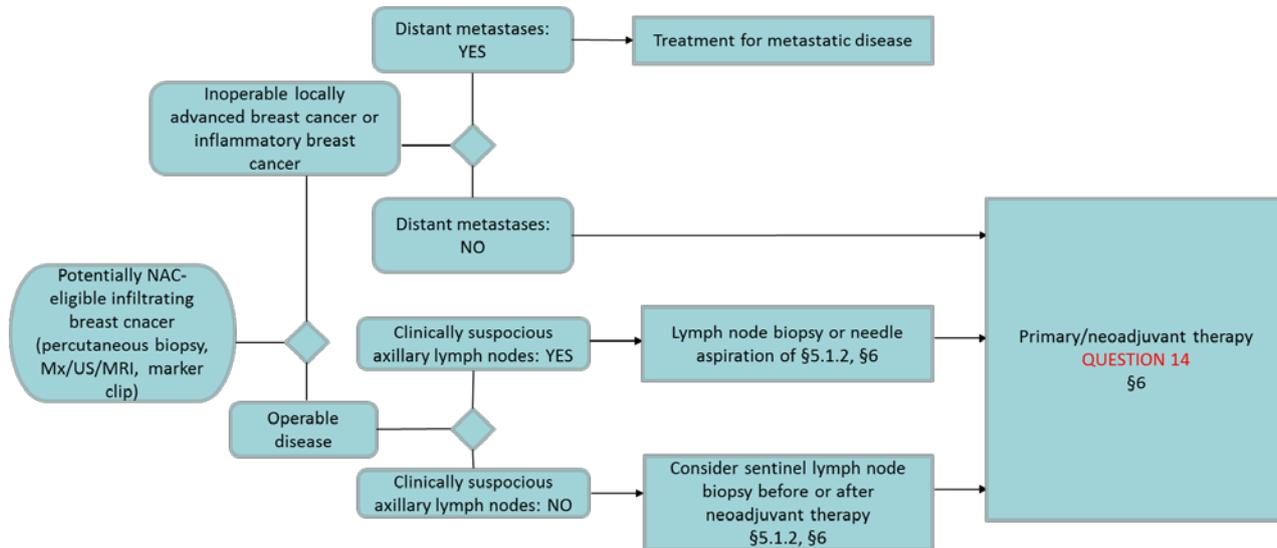
Figure 10 - OLIGOMETASTATIC BREAST CANCER: Initial therapeutic approach to metastatic sites
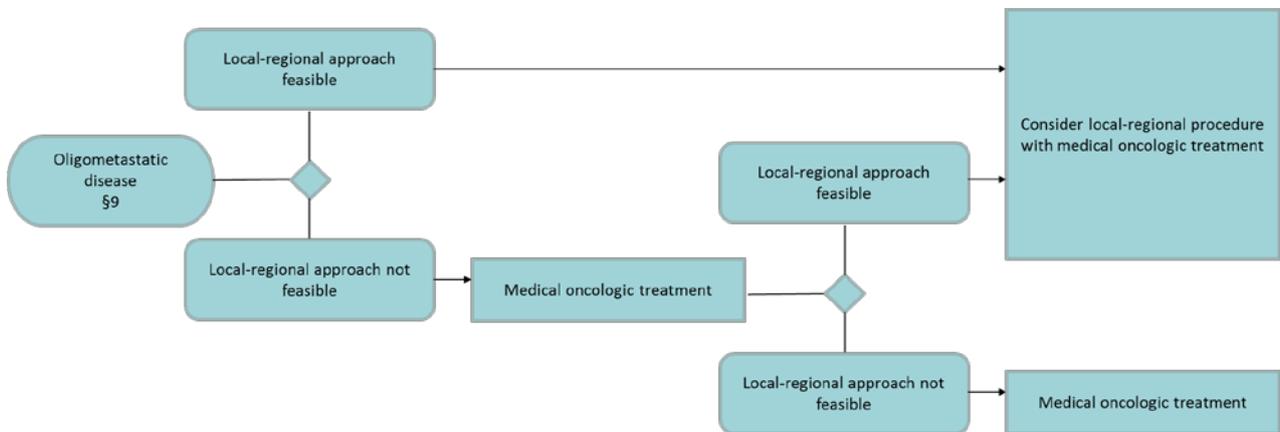
Figure 11 - HER2-POSITIVE METASTATIC BREAST CANCER: Medical therapy based on pathological and clinical characteristics

Metastatic breast cancer HER2+ §9.1.2 §9.5.1

ER+
ER-

Postmenopausal
Premenopausal

Chemotherapy not indicated
Chemotherapy indicated

Aromatase inhibitor + trastuzumab or lapatinib [1] — PD

Pertuzumab + Trastuzumab + Docetaxel [3]

Trastuzumab + chemotherapy

QUESTION 16

I line

PD

T-DM1 [4]

Lapatinib + capecitabina

Trastuzumab + chemotherapy

QUESTIONS 17, 18

II line

PD

Lapatinib + capecitabina

Trastuzumab + chemotherapy

T-DM1 [4]

III line *
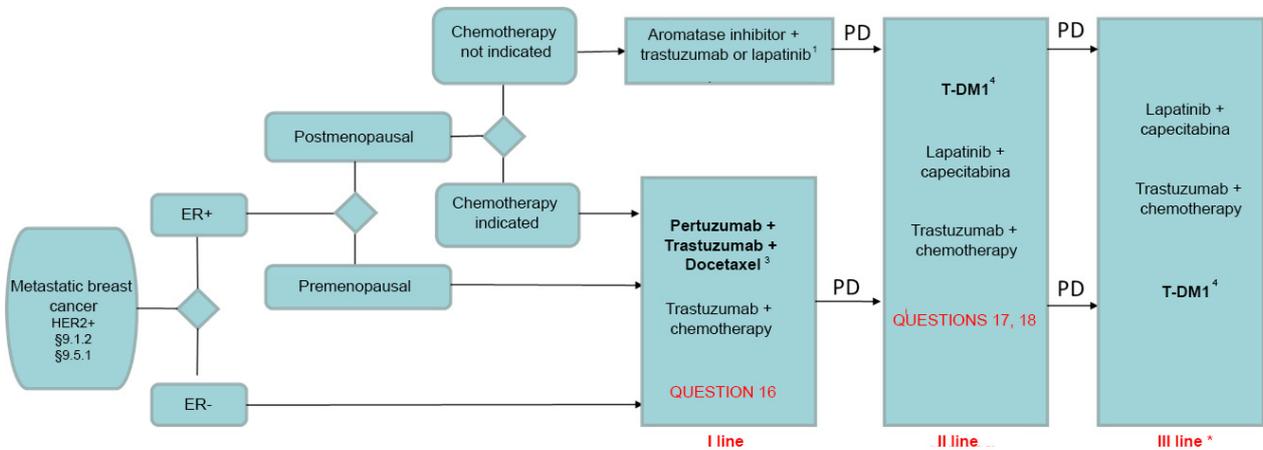
Note 1 - Treatment with AI + an anti-HER2 drug may be an alternative to chemotherapy where this is contraindicated, but no comparison studies exist.

Note 2 - If the patient has received hormone therapy + an anti-HER2 drug, treatment with T-DM1 is indicated if the patient meets the eligibility criteria (previous therapy with trastuzumab and a taxane), otherwise the patient should receive trastuzumab and chemotherapy or capecitabine and lapatinib depending on the type of anti-HER2 drug used in combination with the hormone therapy.

Note 3 - Pertuzumab is indicated in combination with trastuzumab and docetaxel in adult patients with inoperable or metastatic or locally recurrent HER2-positive breast cancer who have never been treated with anti-HER2 therapy or chemotherapy for the metastatic disease (see text for eligibility criteria and characteristics of included patients). Based on the AIFA document (according to law 648), the use of paclitaxel is allowed in case of absolute contraindications to docetaxel (see text).

Note 4 - **AIFA indications:** Trastuzumab emtasine, as monotherapy, is indicated for the treatment of adult patients with HER2-positive, inoperable, locally advanced or metastatic breast cancer, who have previously undergone treatment with trastuzumab and a taxane, administered separately or in combination. Patients should: have been previously treated for locally advanced or metastatic disease, *or* have developed a recurrence during or within 6 months of completion of the adjuvant therapy.

* Therapeutic lines beyond the third line are possible based on the clinical condition of the patient and the existence of reasonable options according to their toxicity/efficacy ratio.

Figure 12 - HER2-NEGATIVE METASTATIC BREAST CANCER: Medical therapy based on pathological and clinical characteristics
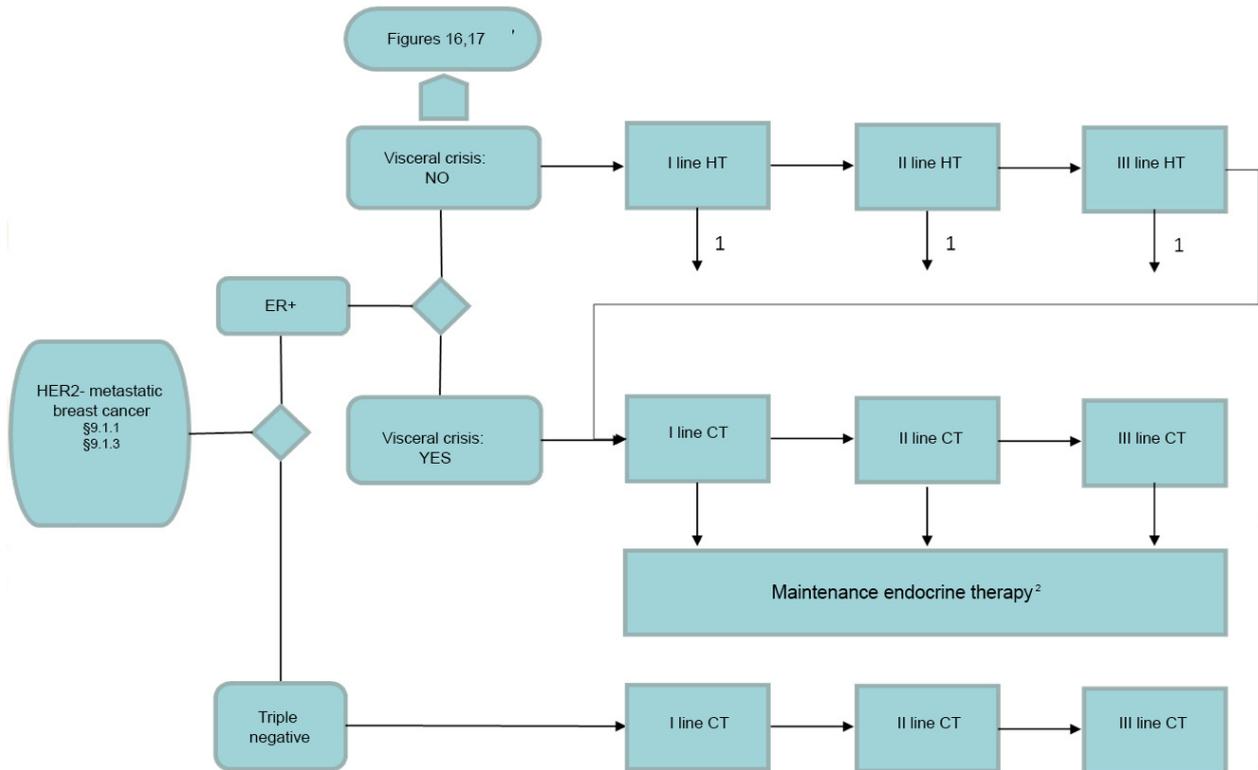
Note 1 - In case of progression during a hormonal therapy line, the transition to a subsequent line of endocrine therapy or chemotherapy should be evaluated on a case by case basis.
Note 2 - Even in the absence of data from prospective studies, the addition of maintenance hormone therapy when interrupting chemotherapy in a responding patient or a patient with stable disease is admissible.
Key: ER, estrogen receptor; HT, endocrine therapy; CT, chemotherapy

Figure 13 – ER+/HER2- METASTATIC breast cancer: Hormone therapy in premenopausal women
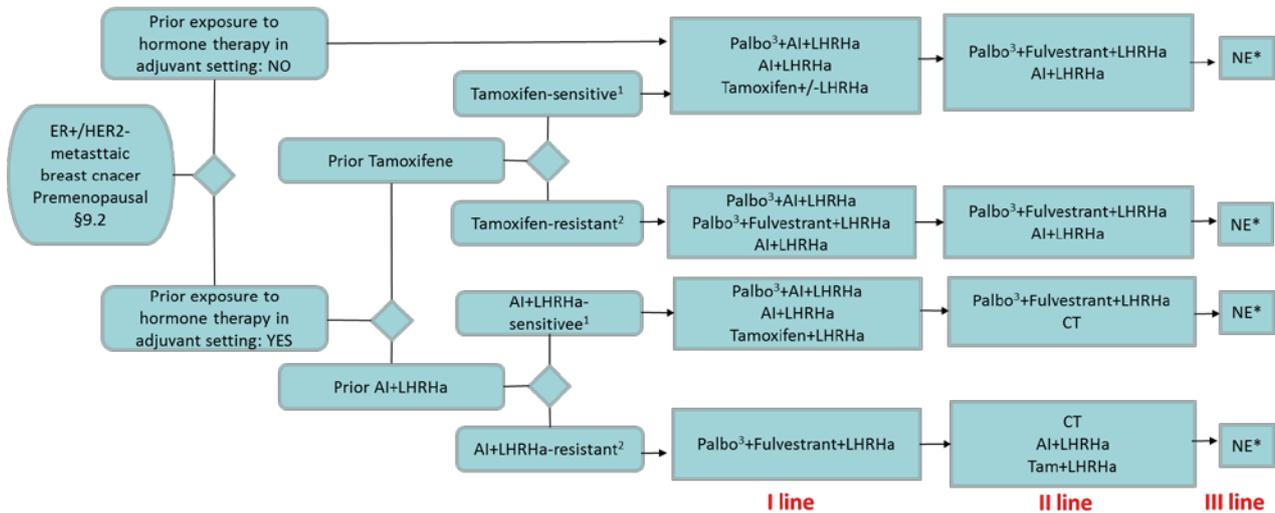
Note 1 - Interval between end of adjuvant treatment and occurrence of metastases > 12 months
Note 2 - Occurrence of metastases during adjuvant treatment or within 12 months after the end of adjuvant treatment
Note 3 - Palbociclib is indicated for the treatment of locally advanced or metastatic breast cancer (HR-positive and HEr2-negative): in combination with an aromatase inhibitor; in combination with fulvestrant in women who have received previous endocrine therapy. In pre- or perimenopausal women, endocrine therapy should be associated with a luteinizing hormone-releasing hormone (LHRH) agonist.
NE*: There is no evidence available to indicate a specific treatment. The choice depends on which medications have not been received yet or on whether or not continuation of hormone therapy is warranted.
Key: LHRHa = luteinizing hormone-releasing hormone; AI = aromatase inhibitor

The choice of II line treatment depends on the medications already received by the patient.

Figure 14 - ER+/HER2- METASTATIC BREAST CANCER: Postmenopausal hormone therapy
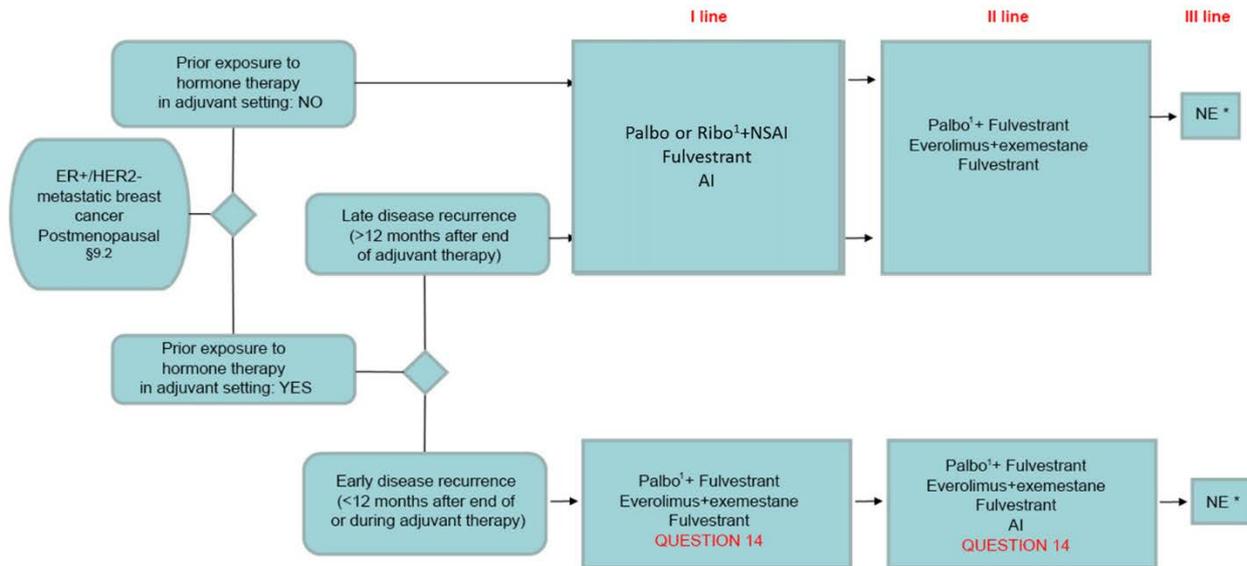
Note 1 - Currently Palbociclib and Ribociclib are approved and reimbursed in Italy. Palbociclib is indicated for the treatment of HR-positive and HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor; in combination with fulvestrant in women who have received previous endocrine therapy. In pre- or perimenopausal women, endocrine therapy should be associated with a luteinizing hormone-releasing hormone (LHRH) agonist. Ribociclib is indicated in combination with an aromatase inhibitor as initial endocrine therapy for the treatment of postmenopausal women with HR-positive and HER2-negative locally advanced or metastatic breast cancer.
NE*: There is no evidence available to indicate a specific treatment. The choice depends on which medications have not been received yet or on whether or not continuation of hormone therapy is warranted.
Key: NSAI = non-steroidal aromatase inhibitor; AI = aromatase inhibitor

1 Epidemiological data

1.1 Incidence

It is estimated that in 2018 about 52,800 new cases of female breast cancer will be diagnosed in Italy. Excluding skin cancer, breast cancer is the most frequently diagnosed cancer in women, a population where about one out of three malignant tumors (29%) is breast cancer.[1] Considering the frequencies in the different age groups, breast cancer represents the most frequently diagnosed tumor among women in the 0-49 years age group (41%), in the 50-69 years age group (35%), and in the older 70+ years age group (22%). The trend of incidence rate for breast cancer in Italy appears to be slightly increasing (+0.3% per year), while mortality continues to fall significantly (-0.8% per year). Analyzing the younger age groups, we can observe that in the 35-44 years age group the incidence appears stable, but mortality rate decreases (-0.9% per year). The expansion of the target population of mammography screening programs in some regions (including Emilia-Romagna and Piedmont) explains the significant increase in the incidence rate in the 45-49 years age group, where the mortality rate decreased by 1.0%. In the age group subject to screening within the national territory (50-69 years), incidence rate and mortality are stable. In women over 70, the incidence rate is stable and there is a reduction in mortality (-0.6% per year). The disease shows wide geographical variability, with higher rates, up to 10 times higher, in the most economically developed countries. The incidence of breast cancer showed a decline in many regions of the world around the year 2000. The significant reduction in incidence observed in the USA in 2003 in women aged ≥50 years, mainly for hormone-responsive tumors, was related to the reduction of hormone replacement therapy prescription to menopausal women[2] after the publication of the results of the WHI3 study (which showed increased incidence of invasive breast cancer and cardiovascular disease with the use of hormone therapy containing estrogen-progestins). In Italy, in consideration of the lower prevalence of hormone replacement therapy among menopausal women, this initial reduction in incidence is mainly related to the saturation effect of the incidence determined by the first rounds of mammography screening programs,[4] which involved large areas of the country in the second half of the 1990s. The differences between macro-areas observed between 2010 and 2014, which confirm a higher incidence in Northern Italy (162.9 cases/100,000 women) than in Central Italy (141.5 cases/100,000 women) and in Southern Italy & Islands (127.1 cases/100,000 women), result from the combination of the various factors involved, from the varying implementation of screening mammography to the uneven distribution of the risk factors indicated above.

1.2 Mortality

In 2015, breast cancer was once again the leading cause of cancer-related death in women, with 12,274 deaths (source: ISTAT).[1] It is the leading cause of death in the different age groups, accounting for 29% of cancer-related causes of death before the age of 50, 21% between 50 and 69, and 14% after the age of 70. There is a continuing downward trend in mortality from breast cancer (-0.8%/year), attributable to the wider availability of early detection programs and therefore early diagnosis, and to therapeutic progress. The differences in mortality observed between the different Italian macro-areas are quite limited, with a standard rate of 35.9 cases per 100,000 women in the North, 30.8 cases in the Centre and 33.5 cases in the South & Islands.[1]

1.3 Survival

The 5-year survival rate of women with breast cancer in Italy is 87%. This value does not differ much across age groups: 5-year survival is 91% in young women (15-44 years), 92% among women aged 45-54, 91% among women aged 55-64, 89% among women aged 65-74, and slightly lower, i.e. 79%, among elderly

women (75+). There are slightly lower survival levels in the South: Northern Italy (87-88%), Central Italy (87%) and Southern Italy (85%). Survival after 10 years of diagnosis is 80%.

1.4   Prevalence

On the whole, there are 800,000 women in Italy who have been diagnosed with breast cancer, equal to 43% of all women living with a prior cancer diagnosis and 24% of all prevalent cases (men and women). Of these women, 15% were diagnosed less than 2 years ago, 20% between 2 and 5 years ago, 26% between 5 and 10 years ago, and 40% over 10 years. The proportion of these cases is higher in women over 75 years of age (5,455 people per 100,000 inhabitants, 17% more than the 60-74 age group and more than twice as many as women between 45 and 59 years) and in Northern Italy (2,495/100,000 in the North-West, 2,332/100,000 in the North-East, 1,749/100,000 in the Centre and 1,356/100,000 in the South & Islands)[1].

2   Risk factors and prevention

2.1   Risk factors

The risk of developing breast cancer increases with **age**, with the probability of developing breast cancer being 2.3% up to 49 years (1 in 43 women), 5.4% in the 50-69 age group (1 in 18 women), and 4.5% in the 70-84 age group (1 in 22 women). This correlation with age could be linked to the continuous and progressive endocrine proliferative stimulus that the mammary epithelium undergoes over the years, together with the progressive damage to DNA and the accumulation of epigenetic changes that modifies the balance in the expression of oncogenes and tumor suppressor genes.

The incidence curve increases exponentially until the age of menopause (around 50-55 years), and then slows down reaching a plateau after menopause, to subsequently increase again after 60 years of age. This specific trend is linked both to the endocrinological history of a woman, and the availability and coverage of mammography screening programs.

Other factors of increased risk have been identified.

- Reproductive factors: a long fertile period, with early menarche and late menopause, and therefore a longer exposure of the glandular epithelium to the proliferative stimuli of ovarian estrogens; nullity, first full-term pregnancy after 30, no breastfeeding.

- Hormonal factors: increased risk in women taking hormone replacement therapy during menopause, especially if based on synthetic estrogen-progestins with androgenic activity; increased risk in women taking oral contraceptives.

- Dietary and metabolic factors: high consumption of alcohol and animal fats and low consumption of vegetable fibers seem to be associated with an increased risk of breast cancer.[1] Diet and behavior leading to obesity and metabolic syndrome are also increasingly important. Obesity is a recognized risk factor, probably linked to the excess of fat tissue that in postmenopausal women is the main source of synthesis of circulating estrogen, resulting in excessive hormone stimulation of the mammary gland. Metabolic syndrome is characterized by the presence of at least three of the following factors: abdominal obesity, altered glucose metabolism (diabetes or prediabetes), high lipid levels (cholesterol and/or triglycerides), and arterial hypertension. Metabolic syndrome increases the risk of cardiovascular disease but also of breast cancer: it is hypothesized that subjects with metabolic syndrome show a resistance to insulin to which the body reacts by increasing the levels of this substance. Insulin acts on the membrane receptor of insulin-like growth factor 1 (IGF-1R), activating the intracellular signal pathways essential for neoplastic growth.

Metabolic syndrome is based on genetic predisposition, but its development is clearly favored by sedentary lifestyles and high-calorie diets rich in fats and simple carbohydrates. Hence, by acting on these modifiable risk factors through regular daily physical activity combined with a balanced diet (as for example the

Mediterranean diet), the risk of developing breast cancer[1] could be reduced by improving the metabolic and hormonal balance of the woman.

As already mentioned above, it is possible to modify the risk of breast cancer by acting on predisposing factors, or those considered as such. In the USA, a significant reduction in the incidence of breast cancer, mainly hormone-responsive tumors, was observed in 2003 in women aged ≥50 years. Among various hypotheses, the most accredited is that this reduction is related to a drastic decline in the prescription of hormone replacement therapy after the publication of the results of a large study (Women's Health Initiative) that showed an increased incidence of breast cancer and ischemic heart disease with the use of hormone therapy containing estrogen-progestins.

The increase in risk attributable to the use of preparations containing estrogen and progestins was found to be related to the duration of the replacement therapy and to be reversible upon its suspension.[2-4] In addition, a recently published study presented a predictive model of absolute risk for Italian women that identifies three modifiable factors (physical activity, alcohol consumption, and body mass index) on which prevention strategies can be based, and specifically regular daily physical activity combined with a balanced (Mediterranean) diet, factors that improve the metabolic and hormonal balance. This study shows how intervening on these factors can reduce the risk over 20 years by 1.6% in menopausal women, and by up to 3.2% in women with a positive family history and 4.1% in women at high risk for other causes (about 10% of the entire population).[5]

- Prior radiotherapy (of the chest, and especially before 30 years of age) and **prior** breast **dysplasia or neoplasm**.

- Familiarity and heredity: although most breast cancers are sporadic forms, 5%-7% are linked to hereditary factors, 1/4 of which are determined by the mutation of two genes: BRCA-1 and BRCA-2. In women with BRCA-1 mutations, the life-time risk of breast cancer is 65%, and 40% in women with BRCA-2 mutations[6] (see section 9.4).

Other hereditary factors are represented by:

-        Mutations of the ATM gene (Ataxia Telangiectasia Mutated)[7] or CHEK2 gene[8,9]
-        Mutation of the PALB210 gene
-        Li-Fraumeni Syndrome (p53 mutation)
-        Cowden Syndrome (PTEN gene mutation)
-        Ataxia-telangiectasia, Peutz-Jeghers syndrome.

2.2 Screening

SCREENING IN THE GENERAL POPULATION

Screening is a periodic secondary prevention activity aimed at asymptomatic women in order to detect make breast cancer at an early stage with potential to reduce morbidity and mortality from breast cancer. Mammography is still considered the most effective screening test. The organized population-based mode is preferable to a spontaneous approach, and digital techniques (digital mammography, DM) is preferable to film-screen mammography.[11,12]

Mammography has variable relevance and efficacy according to age:

- In women aged 50-69 years, mammography is recommended every two years;
- In women aged 40-49 years, mammography should be performed by considering known risk factors such as family history and breast tissue density. The Italian National Prevention Plan (PNP) 2005-2007 (http://www.ccm-network.it/screening/intro_legislation) recommends that regional governments consider extending the screening program to women aged 45-49 (frequency is usually once per year);
- In women aged 70 and over: the Italian PNP 2005-2007 suggests that Italian Regions consider extending the screening program to women aged 70-74.

The reduction in mortality for women aged 50-69 was estimated by the IARC working group to be 23% for all invited women (adherents and non-adherents) and 40% for women participating in the screening program.[13]

The same IARC report defines the mortality reduction as "substantial" in women aged 70-74, and as "less pronounced" in women aged 40-49.

Promoters of screening state that mammography screening reduces mortality from breast cancer, while opponents claim that the benefit of mammography screening has decreased over the last decades in terms of its impact on reducing mortality from breast cancer as a result of the wide application of adjuvant systemic therapies (hormonal therapy and chemotherapy).[20,21] However, this position against screening is largely contradicted not only by 2005 estimates[14], which attributed the merit of reducing breast cancer mortality by 46% to screening and 54% to adjuvant therapy, but also by a recent Dutch study[15] that showed that, even in the age of modern therapies (2006-2012), the small size of the tumor at diagnosis (T parameter) continues to have a significant impact on survival (T1c versus T1a mortality, 1.54 hazard ratio, 95% CI 1.33-1.78).

Opponents also argue overdiagnosis is a limitation to mammography. Indeed, some cancers such as in situ and and some invasive carcinomas would not impact on survival even if not detected at all in a lifetime. The IARC working group[13] adopted the estimate of the EUROSCREEN working group,[16] estimating an overdiagnosis of 6.5% (range 1-10%).

The EUROSCREEN working group proposed an operative representation of the balance between the advantages and disadvantages of screening.[17] Every 1,000 women who perform biennial mammography between 50 and 69 years and subsequently followed-up until 79 years of age, we will have:

- 8 women diagnosed with breast cancer who were treated and survived thanks to the screening;

- 47 other women diagnosed with breast cancer who were treated and survived;

- 4 women with overdiagnosis (and therefore overtreatment) of breast cancer;

- 12 women who died of breast cancer;

- 30 women who had needle biopsy for benign findings;

- 170 women who had additional diagnostic tests for benign findings;

- 729 women who are never recalled for further investigation and were reassured about the absence of breast cancer.

Women should be adequately informed about the possibility of experiencing false positives or overdiagnosis, defined as the diagnosis and treatment of a tumor that would not have become clinically evident in their lifetime without the screening.[16,18]

The question of the age until which to continue screening mammography is a difficult one, even in view of the continuing trend of increasing life expectancy. In this context, the American Cancer Society, which correlates the indication to mammography screening to life expectancy, suggestis that mammography should be continued as long as the woman is in good health and has a life expectancy of 10 years or more.[19]

The use of *digital breast tomosynthesis* (DBT) in the screening of the general population is under investigation. The results are promising and this method is likely to be adopted as a generalized screening tool in the next years. DBT is pseudo 3D imaging technique allowing to overcome some limitations of DM caused by tissue overlaps, resulting in a decrease of false negatives and false positives especially in dense breasts.[20] Several studies have evaluated the potential of DBT as a first-level screening examination.[21-26] A report that grouped together some of the above results[27] reported that DBT guarantees an increase in the detection rate of 0.5 to 2.7/ 1000 screened women, and a reduction in the recall rate of 3.6 to 0.8 every 100 screened women. Exposure to an increased dose of radiation is a problem that is solved by the use of two-dimensional images reconstructed from DBT data, with consequent dose savings.[28] Interestingly, two studies[29,30] reported that 54-57% of additional cancers detected by additional ultrasound after a negative DM were detected by DBT. This is a significant argument in favor of DBT, considering the practical barriers to the addition of ultrasound to DM in a population screening context.

However, in the context of organized screening, a simple increase in the overall sensitivity and diagnostic performance of a new instrument, even if statistically significant and clinically relevant, is not sufficient *per se* for its generalized adoption.[31] Particular attention should be paid to ongoing randomized trials and their results in terms of reduction of interval cancers, staging of tumors detected by DBT and finally mortality reduction. Other clinical and diagnostic examinations used for in symptomatic patients or detection or staging purposes have not been shown to be effective as breast cancer screening in the general population. The clinical

and diagnostic examination which resuted not effective so far are: self-palpation;[32] clinical examination of the breast;[33.34] breast ultrasound;[35] breast magnetic resonance imaging (MRI).[36.37]

SCREENING OF HIGH-RISK WOMEN

In women at high risk because of family history of breast cancer or BRCA1 and/or BRCA2 mutation, instrumental examinations should start at the age of 25, or 10 years before the age of tumor onset in the youngest family member.
Breast Magnetic Resonance Imaging with gadolinium (CE-MRI), with annual screening frequency is indicated[38] in high-risk women, defined as follows:
- *BRCA1* or *BRCA2* mutation;
- Lifetime risk of 20-25% according to common risk prediction models;
- Li-Fraumeni, Cowden or Bannayan-Riley-Ruvalcaba syndrome;
- Prior chest radiotherapy between 10 and 30 years of age.

In women at increased risk on a hereditary/family basis, numerous studies have shown that if an annual MRI is performed, the contribution of mammography in terms of further detection is limited, particularly in *BRCA1*[39] mutation carriers. In the women, if MRI is performed, mammography could be avoided. In addition, the increased risk of radio-induced carcinogenesis related to the reduced oncosuppressive action is against the use of mammography.[40] If MRI is performed, ultrasound too does not provide diagnostic benefits,[41] even if performed every six months.[42] The combination of mammography and ultrasound is appropriate in high-risk women who cannot undergo MRI.
Women treated with chest radiotherapy (CRT) in childhood or young-adult age, and especially those treated with high-dose CRT, present an increased risk of developing breast cancer. The cumulative incidence of breast cancer between 40 and 45 years is 13-20%,[43] similar to that of women with a BRCA mutation. However, compared to women at high risk due to their family history, in those undergoing CRT a relatively higher sensitivity of mammography and relatively lower sensitivity of CE-MRI were observed (compared to women with a genetic/family risk); this result is related to the higher incidence of ductal carcinoma in situ with microcalcifications and lower neoangiogenesis. Based on the available evidence, women who have undergone CRT before the age of 30 with a cumulative dose $\geq$ 10 Gy should be invited to participate in a specific surveillance program from the age of 25 or at least 8 years after CRT, including the following assessments:
- Annual bilateral CE-MRI with the same protocol used to screen women at high risk for hereditary/family factors;
- Annual bilateral mammography or tomosynthesis with 2D reconstruction. Mammography and MRI can be performed simultaneously or alternately every six months. Upon reaching the age for invitation to organized screening programs, the woman's risk profile should be reassessed and discussed to decide for annual or biennial mammography-based screening (possibly with tomosynthesis) or continuation of annual mammography and MRI.

2.3 Chemoprevention

Recently, a meta-analysis **(Level of Evidence 1++)** was published that evaluated data from nine phase 3 placebo-controlled studies of chemoprevention on 83,399 women at high risk of disease, for a total of 306,670 person-years, using selective estrogen-receptor modulators (SERMs; tamoxifen, raloxifene, arzoxifene, and lasofoxifene). At a median follow-up of 65 months, the use of SERMs resulted in a 38% reduction (hazard ratio [HR]=0.62, 95% CI 0.56-0.69) of the incidence of infiltrating and in situ ductal carcinoma (42 women to be treated to prevent one event in the first 10 years of follow-up). The reduction was greater in the 5 years of

treatment, but was also maintained in the following 5 years of follow-up (42%, HR=0.58, 95% CI 0.51 -0.66; p <0.0001 vs 25%, HR=0.75, 95% CI 0.61-0.93; p = 0.007).
The use of SERMs resulted in a significant increase in thromboembolic events (odds ratio= 1.73, 95% CI 1.47 -2.05; p <0.0001) and a significant reduction (34%) in the incidence of vertebral fractures (0.66, 0.59 -0.73), and a small but significant effect on nonvertebral fractures (0.93, 0.87 -0.99).[44]

The use of aromatase inhibitors in chemoprevention has been shown to be effective in two phase 3 placebo-controlled trials[45,46] **(Level of evidence 1++)**.

The NCIC CTG MAP.3 study, a randomized double-blind placebo-controlled trial, evaluated the role of exemestane 25 mg/day for 5 years in 4,560 postmenopausal women at increased risk of breast cancer (age > 60 years, risk at 5 years calculated according to Gail over 1.66%, previous diagnosis of atypical ductal/lobular hyperplasia, lobular carcinoma in situ, DCIS treated with mastectomy).[45] At a median follow-up of 35 months, 11 infiltrating breast cancers were reported in the exemestane group vs 32 in the placebo group, with a benefit of 65% in terms of relative reduction (0.19% vs 0.55%; HR=0.35; 95% CI 0.18-0.7; p=0.002) of the annual risk of occurrence of infiltrating breast cancer. This benefit seems to be confirmed also in women with previous diagnosis of contralateral DCIS treated with mastectomy (5% of the entire study population). The study did not show significant differences in severe adverse events, but there was an excess of symptoms related to exemestane (hot flashes, joint and tendon/muscle pain, diarrhea). However, the incidence of osteoporosis has not been systematically evaluated, and the assessment of the cost/benefit ratio appears difficult due to the immaturity of the study.[47]

The IBIS-II[46] study recruited 3,864 postmenopausal women at increased risk according to the Tyrer-Cuzick model who received anastrozole or placebo. At a median follow-up of 5 years (range 3-7.1), 40 women in the anastrozole arm (2%) and 85 in the placebo arm (4%) developed breast cancer (HR=0.47, 95% CI 0.32-0.68, p<0.0001). Distribution according to receptor status was as follows: 20 in the anastrozole arm versus 47 in the placebo arm (HR=0.42, 0.25-0.71) in ER+ tumors and 11 vs 14 in ER- tumors (HR=0.78, 0.35-1.72). The number of women to be treated with anastrozole to prevent 1 breast cancer after 7 years was 36 (95% CI, 33-44). The risk reduction in the group with prior atypical hyperplasia or LCIS was 69% (HR=0.31, 0.12-0.84). Anastrozole reduced the onset of skin and colorectal tumors (RR=0.58, 0.39-0.85), while the number of deaths was 18 vs 17. No excess fractures were observed, while symptoms related to estrogen deprivation in the anastrozole group were more frequent.

Based on these studies, NICE published its guidelines in June 2013 and updated them in March 2017 (https://www.nice.org.uk/guidance/cg164), indicating that preventive treatment with premenopausal tamoxifen and postmenopausal anastrozole, except in the presence of severe osteoporosis, should be offered to high-risk women, defined as those having a risk of developing breast cancer > 30% in their life-time (up to 85 years) or >8% over 10 years in the decade between 40 and 50 years, and at moderately high life-time risk (between 17% and 30%) according to the Tyrer-Cuzick model.[48]
High risk women include women with known germ mutation of BRCA1, BRCA2, TP53 genes and rare conditions involving an increase breast cancer risk, such as Peutz-Jeghers syndrome (STK11), Cowden syndrome (PTEN), and hereditary diffuse gastric cancer (E-cadherin).
In postmenopause, as an alternative to anastrozole, the use of tamoxifen for 5 years may be considered in women who have no personal history and who are not at risk of thromboembolic events or endometrial carcinoma, or raloxifene in non-hysterectomized women who do not wish to take tamoxifen.
The use of tamoxifen and raloxifene (postmenopausal only) to reduce the risk of breast cancer is FDA-approved in women at increased risk according to the Gail model (>1.66% at 5 years). It should be noted that, in the NSABP-149 study, tamoxifen reduced the risk of cancer by 86% in women with previous atypical ductal hyperplasia (HR=0.14; 0.03-0.47). In the rest of Europe, with the exception of the United Kingdom, the use of SERMs in chemoprevention is still off-label.

In Italy, with the determination of 29.11.2017, AIFA has included tamoxifen in the list of medications that can be fully reimbursed by the National Health Service, established pursuant to Law no. 648 of 23 December 1996, for the preventive treatment of breast cancer in women at high risk (women with a risk

of developing breast cancer in the subsequent 5 years ≥ 1.66% according to the Gail model, or with a risk > 8% over 10 years between 40 and 50 years of age or >30% life-time risk according to the Tyrer-Cuzick model).

In addition, with the same determination of 29.11.2017, AIFA has included raloxifene in the list of medications that can be fully reimbursed by the National Health Service for the preventive treatment of breast cancer in high-risk postmenopausal women (risk of developing breast cancer in the subsequent 5 years ≥ 1.66% according to the Gail model, or with a risk > 8% over 10 years between 40 and 50 years of age or >30% life-time risk according to the Tyrer-Cuzick model).

To date, the indication for use of aromatase inhibitors for the chemoprevention of breast cancer is not registered in any country and such use is therefore off-label.

3 Diagnostic framework

3.1 Histological classification

The histopathological classification of breast cancer according to the 2003 WHO blue book[1] has recently been reviewed and the 2012WHO [2] classification includes the histological types listed in Table 3.1.

Invasive carcinoma of no special type (NST), formerly known as invasive ductal carcinoma, not otherwise specified, constitutes the largest group of invasive breast carcinomas (70%-80%) and represents an entity that cannot be easily defined, since it includes a heterogeneous group of tumors that do not have sufficient characteristics to be classified as a special histological type (as is the case for other tumors, e.g. lobular or tubular carcinoma).

Table 3.1. Summary of histological classification of breast cancer according to WHO 2012[2]
EPITHELIAL TUMORS Microinvasive carcinoma
Infiltrating breast cancer
Invasive carcinoma of No special type (NST)
Special histologic type Infiltrating lobular carcinoma Tubular carcinoma Cribriform carcinoma Mucinous carcinoma and signet ring cell carcinoma Carcinoma with medullary features Apocrine carcinoma Invasive micropapillary carcinoma Metaplastic carcinoma Carcinoma with neuroendocrine features Invasive papillary carcinoma Mucoepidermoid carcinoma Polymorphous carcinoma Salivary gland/skin adnexal tumors
Extremely rare variants Secretory carcinoma Oncocytic carcinoma

Table 3.1.
Summary of histological classification of breast cancer according to WHO 2012[2]

Sebaceous carcinoma
Lipid-rich carcinoma
Glycogen-rich clear cell carcinoma
Acinic cell carcinoma
Epithelial-myoepithelial tumors

Precursors
  Ductal carcinoma in situ*
Lobular neoplasia**
    Lobular carcinoma in situ
      Classic lobular carcinoma in situ
      Pleomorphic lobular carcinoma in situ
    Atypical lobular hyperplasia

Intraductal proliferative lesions*
   Usual ductal hyperplasia
   Columnar cell lesions including flat epithelial atypia
   Atypical ductal hyperplasia

Papillary lesions
    Intraductal papilloma
    Intraductal papillary carcinoma
    Encapsulated papillary carcinoma
    Solid papillary carcinoma

Benign epithelial proliferations
Sclerosing adenosis
Apocrine adenosis
Microglandular adenosis
Radial scar/complex sclerosing lesion
Adenomas

EPITHELIAL- MYOEPITHELIAL TUMORS
Epithelial-myoepithelial lesions
Adenomyoepithelioma
Adenomyoepithelioma with carcinoma

MESENCHYMAL TUMORS
   (e.g. angiosarcoma, etc.)

FIBROEPITHELIAL TUMORS
Fibroadenoma
   Phyllodes tumors (benign, borderline, malignant)

NIPPLE TUMORS
    Nipple adenoma
    Syringomatous tumor
    Paget's disease of the nipple

MALIGNANT LYMPHOMAS

METASTATIC TUMORS

| Table 3.1. |
| Summary of histological classification of breast cancer according to WHO 2012[2] |

MALE BREAST TUMORS
Invasive carcinoma
Carcinoma in situ

CLINICAL SCENARIOS
Inflammatory carcinoma
Bilateral breast cancer

For some of these forms there may be histological variants[2] or mixed forms with the association of two or more histological types. The determination of the degree of differentiation[3] is essential and must be carried out for all invasive histotypes.
* INTRADUCTAL PROLIFERATIVE LESIONS *(see Annex 2)*
** LOBULAR NEOPLASIA *(see Annex 2).*

3.2 Determination of HER2 status in breast cancer: ASCO/CAP recommendations *(see Annex 3)*

3.3 Molecular classification – Gene profiles

According to molecular biology testing, namely microarray gene expression analysis that has identified an "intrinsic gene list" of 496 genes, four subtypes of invasive carcinomas were identified:[4]

- "Luminal A": neoplasms with marked hormone receptor expression, favorable prognosis;
- "Luminal B": neoplasms that, although expressing hormonal receptors, are at high risk of recurrence due to the high proliferative index related to high expression of proliferation genes;
- "HER2-enriched": characterized by the presence of HER2 expression;
- "Basal-like": neoplasms with no expression of hormone and HER2 receptors and with increased expression of basal (myoepithelial) cytokeratins (e.g. CK5/6 and CK14).

These subgroups have been demonstrated to be clinically meaningful, i.e. holding an important prognostic impact, with Luminali A carcinomas having a good prognosis, far better than Luminal B carcinomas, and HER2-enriched and Basal-like showing the worst prognosis overall.

Within these subtypes there is a high degree of heterogeneity. In the light of new pathological and molecular knowledge, additional subtypes of breast cancer were defined. Recently, for example, another subgroup of neoplasms has been identified with no hormonal receptor expression and HER2, but with stem cell markers, low expression of claudins (cellular-cellular junction proteins), and lymphocytic infiltrate accompanying tumor growth, called "claudin low" and characterized by poor prognosis.[5,6] Moreover, an analysis of the gene expression of 587 triple-negative breast cancers allowed to identify six different subtypes characterized by a different molecular biology and a different clinical behavior: basal like 1 and 2 (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR).[12] A recently published work has further clarified that the stem-like immunomodulatory and mesenchymal subtypes are actually determined by the lymphocytic/inflammatory infiltrate and not by the cancer cells.[7]

The creation of cell lines derived from each subtype subsequently allowed to demonstrate a different sensitivity to chemotherapy agents and target therapies.[8] In clinical practice, the immunohistochemical evaluation of the status of hormone receptors, Ki67 and HER2 allows to identify in a surrogate way the 4 phenotypic subgroups of breast cancer that have a "relative" correspondence with the 4 types derived from gene expression profiles.[9] The immunophenotypic groups of clinical relevance and with important therapeutic implications, also for adjuvant therapy, are:

- **Luminal A:** hormone-receptor positive, HER2 negative with low proliferative activity (frequently including special histotypes such as tubular carcinoma, classic lobular carcinoma). According to the San Gallen 2013

Consensus,[10] Luminal A breast tumors are tumors positive to estrogen receptors, positive to progestin receptors with positive values higher than 20%, HER2 negative, and with low Ki67 (cut off 20% instead of 14% as reported in the 2009 Consensus).

- **Luminal B/HER2 negative:** hormone-receptor positive, HER2 negative and high proliferative activity;
- **Luminal B/HER2 positive:** hormone-receptor positive, over-expressed (3+ score for immunohistochemical reactions) or amplified HER2, any value of proliferative activity.
- **HER2 positive (non-luminal):** overexpressed (3+ score of immunohistochemical reactions) or amplified (FISH or other methods) HER2 and hormone receptors both negative.
- **Triple-negative:** no hormone receptor expression and HER2 negative. The correspondence between the "triple negative" phenotype identified on an immunohistochemical basis and the intrinsic "basal like" subgroup identified on a gene basis only exists in about 80% of cases, further demonstrating the extreme heterogeneity within these subgroups. The "triple negative" subgroup also includes some special histotypes such as typical medullary and adenoid-cystic tumor, with low risk of recurrence. Retrospective analyses associated the four subtypes with differences in disease-free survival, disease recurrence sites and overall survival.[11]

To define the prognosis more precisely and select the best treatment for the individual patient, gene profiles with a more limited number of genes are being studied and some of these tests, evaluated mainly in retrospective studies, are already in use in some countries. Various gene profile analysis tests such as Prosigna, Mammaprint, Oncotype DX, Breast Cancer Index and Endopredict are now available on the market. All of them require paraffin-embedded tissue, while the Mammaprint test can also be carried out on fresh frozen tissue. Prosigna (PAM50) and Mammaprint have been approved by the FDA in the US.[12]

Although robust retrospective validation in prospective clinical trials has been provided the value of these signatures has been assessed in three prospective randomized trials comparing gene profiles with standard criteria in the selection of **patients with hormone receptor positive breast cancer and HER2 negative breast cancer** who may benefit from adjuvant chemotherapy in addition to hormone therapy. The first two American studies, TAILORx and RxPONDER, evaluate the **Oncotype Dx** test that analyzes the expression of 21 genes on paraffin-embedded tissue (RNA molecules with the RT-PCR method) and classifies hormone-receptor positive tumors into three groups based on a "recurrence score". Patients with negative axillary lymph nodes[13] are enrolled in TAILORx, while patients with 1-3 positive axillary lymph nodes are enrolled in the RxPONDER study (started in 2011). The third study conducted in Europe, MINDACT, uses the **MammaPrint** test that analyzes 70 genes in fresh frozen tissue (DNA microarray) and classifies tumors as at low and high risk of recurrence.[14] Patients with 1-3 positive axillary lymph nodes were also enrolled in the latter study.

The prospective study TAILORx[15,16] globally enrolled 10,273 women with hormone receptor positive, HER2 negative breast cancer with negative axillary lymph nodes, whose clinical and pathological characteristics are in line with the recommendation for adjuvant chemotherapy according to the NCCN Guidelines, including a primary tumor diameter between 1.1 and 5 centimeters or a G2-G3 tumor between 0.6 and 1 centimeter. In all these women, the Recurrence Score was evaluated with Oncotype DX: patients with RS <11 received hormonal therapy alone, patients with RS >25 received chemotherapy and hormone therapy, and patients with RS between 11 and 25 were randomized to receive hormone therapy with or without chemotherapy. The study results for 1,626 patients with low recurrence scores (15.9% of eligible patients) showed a 93.8% disease-free survival rate at 5 years (95% CI 92.4-94.9); the rate of distant recurrence-free patients was 99.3% (95% CI 98.7-99.6), and survival was 98% (95% CI 97.1-98.6). More recently, results have been published for the group of patients with RS between 11 and 25 (69% of patients enrolled): the primary endpoint of the study was non-inferiority of hormone therapy compared to hormone therapy + chemotherapy in this group. The rates of 9-year disease-free survival were similar in the two treatment arms: 83.3% (hormone therapy) and 84.3% (hormone therapy + chemotherapy), HR 1.08 (95% CI 0.94-1.24, pre-defined limit to demonstrate non-inferiority = 1.322; p=0.026). Rates of distant recurrence-free survival, local-regional or distant recurrence-free survival and overall survival were also comparable in the two treatment arms.

An unscheduled analysis of subgroups in this non-inferiority study suggested a benefit with CT for women under 50 years of age in terms of 10-year DFS of 6.6% for RS 16-20 (mainly local-regional events) and 8.7% for RS 21-25 (mainly systemic events), with an increase in 10-year survival in the latter group of 1.2%.

Data from the phase III study MINDACT, whose primary objective was to prospectively evaluate the clinical usefulness of adding the 70-gene signature to the traditional clinical-pathological criteria in selecting patients

for adjuvant chemotherapy, have also been published. In the 1,550 patients at high clinical risk and low genomic risk not randomized to chemotherapy, the 5-year metastasis-free survival was 94.7% (95% CI 92.5-96.2). The absolute difference in survival between these patients and those receiving chemotherapy was 1.5%, and the study authors concluded that, in view of these results, about 46% of patients at high clinical risk may not receive adjuvant chemotherapy in addition to hormone therapy.[17]

In 2016, ASCO/CAP[18] produced recommendations for the use of gene expression profile (GEP) molecular testing to guide the addition of adjuvant chemotherapy to hormone therapy in patients with hormone receptor positive and HER2 negative breast cancer, also taking into consideration their lymph node status. In particular, Oncotype DX® and PAM50-Prosigna® (both produced in the USA) should be recommended based on a high level of evidence in ER/PgR positive, HER2 negative carcinomas without lymph node metastases while, as in European guidelines, the use of these tests is still under discussion in tumors with lymph node metastases and is not recommended in HER2+ or triple-negative tumors.

The report of the 15th Saint Gallen Conference of 2017,[19] during which the terms of use of molecular tests were re-discussed, was also recently published. In particular, the Panel of Experts agreed that GEPs, if available, are preferable to standard pathology assessments when reproducibility is not guaranteed and, after much discussion of indications, established that GEPs have no role in cases at low clinical risk (pT1a/b, grade 1(G1), high levels of ER, N0) and in similar settings where chemotherapy would not be administered under any circumstances. In addition, there was unanimity in defining Oncotype DX®, Mammaprint®, PAM50 ROR (Prosigna®), EpClin® and Breast Cancer Index® as prognostic markers useful in the adjuvant endocrine therapy setting in breast cancer with negative lymph nodes, as they all define "low-risk cases with negative lymph nodes", with an excellent prognosis that would not require chemotherapy. Conversely, the Panel was not unanimous on the use of GEPs to make therapeutic decisions regarding adjuvant chemotherapy in cases with positive lymph nodes. Accordingly, the Panel did not recommend the use of GEPs to choose whether to extend adjuvant endocrine therapy, as there is no prospective data and retrospective data are not recognized as sufficient to justify the routine use of genomic tests in this setting. The main role of molecular testing is for or against adjuvant chemotherapy, therefore, in patients who are not candidates for adjuvant chemotherapy according to comorbidity or stage/risk of cancer, or in patients who "obviously" need chemotherapy, which typically include stage III breast cancer, there is no need for routine use of genomic testing. In general, the "middle" zone is where tests can be useful, i.e. tumors between 1 and 3 cm, with 0 up to 2 or 3 positive lymph nodes and an intermediate proliferation index. However, multigene testing should not be the only tool used to decide whether to administer or avoid chemotherapy.

In 2017, the Higher Health Council of the Ministry of Health issued "The Prescription of Breast Cancer Multigene Molecular Prognostic Tests (MMPTs)", which specifies that in Italy MMPTs are not currently included in the Essential Levels of Care (LEA in Italian) and are therefore not reimbursable; these tests are used not according to specific institutional rules, but in individual cases based on clinical needs and on the possibility of the patient to directly cover their cost. However, their introduction in clinical practice as a service provided by the NHS requires regulations governing their implementation, quality and application in order to protect patients, as well as a cost analysis aimed at an effective and efficient financial health policy. This document therefore contains a number of recommendations set out in Annex 4.

3.4   Classification according to the TNM system

The extent of the disease is described according to traditional classification criteria, and the TNM system is the most frequently adopted.

Since January 2018, the TNM classification system revised by the American Joint Committee on Cancer (AJCC - Eighth edition) has been in use (Tables 4 and 5).[20]

The Eighth Edition of the AJCC classification includes the anatomic classification, solely based on the anatomic extent of breast cancer (T, N, M), and a prognostic classification (Prognostic Stage Group) that includes not only anatomic variables (T, N and M), but also tumor grade, hormone receptor status and HER2 status (Annex no. 5). In addition, within ER+/HER2- tumors, if a prognostic signature is used and renders a low risk results dowstaging is performed.

The prognostic classification shall be used in the USA.

The anatomic classification is applicable to all of the regions of the world where biomarkers and prognostic signatires cannot be routinely obtained.

Compared to the 2010 edition, the main changes in the new version include:

- Removal of lobular carcinoma in situ (LCIS) from TNM staging, as it is considered as a benign entity: in the case of a pure LCIS form there will be no pTis stage, which is reserved exclusively for ductal carcinomas in situ (DCIS).

- More precise information on methods of pathological measurement of tumor and lymph node metastases:
  - Tumors with a diameter > 1 mm and < 2 mm are rounded up to 2 mm;

  - It is pointed out that incidentally identified peritumoral microscopic deposits should not alter the measurement of the tumor size, which is well approximated by the larger diameter of the tumor node that is considered a reasonable approximation of the tumor burden;

  - For multifocal carcinomas, it is recommended to perform radiological correlations that can guide the identification of two tumors as distinct; it is not excluded that a multifocal tumor may be found only at a histopathological microscopic level, without radiological evidence. Whenever a multifocal tumor is identified, the suffix "m" should be used;

  - For skin nodules that identify a pT4b stage, it is pointed out that these must be identified by macroscopic observation and must be separated from the primary tumor;

  - For inflammatory carcinoma that identifies a pT4d stage tumor, it is pointed out that this definition must be necessarily based on clinical data that show skin edema and erythema in at least one third of the breast;

  - For the anatomic and pathological evaluation of tumors undergoing neoadjuvant therapy, it is reiterated that the evaluation of tumor size (ypT) should be carried out exclusively by measuring the major focus of residual neoplasm (if present), and not the tumor bed detectable by the fibrous scar that often remains; the presence of multiple residual foci should be indicated by the letter (m). In parallel, the definition of pathological N after neoadjuvant therapy is clarified and should be based on the larger focus of residual tumor within the lymph node, if present. Treatment-related fibrosis adjacent to tumor deposits in the lymph node should not be included in the size and classification of ypN.

  - For metastatic lymph nodes (definition of pathological pN), the largest aggregate of contiguous tumor cells should be measured without adding up separate tumor clutters: if present, this is especially important in differentiating micrometastases and macrometastases, and creates problems for the use of the OSNA (*One Step Nucleic Acid amplification*) molecular method, which could lead to pN overstaging, being a method based on the extraction of mRNA from a lymph node homogenate, therefore preventing the measurement of the larger metastatic deposit.

  - Better definition of the cNx category to be applied only in cases where lymph nodes have been removed and cannot be examined with imaging or clinical examination. Category cN0 should be assigned when lymph node assessment is feasible and imaging and clinical examination are negative.

  - Definition of pM1 category to be used only in cases where cM1 classification is confirmed microscopically.

Table 3.2. AJCC 2017 Classification (Eighth edition)

Clinical classification

Table 3.2. AJCC 2017 Classification (Eighth edition)

Primitive tumor (T):

Tx: primary tumor cannot be assessed

T0: no evidence of primary tumor

Tis: carcinoma in situ:

Tis (DCIS) Ductal carcinoma in situ

Tis (Paget) Paget disease of the nipple not associated with invasive and/or carcinoma in situ in the underlying breast parenchyma[1]

T1: tumor up to 20 mm in greatest dimension

T1mi: microinvasion ≤1 mm

T1a: tumor size between 1 mm and 5 mm (round any measurement between 1.0-1.9 mm to 2 mm)

T1b: tumor size >5 mm and ≤10 mm

T1c: tumor size >10 mm and ≤20 mm

T2: tumor >20 mm but <50 mm in greatest dimension

T3: tumor >50 mm in greatest dimension

T4: tumor of any size with direct extension to the chest wall and/or to the skin (skin ulceration or nodules)[2]

T4a: extension to the chest wall (excluding only adherence to/invasion of the pectoral muscle)

T4b: ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma

T4c: both T4a and T4b are present

T4d: inflammatory carcinoma[3]

Regional lymph nodes (N):

Nx: regional lymph nodes cannot be assessed (e.g., previously removed)

N0: no regional lymph nodes metastases (instrumental and clinical examination)

N1: metastases to movable ipsilateral axillary lymph nodes (level I-II)

cN1mi: micrometastases (approximately 200 cells, deposition greater than 0.2 mm, but none larger than 2.0 mm)[4]

N2: metastases in ipsilateral axillary nodes (level I-II) that are clinically fixed or matted; or in clinically detectable ipsilateral internal mammary nodes in the absence of clinically evident metastases in the axillary nodes

N2a: metastases in ipsilateral axillary lymph nodes (level I-II) fixed to one another or to other structures

N2b: metastases only in ipsilateral internal mammary lymph nodes and no metastases in axillary lymph nodes (level I-II)

N3: metastases in one or more ipsilateral subclavicular lymph nodes (level III axillary) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph nodes with level I-II axillary lymph node metastases; or metastases in one or more ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement

N3a: metastases in ipsilateral subclavicular lymph nodes

N3b: metastases in internal mammary and axillary lymph nodes

N3c: metastases in supraclavicular lymph nodes

Distant metastasis (M):

Mx: distant metastases cannot be ascertained (but diagnostic imaging is not required to assign category M0)

M0: no clinical or radiological evidence of distant metastases

cM0(i+): no clinical or radiological evidence of distant metastases, but deposits of tumor cells detected by molecular biology or microscopically in blood, bone marrow or other tissues other than regional lymph nodes, not exceeding 0,2 mm in a patient without signs or symptoms of metastases.

M1: distant metastases detected by typical clinical and radiological exams and/or histologically proven metastases greater than 0,2 mm (pM).

Pathological classification

Table 3.2. AJCC 2017 Classification (Eighth edition)

pT: Primary tumor
The pathological classification of the primary tumor corresponds to the clinical classification.
pN: Regional lymph nodes [5]
pNx: regional lymph nodes cannot be assessed (e.g. not removed for pathological study or previously removed)
pN0: no regional lymph node metastases identified or isolated tumor cells (ITCs) only
Note: isolated tumor cells (ITCs) are defined as small aggregates of cells no larger than 0.2 mm or single tumor cells or a small grouping of cells with less than 200 cells in a single histological section. Isolated tumor cells can be detected by traditional histological methods or by immunohistochemical methods. Lymph nodes containing only isolated tumor cells are excluded from the total count of positive lymph nodes for N classification purposes, but should be included in the total number of lymph nodes tested.
pN0 (i-): no regional lymph node metastases by histology (standard hematoxylin & eosin staining), negative by immunohistochemistry
pN0 (i+): presence of malignant cells (ITCs) in regional lymph nodes not exceeding 0,2 mm (detected by hematoxylin & eosin staining or immunohistochemistry)
pN0 (mol-): no metastases in histologically established regional lymph nodes, RT-PCR (real time-polymerase chain reaction) negative
pN0 (mol+): RT-PCR positive but no regional lymph node metastases by histology or immunohistochemistry; no ITCs detected
pN1: micrometastases; or metastases in 1-3 ipsilateral axillary lymph nodes; and/or micrometastases or macrometastases in ipsilateral internal mammary lymph nodes detected by sentinel node biopsy but not clinically detectable[5]
pN1mi: micrometastases (aggregate of contiguous tumor cells larger than 0,2 mm and/or more than 200 cells, but no larger than 2 mm)
pN1a: metastases in 1-3 axillary lymph nodes, including at least one metastasis larger than 2 mm in greatest dimension
pN1b: metastases in internal mammary lymph nodes, excluding ITCs
pN1c: combination of pN1a and pN1b
pN2: metastases in 4-9 ipsilateral axillary lymph nodes; or in ipsilateral internal mammary lymph nodes at instrumental examinations with no axillary lymph node metastases
pN2a: metastases in 4-9 axillary lymph nodes, including at least one tumor deposit larger than 2 mm in greatest dimension
pN2b: clinically detectable[6] metastases in internal mammary lymph nodes, with or without histological confirmation, without axillary lymph node metastases
pN3: metastases in 10 or more ipsilateral axillary lymph nodes; or in ipsilateral subclavicular (level III axillary) lymph nodes; or metastases in ipsilateral internal mammary lymph nodes confirmed by imaging with metastases in one or more positive level I-II axillary lymph nodes; or metastases in more than 3 axillary lymph nodes and in internal mammary lymph nodes, with microscopic or macroscopic metastases shown by sentinel lymph node biopsy but not clinically detectable[6]; or metastases in ipsilateral supraclavicular lymph nodes
pN3a: metastases in 10 or more ipsilateral axillary lymph nodes (at least one larger than 2 mm in greatest dimension; or metastases in subclavicular lymph nodes (level III axillary lymph nodes)
pN3b: pN1a or pN2a in the presence of cN2b (ipsilateral internal mammary lymph nodes positive by imaging), or pN2a in the presence of pN1b
pN3c: metastases in ipsilateral supraclavicular lymph nodes

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[1] Carcinomas in the breast parenchyma associated with Paget's disease are classified according to the diameter and characteristics of the parenchymal disease, although Paget's disease should be noted.
[2] Invasion of the dermis alone does not allow classification of the tumor as pT4.
[3] Inflammatory carcinoma is characterized by typical skin changes involving one third or more of the breast skin. It is important to underline that inflammatory carcinoma is primarily a clinical diagnosis. The skin changes may be due to lymphedema caused by tumor emboli in lymphatic vessels, but histological findings of these embolisms are not necessary for the diagnosis of inflammatory carcinoma. Tumor emboli in lymphatics not associated with skin changes should be categorized according to tumor diameter.

(4) cN1mi is rarely used but may be appropriate in rare cases where the sentinel lymph node biopsy has been performed prior to surgery, most likely in cases treated with neoadjuvant therapy.

(5) Suffixes (sn) and (fn) should be added to category N to denote confirmation of metastases based on sentinel lymph node or FNA/core biopsy, respectively.

(6) Clinically detectable = detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and with strongly suspected malignant characteristics or presumed pathological macrometastases based on fine needle aspiration and cytological examination.

Table 3.3- Breast cancer staging - AJCC 2017 (Eighth edition)

Stage 0	Tis	N0	M0
Stage I A	T1*	N0	M0
Stage I B	T0 T1*	N1 mi N1 mi	
Stage IIA	T0 T1* T2	N1** N1** N0	M0
Stage IIB	T2 T3	N1 N0	M0
Stage IIIA	T0 T1* T2 T3 T3	N2 N2 N2 N1 N2	M0
Stage IIIB	T4 T4 T4	N0 N1 N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mic

** T0 and T1 tumors with only lymph node micrometastases are excluded from stage II A and classified as stage I B.

- M0 includes M0(i+).

- The designation pM0 is not valid; any M0 diagnosis should be clinical.

- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered IV and remains IV regardless of the response to neoadjuvant therapy.

- The stage designation may change if diagnostic imaging tests reveal the presence of distant metastases, provided they were performed within four months of diagnosis in the absence of disease progression and the patient has not received neoadjuvant therapy.

- The prefixes "yc" and "yp" applied to the T and N classifications indicate staging after neoadjuvant therapy. No stage group is assigned if a complete pathological response is obtained (e.g. ypT0ypN0cM0).

NOTE - *In some centers, a molecular method for the analysis of the entire sentinel lymph node tissue is currently used, i.e. One Step Nucleic Acid amplification (OSNA), which is based on the analysis of the presence of RNA for CK19 expressed electively by breast cancer. OSNA defines 3 diagnostic categories: OSNA-: negative lymph node with RNA levels attributable to isolated tumor cells; OSNA+: presence of micrometastases; OSNA++: presence of macrometastases. The diagnostic value of this test has been proven in some studies[27-31]*

As mentioned above, this version of the AJCC classification also recommends the collection of information on prognostic factors such as histological grading, hormonal receptor status (ER and PgR) and HER2 status, which may influence staging in the prognostic version of staging itself. Although Breast Cancer Classification should continue to be based on anatomic factors (TNM), the recognition of the prognostic value of tumor grade, expression of tumor receptors, and HER2 amplification has determined their inclusion in the Prognostic Classification. This change, which should make the staging system more precise, flexible and personalized, was introduced based on the analysis of large databases.[21,22] In addition, for ER+/HER2- pN0 tumors, the use

of multigene prognostic molecular tests is proposed, which may cause downstaging (but never overstaging) of the tumor in the event of a result of low recurrence risk. All major prognostic molecular tests are taken into consideration (Oncotype Dx, Mammaprint, Prosigna, Endopredict, Breast Cancer Index), however we must remind that the most important level IA evidence is reported for the Oncotype Dx and that this test represents the only multigene panel included in the Prognostic Stage Group Table of this classification, since it is supported by Level 1 prospective data.

Tables are provided in Annex 5 (to which reference should be made) on the basis of which, depending on the grade and ER/PgR/HER2 status, the final clinical stage may be subject to final category changes.[21]

In Italy, it should be noted that currently multigene molecular tests are not included in the Essential Levels of Care, and are therefore not reimbursable.

3.5 Prognostic and predictive factors

Prognostic factors are related to the patient's prognosis (survival), while predictive factors are related to the potential effectiveness of an anticancer treatment.

Some prognostic factors that have been shown to be important[23] and useful in the selection of the type of treatment, such as:

- Tumor size;
- Axillary lymph node status;
- Histological grade;
- Proliferative activity (Ki67);
- Histological type;
- Vascular invasion;
- HER-2 status;
- Hormonal receptor status;
- Patient's age of (< 35 years: worst prognosis)
- Gene expression profiles (see section 3.3).

Tumor size: it is difficult to define a threshold value below or above which the tumor can be considered as having a poor or good prognosis, except for very small tumors. However, even in pT1a and pT1b tumors, the risk assessment cannot ignore other prognostic parameters, such as axillary lymph nodes status, biological factors (Ki-67, hormonal receptor status, HER2 status, grading) and the age of the patient.

Axillary lymph node status: this should be evaluated together with other prognostic factors.

The impact of the presence of isolated cancer cells (ITCs) or micrometastases in the sentinel lymph node on the prognosis does not appear to be significant.[24-6]

Histological grade: a high histological grade (G3) is considered an unfavorable prognostic factor. The evaluation of an intermediate histological grade (G2) is more difficult: analyzing the gene profile (97 genes) of the intermediate histological grade (test not yet available for routine use), it has been observed that G2 is often reclassified as G3 or G1.[27]

Proliferative activity: proliferative activity as measured by the Ki67 labeling index (percentage of tumor cell nuclei that are stained with Mib1 protein antibody encoded by the KI67 gene) is now a recognized prognostic factor.

Some studies have shown its prognostic value and usefulness in predicting response and clinical outcome.[28] In a study conducted on 357 breast tumors examined by gene expression profiles, in the 144 cases identified as luminal according to the molecular method, a 14% cut-off value for Ki67 was identified at immunohistochemistry as capable of differentiating luminal A cases from luminal B/HER2-negative cases.[9] (See section 3.3). To date, it is not yet possible to define a single threshold value below or above which the tumor can be defined as having low or high proliferative activity in order to predict the effectiveness of chemotherapy or hormone therapy. The standardization of result interpretation methods is also problematic.[29]

Histological type: tubular, medullary, adenoid cystic and apocrine histotypes have a favorable prognosis.[30] However, it must be stressed that medullary carcinomas are rare and their difficult diagnosis requires precise histological parameters. These tumors represent less than 1% of all breast cancers[2] if all the characteristics

listed by Ridolfi in 1997[31] are included in the diagnostic process (expansive growth front corresponding to the rounded macroscopic aspect of these tumors; large and pleomorphic tumor cells arranged in syncytia with very atypical nuclei, large nucleoli and numerous mitoses; absence of tubular and glandular structures; poorly defined cell boundaries in over 75% of the neoplasm; abundant peripheral lymphoplasmacellular infiltrate; absence of intraductal component, tolerated by some authors if minimal or present in the surrounding parenchyma).

Subsequent studies have shown that the expression of high levels of genes related to the inflammatory component are independent prognostic factors,[32] therefore it is suggested that the relatively good prognosis of carcinoma with medullary features may be related to their inflammatory component.[2]

Vascular invasion: vascular invasion is not universally accepted as a prognostic factor, but in several studies it has been reported to be predictive of lower recovery-free survival and overall survival in N- patients and patients with other risk factors, such as histological grade, tumor size and hormone receptor status.[33,34] Recently, a population study of a large number of cases also found that in women with operable breast tumors (N- and N+), vascular invasion was predictive of lower invasive disease-free survival and overall survival in the presence of other unfavorable prognostic factors.[35]

HER2 status: HER-2 overexpression by immunohistochemistry or HER2 gene amplification, present in approximately 13%-15% of breast cancers, is a well-established prognostic factor and predictive factor for response to HER2 drugs and likely for hormone therapy resistance.[36] It is extremely important that testing is carried out in accredited laboratories. The two most commonly used methods are immunohistochemistry, which evaluates the possible overexpression of the HER-2 receptor, and fluorescence in situ hybridization (FISH), which measures gene amplification. A tumor is defined as HER-2 positive if a positive 3+ score is attributed by the immunohistochemical method or if gene amplification is present with the FISH method. In 2+ cases, it is important to evaluate gene amplification. See Annex 3 for ASCO/CAP recommendations for HER2 determination.

Status of hormone receptors (ER and PgR): it is important to define the status of both estrogen and progestin receptors and report the percentage of positive cells, which must be evaluated as a continuous quantitative variable. The new ASCO recommendations for hormone receptor immunohistochemical determination consider tumors with at least 1% positive cells to be positive.[37] However, there is a relationship between the levels of receptor positivity and the benefits obtained with hormonal treatments in both metastatic disease and in the adjuvant and neoadjuvant settings. Therefore, tumors with high levels of receptors are the most likely to benefit from hormone therapy, even if many other factors may influence the hormone responsiveness of tumors, such as HER-2 status, histological grade and Ki67.

Multifocality: multifocality refers to the presence of several cancer foci separated by healthy parenchyma. "Satellite nodes" of the primary node are defined as lesions located less than 5 mm from it and separated by healthy parenchyma. It is good practice to report the number of invasion foci on the diagnostic report. The TNM system indicates that the T score is attributed according to the size of the major focus when several tumors are present in the same breast. It has been shown that multifocality has an impact on lymph node metastases, increased local recurrences and increased risk of cancer-related death.[38] This aspect is controversial. A review of 3,924 cases by the MD Anderson Cancer Center found that multifocality/multicentricity are not independent prognostic factors for survival, as they are more frequently associated with larger tumors, grade 3, lymphovascular invasion and lymph node metastases.[39] Recently, the term "diffuse carcinoma" has been coined, indicating a tumor that usually shows a lobular growth pattern and spreads to one or more quadrants. Often these tumors are difficult to identify in radiology and ultrasound scans. Both multifocal and diffuse growth carry a risk of disease-related death that is 4.14 and 2.75 times higher, respectively, regardless of the tumor immunophenotype.[38]

Intratumoral lymphocytes: breast carcinomas with a pronounced intratumoral stromal lymphocytic infiltrate have a better prognosis than carcinomas with lymphocytic depletion.[40,41] Triple negative and HER2-positive breast cancers are subgroups of breast cancers that show the highest degree of lymphocyte stroma enrichment (tumor infiltrating lymphocytes, TILs).[42] TILs have a level of evidence I as a prognostic indicator in triple-negative breast cancer treated with chemotherapy[40,43,44] (PMID: 25071121).

It should be specified that the evaluation of TILs has a prognostic value, and does not allow to predict response to therapies, so this criterion is not used to decide whether or not to administer chemotherapy or other systemic therapies such as immunotherapy. The predictive value of TILs in patients treated with immunotherapy is being studied in randomized clinical trials.

The evaluation of TILs follows the recommendations of the TIL Working Group.[45]

3.6   Examinations required for staging

Physical examination, complete blood count and complete biochemical profile should be performed in all patients with operated breast cancer in order to confirm their eligibility to receive the planned treatment and exclude or diagnose comorbidities.

MRI is not recommended as a mandatory complementary test to mammography and ultrasound in patients diagnosed with breast cancer. Specifically, for breast MRI indications refer to chapter 3.7 (see chapter 2.2 for screening indications).[46]

Several studies[47] have shown that tomosynthesis (DBT) has at least as much diagnostic accuracy as additional mammographic projections with standard digital mammography (DM) (magnification, focused spot compression, etc.) while reducing the radiation dose. In symptomatic women, diagnostic accuracy is improved by DBT, reducing the number of unnecessary biopsies.[48]
These studies allow to indicate DBT as initial examination for symptomatic women and for the study of suspected mammographic findings detected during screening.

Systemic Staging
The stage of disease is fundamental for the management of patients with primary breast cancer in local-regional and distant staging. Particularly in patients with stage I and II breast cancer, the risk of detecting asymptomatic distant metastases by bone scintigraphy, liver ultrasound and chest X-ray is so low that local-regional staging alone is indicated.[49-51] In fact, a retrospective study conducted in women with stage I-III breast cancer, staged by bone scintigraphy, liver ultrasound and chest X-ray, identified bone metastases in 5.1%, 5.6% and 14% of patients with stage I, II and III disease, respectively, while no metastases were identified by liver ultrasound and chest X-ray in stage I-II patients.[52] Therefore, systemic preoperative staging by imaging may be omitted in the absence of symptoms and/or signs of systemic disease in patients with a lower probability of metastatic disease at onset (stage I-II).
Chest CT, ultrasound or abdominal CT and bone scintigraphy are indicated in patients at higher risk of asymptomatic metastatic disease at onset: clinically positive axillary lymph nodes, large tumors (larger than 5 cm) and aggressive tumor biology. The same indications are valid for patients who are symptomatic or present clinical or laboratory signs suggesting the presence of metastases.[51-52]
CA-PET/CT is only indicated as a diagnostic examination in cases where the conventional methods described above are inconclusive.[51, 53-62]

3.7   Recommendations for the use of breast MRI

The following are the indications for breast magnetic resonance imaging (for screening indications, see chapter 2.2):[46]

1-   Preoperative staging of newly diagnosed breast cancer (ipsilateral and contralateral)
MRI is more sensitive than conventional imaging (mammography and ultrasound) in the local staging of breast cancer (size of index lesion, multifocality, multicentricity, contralateral malignant lesions). In the presence of a breast cancer diagnosis, MRI can then be used to assess the extent of the disease and search for satellite lesions in both the affected breast and the contralateral breast in all cases where multifocality is suspected with traditional imaging techniques or if there is a mismatch between the size of the tumor with traditional imaging techniques. MRI is better at assessing tumor size than mammography or ultrasound, although overestimation and underestimation of tumor size continue to occur in up to 15% of patients. It should be specified that there

is no definitive data to show that MRI increases the incidence of negative margins or decreases the incidence of re-excision or local recurrence in preoperative staging. MRI is associated with an increase in mastectomies.[63]

- In patients with invasive lobular carcinoma, notoriously underestimated by mammography and ultrasound, a reduction in re-excision from 18% to 11% was observed,[64] although this value was not statistically significant in a meta-analysis.[65]
- Other suggested indications are the discrepancy in tumor size between different methods (including clinical examination) if this may change the treatment strategy, breast cancer diagnosed in high-risk women and staging before partial breast irradiation.[46,66]

Despite these indications, randomized studies that evaluated the surgical outcome of preoperative MRI gave different results,[67-70] therefore meta-analyses of these studies suffer from the limitations of included studies. Observational studies have selection bias due to the acquisition of preoperative MRI in patients that are most likely to be treated with mastectomy a priori.[71] Finally, it should be remembered that even today two aspects remain unclear: a) the biological significance of additional disease foci detected by MRI, or whether they are indolent disease foci or not; b) the role of radiotherapy on the residual breast after conservative surgery on cancer foci diagnosed only with MRI. MRI can be particularly useful where there is suspicion of multifocal/multicentric lesion, to assess local-regional lymph node extension and pectoral muscle infiltration.

2- Evaluation of the effect of neoadjuvant chemotherapy

MRI is the best tool to evaluate ongoing response and response at the end of neoadjuvant chemotherapy (NACT), and allows a more accurate estimate than clinical examination and mammography with breast ultrasound. Two recent meta-analyses confirmed this statement: the first one[72] studied the correlation between tumor size measured at MRI and histological examination after NACT based on individual patient data (300 patients included in 24 studies); although there may still be cases of over- or under-estimation of response to therapy, MRI has been shown to be more accurate than clinical examination, mammography and breast ultrasound. According to the authors, a combination of these tests (not yet evaluated) would ensure even more reliable results. The other meta-analysis[73] included 57 scientific papers (5,811 patients) and confirmed the superiority of MRI over mammography and ultrasound in the evaluation of complete disease response.

3- Differential diagnosis of lesions around a surgical scar
4- CUP syndrome (detection of occult breast cancer in patients with axillary lymph node metastases and negative mammography and ultrasound)
5- Equivocal results of mammography/ultrasound if biopsy is not possible
6- Evaluation of women with breast implants.

4   Treatment of in situ and microinvasive carcinoma (Figure 1)

4.1   Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ is a pre-invasive lesion which, if left untreated, has the potential to evolve towards an invasive form of cancer.
Therefore, the main objective of the local and systemic treatment of DCIS is to prevent the onset of invasive cancer (Figure 1).

4.1.1   Local therapy

Historically, the standard therapy for ductal carcinoma in situ (DCIS) has been simple mastectomy,[1] which heals 98% of patients. With the emergence of conservative surgical treatments for patients with invasive tumors, wide margin excision has progressively become the most common intervention for DCIS, in the absence of contraindications. There is evidence that local recurrence after conservative treatment for DCIS has decreased over time, as a result of screening and early diagnosis, the achievement of negative margins, and the use of adjuvant therapies.[2] After conservative surgery, in view of the proven efficacy in reducing local recurrence, radiation therapy of residual breast tissue should be considered.
However, there are no randomized studies comparing mastectomy and conservative surgery associated with radiotherapy. Mastectomy is still indicated if the disease is too extensive to be conservatively resected with good esthetic results, if there is no possibility of achieving negative resection margins, or in the presence of contraindications to radiotherapy. Nipple Sparing Mastectomy is commonly used in this setting if immediate breast reconstruction is planned, in the absence of blood secretion and of microcalcifications close to the areola-nipple complex, and if no disease is detected at the histological examination of the retroareolar margin.

To date, despite attempts to identify low-risk patients to whom conservative surgery alone without radiotherapy should be offered, there are no available data from prospective randomized studies supporting the omission of radiotherapy. In any case, the choice of an individual patient not to undergo radiotherapy after conservative surgery, accepting the potential risk of local recurrence, must be considered, bearing in mind that there is no direct evidence of an impact of radiation therapy on survival.
There is considerable controversy over the required width of resection margins in carcinoma in situ. The presence of negative resection margins after conservative surgery is associated with a lower risk of local recurrence than positive, close or unknown margins.[3]
A systematic review of 22 published studies (randomized, prospective and retrospective) including 4,660 cases revealed a resection margin threshold of 2 mm below which the risk of intramammary recurrence after conservative surgery and radiotherapy increases significantly.[3] Recently, a joint Consensus Guideline (SSO-ASTRO-ASCO) based on a systematic review of 20 studies in 7,883 patients recommended a distance of 2 mm from the inked margin as the appropriate standard for DCIS treated with adjuvant radiotherapy. The use of this standard is associated with low risk of local recurrence and decreased re-excision rate, and has the potential to improve the esthetic results of conservative therapy and optimize treatment costs for the healthcare system.[4] In the presence of positive margins, the recommendation is to consider surgical widening of margins before radiation therapy. For negative margins <2 mm, clinical judgment following a multidisciplinary discussion is appropriate to determine the need for re-excision on a case-by-case basis.[5] This approach can be adopted in selected cases even in the presence of minimal/focal DCIS involvement.

In extended forms of DCIS, foci of microinvasion and/or infiltration can sometimes be identified a posteriori at the histological examination. Sentinel lymph node biopsy is not indicated in conservative surgery regardless of tumor grade, but may be indicated only in the presence of multiple clusters of microcalcifications and extensive lesions requiring mastectomy, or in patients where surgical treatment may compromise the subsequent sentinel lymph node biopsy procedure.[6,7]

CLINICAL QUESTION No. 1 (Figure 1)

In patients with high/medium grade ductal carcinoma in situ (DCIS) of the breast, is radiotherapy after conservative surgery indicated rather than conservative surgery alone to reduce ipsilateral breast recurrence (both in situ and infiltrating)?

A recent meta-analysis (EBTCG) of individual data from 4 randomized trials has shown that post-excision radiation therapy of residual breast tissue reduces the absolute risk of ipsilateral breast cancer recurrence (both ductal in situ and infiltrating) at 10 years by 15.2% (from 28.1% with surgery alone to 12.9% with surgery associated with radiation therapy), with no impact on survival.[7] It also showed that radiotherapy is effective in reducing local recurrence in all the subgroups under examination (age, type of surgery, use of tamoxifen, margin status, focality, different anatomopathological picture, T size, and diagnostic method).[8]

Long-term analysis of patients with local recurrence in the NSABP B-17 and B-24 studies showed that local infiltrating recurrence, unlike in situ recurrence, is associated with an increased risk of mortality (HR=1.75; 95% CI = 1.45 to 2.96, p<0.001) affecting survival.[9]

The worst prognosis of infiltrating recurrence also emerges from the 15-year update of mortality data from the EORTC study (HR=5.2 in recurrent patients compared to non-recurrent patients).[10]

The incidence of local in situ or non-infiltrating recurrence tends to reach a plateau 10 years after treatment, while the incidence of infiltrating recurrence remains stable over time, underlining the need for adequate follow-up (at least 10 years) to correctly evaluate the effect of treatment.[9] Furthermore, the long-term results of the EORTC study suggest that, while the protective effect against in situ recurrence continues throughout the follow-up period, the protective effect on infiltrating recurrence is mainly observed in the first 5 years of follow-up.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
High	In patients with high/medium grade ductal carcinoma in situ (DCIS), radiation therapy after conservative surgery should be considered rather than conservative surgery alone to reduce ipsilateral breast recurrence (both in situ and infiltrating).[8]	**Strong Positive**

Pending the results of recently started randomized clinical trials (TROG-BIG 3-07, BONBIS), surgical bed radiation boost may be proposed to patients aged < 45-50 years with high-grade ductal carcinoma in situ (grade III DCIS).[11,12] A retrospective analysis was conducted in 4,131 patients (median age 56.1 years; range, 24-88 years), which evaluated the role of boost radiotherapy after conservative surgery.[12] Boost radiotherapy was administered more frequently in the presence of positive surgical margins, unknown receptor status, and comedonecrosis. In the entire cohort, radiation boost was significantly associated with a lower incidence of ipsilateral breast recurrence (hazard ratio [HR], 0.73; 95% CI, 0.57-0.94; p = 0.01) and with a higher probability of recurrence-free survival at 5 years (97.1% vs 96.3%), 10 years (94.1% vs 92.5%), and 15 years (91.6% vs 88.0%). In a multivariate analysis, radiation boost remained significantly associated with reduced incidence of local recurrence regardless of age and use of tamoxifen (HR 0.68; 95% CI, 0.50-0.91; p = 0.01). According to this analysis, in patients with intraductal breast cancer and life expectancy >10-15 years, the addition of boost radiotherapy of the tumor bed results in increased local control after conservative surgery and radiotherapy. The analysis has the main limit of being retrospective and, for some subgroups (e.g. patients with positive surgical margins), the sample size is limited. Subject to these considerations, the results are convincing and come from the highest number of case studies ever analyzed on the role of boost radiotherapy in DCIS. It should be noted that the extent of the benefit observed is similar to that documented with the use of boost radiotherapy in invasive forms of breast cancer.

CLINICAL QUESTION No. 2 (Figure 1)

Is radiotherapy after conservative surgery indicated in patients with low-grade ductal carcinoma in situ (DCIS) of the breast rather than conservative surgery alone to reduce ipsilateral breast recurrence (both in situ and infiltrating)?

The absolute risk of intramammary recurrence after conservative surgery alone is however highly variable from case to case and depends mainly on age, nuclear grade, necrosis, T size and margin width. It was calculated that, with a benefit of 50% relative recurrence reduction and a low recurrence risk profile (e.g. 10%) after conservative surgery alone, the number of patients who would need to be treated to prevent a single local recurrence is high (N=20).[13]
Therefore, attempts have been made to classify patients according to risk factors, in order to identify the ones that could potentially avoid irradiation.
The Van Nuys Prognostic Index (USC/VNPI) is a scoring system that evaluates age, tumor diameter, grade, and margin width, and has been proposed in support of or against RT indication after conservative surgery for ductal carcinoma in situ. For women with a low score (4-6), the possibility of avoiding radiotherapy has been proposed on the basis of the comparable results obtained with surgery alone. To date, however, this experience has not been validated by prospective studies.[14]

In the RTOG 9804 study, only patients with a single lesion identified in the mammogram or incidentally in an otherwise benign biopsy, with a maximum clinical or pathological size of 2.5 cm, low or intermediate nuclear grade, completely resected (at least 3 mm from inked margin), and with a negative postoperative mammography were selected. After surgical excision, patients were randomized to observation or postoperative radiotherapy (without radiation boost of the tumor bed).[15] Although only slightly more than a third of the expected patients were randomized (636/1,790 planned), at a median follow-up of 7.2 years, the percentage of local recurrence was 0.9% in the group that had RT and 6.7% in the group not treated with RT (HR 0.11; 95% CI, 0.03 to 0.47; p<0.001). Therefore, the results of this study seem to confirm the benefit of adjuvant RT also in the subgroup of patients with favorable prognosis.

In addition to the RTOG 9804 study, two other clinical studies have attempted to select *a priori* a group of patients at low risk of recurrence where postoperative RT may be omitted. In the first one, 158 patients with grade 1-2 DCIS, diameter ≤2.5 cm and free margins ≥1 cm were treated with excision alone, but the risk of local ipsilateral recurrence was so high (about 12%) that the study was closed before reaching the expected patient enrolment number.[16]

In the second prospective, non-randomized study, 665 patients with low/medium grade DCIS ≤2.5 cm diameter or high-grade DCIS with diameter equal to or less than 1 cm were enrolled to receive local excision ± tamoxifen.[17,18] In the 561 patients with low or medium grade DCIS, the risk of recurrence in the ipsilateral breast at 12 years was 14.4% (median size of the tumor was 6 mm and free margins between 5 and 10 mm). Local recurrences were much higher in the subgroup of 104 patients with small but high-grade DCIS (24.6%). The prevalence of invasive forms was about 50% in both subgroups. It was observed that the risk of developing a recurrence and an invasive recurrence increased over the years, without reaching a plateau.[18]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
High	In patients with low-grade ductal carcinoma in situ (DCIS), radiotherapy after conservative surgery may be considered rather than conservative surgery alone to reduce ipsilateral breast recurrence (both in situ and infiltrating)[8,15]	**Weak Positive**

- For Paget's disease with no lump, central quadrantectomy followed by complementary RT or radical mastectomy (in the case of small breast) with or without breast reconstruction is indicated.[19]

4.1.2 Systemic therapy

In patients with ductal carcinoma in situ (DCIS) positive to estrogen receptors, after conservative surgery and radiotherapy, treatment with tamoxifen may be considered (weak positive recommendation). At the time of writing, aromatase inhibitors cannot be used in Italy for this indication. There is no evidence supporting chemotherapy in the systemic treatment of DCIS.

Tamoxifen

CLINICAL QUESTION No. 3 (Figure 1)

In patients with ductal carcinoma in situ (DCIS) of the breast positive to estrogen receptors, treated with conservative surgery and radiotherapy, is treatment with tamoxifen indicated rather than local-regional treatment alone to reduce ipsilateral and contralateral breast recurrence?

The NSABP (National Surgical Adjuvant Breast and Bowel Project) B-24 study enrolled 1,804 women with DCIS randomized to conservative surgery + RT + Tamoxifen for 5 years versus conservative surgery + RT + Placebo for 5 years, reporting fewer breast events at 5 years with tamoxifen compared to placebo (8.2% versus 13.4%; p=0.0009).[20,21] This benefit has been demonstrated in the risk reduction of both ipsilateral invasive recurrence and contralateral breast cancer. The cumulative incidence of all invasive breast events in the tamoxifen group was 4.1% at 5 years: 2.1% in the ipsilateral breast, 1.8% in the lateral breast and 0.2% in regional or distant sites. The most recent analysis of the study,[21] at a median follow-up of 163 months, showed a reduction in the rate of ipsilateral invasive recurrence in the group of women treated with conservative surgery + RT + tamoxifen (8.5%) compared to the group of women treated with conservative surgery + RT + placebo (10%), with a reduction in the recurrence risk of 32% (HR = 0.68; 95% CI = 0.49-0.95; p = 0.025). In terms of non-invasive recurrence, the addition of tamoxifen to local-regional treatment resulted in a not significant reduction in the risk of events: 7.5% vs 8.3% (HR = 0.84; 95% CI= 0.60-1.19; p= 0.33).
In the NSABP B-24 study, the cumulative 15-year incidence of contralateral breast cancer, either as a first event or as following a contralateral recurrence, was 7.3% among patients treated with tamoxifen and 10.8% among patients who received placebo: tamoxifen produced a 32% reduction in the risk of contralateral breast cancer (HR = 0.68; 95% CI = 0.48-0.95; p = 0.023).

The NSABP-B24 study enrolled patients with unknown hormone-receptor status, and a retrospective analysis, conducted on 41% of the original population of the study and only partially centralized, assessed the relationship between hormone-receptor expression and benefit from tamoxifen[22] (**SIGN Level of evidence 1+, as the determination of ER status was not centralized).** In the presence of positive estrogen receptors (76% of cases), treatment with tamoxifen (versus placebo) significantly reduced the risk of subsequent breast cancer (defined as event) at 10 years (HR=0.49; p<0.001) and 14.5 years (HR=0.60; p=0.003), even after the multivariate analysis (HR=0.64; p=0.003). Similar, though less significant, results were obtained from the

separate analysis of events: ipsilateral and contralateral carcinomas, invasive and non-invasive carcinomas. No benefit has been observed with the use of tamoxifen in patients with DCIS and no estrogen-receptor expression. In a recent pooled analysis of the two studies conducted on DCIS (NSABP study B-17 and NSABP study B-24),[23] ipsilateral invasive recurrence was found to be associated with an increased risk of death, while no association between recurrence as DCIS and mortality was found. Furthermore, no difference in survival (either overall or breast-specific) was found between the different treatment groups: surgery, surgery + RT, and surgery + RT + tamoxifen.

The UK/ANZ DCIS phase III randomized trial evaluated the role of radiotherapy and the role of tamoxifen or both in the treatment of patients undergoing DCIS conservative surgery, with a 2x2 factorial design. The study enrolled 1,701 resected patients and analyzed the following therapeutic approaches: surgery alone, surgery followed by radiotherapy, surgery followed by radiotherapy and tamoxifen (20 mg/day for 5 years), surgery followed by tamoxifen (20 mg/day for 5 years).[24] With regard to the use of tamoxifen, at a median follow-up of 12.7 years, the study showed a benefit in terms of reduction of all breast events (HR=0.71; 95% CI 0.58-0.88); p= 0.002), reducing the risk of ipsilateral DCIS (HR=0.70; 95% CI 0.51-0.86; p=0.03) and contralateral tumors (HR=0.44; 95% CI 0.25-0.77; p=0.005), but no effect on ipsilateral invasive disease. However, the subgroup analysis showed that the benefit of tamoxifen is observed only in patients treated with surgery alone and not in the other subgroups, including the one treated with surgery + RT + tamoxifen. This study did not include a differentiated statistical plan of analysis for the two endpoints, represented by the incidence of invasive ipsilateral carcinoma with regard to the use of radiotherapy or not and the incidence of all breast events (including contralateral carcinomas and DCIS) with regard to treatment with tamoxifen or not (**SIGN Level of evidence 1+**).

A recent combined analysis of the NSABP-B24 and UK/ANZ25 trials concluded that treatment with tamoxifen after conservative surgery and radiotherapy reduces the risk of developing ipsilateral infiltrating breast cancer (pooled RR=0.61); 95% CI 0.41-0.92) and contralateral DCIS (RR=0.4; 95% CI 0.16-0.96), and that this benefit is independent of age, but that treatment with tamoxifen does not change overall survival or specific mortality from breast cancer (**SIGN Level of evidence: 1++**). A potential conceptual heterogeneity between the two studies, due to the different duration of follow-up and the different periods of conduction, should be underlined.
In conclusion, the decision whether or not to offer tamoxifen as a DCIS treatment should be based on the analysis of the relationship between benefits and expected side effects in the individual patient.
The two studies mentioned above were conducted in different time periods and had a different duration of follow-up, so there are reasons to assume a conceptual heterogeneity between them.

SIGN Quality of Evidence	Clinical recommendation	Strength of clinical recommendation
B	In patients with ductal carcinoma in situ (DCIS) and positive estrogen receptors, treatment with tamoxifen could be considered after conservative surgery and radiotherapy.[25]	**Conditional Positive**

Aromatase Inhibitors (AI)

Evidence on the efficacy of anti-aromatase agents in the treatment of DCIS is still limited. The results of the phase III study NSABP B35 have been published, where 3,104 postmenopausal patients, diagnosed with DCIS with positive hormone receptors and treated with conservative surgery plus radiotherapy, were randomized to receive tamoxifen 20 mg/day versus anastrozole 1 mg/day for a total of 5 years. At a median follow-up of 8.6 years, treatment with anastrozole significantly improved the breast cancer-free interval (HR 0.73; p=0.03), the primary endpoint of the study; after stratification according to age, the benefit with anastrozole was maintained in patients < 60 years (HR 0.52; p=0.003).[26] The NCIC CTG MAP.3 study, a randomized placebo-controlled double-blind trial, evaluated the role of exemestane 25 mg/day for 5 years in

4,560 postmenopausal women at increased risk of breast cancer (age > 60 years, risk calculated according to the Gail model as greater than 1.66%, previous diagnosis of atypical ductal/lobular hyperplasia, lobular carcinoma in situ, DCIS treated with mastectomy).[27] At a median follow-up of 35 months, 11 infiltrating breast cancers were reported in the exemestane group vs 32 in the placebo group, with a benefit in terms of relative reduction of 65% (0.19% vs 0.55%; HR=0.35; 95%CI 0.18-0.7; p=0.002) of the annual risk of occurrence of infiltrating breast cancer. This advantage seems to be confirmed also in women with previous diagnosis of DCIS (5% of the entire study population). However, the short duration of follow-up and the small number of subgroups diagnosed with DCIS do not allow the results to be translated to clinical practice.

Chemotherapy

There is no evidence to support chemotherapy in the systemic treatment of DCIS.

4.1.3 Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ (LCIS) is considered a benign lesion.[28] However, the association between the presence of LCIS and an increased risk of onset of ipsilateral and contralateral breast cancer is recognized. This is considered a risk marker rather than a precursor of infiltrating tumor (see Chapter 3.4 and Annex 2).

In an NSABP study involving 180 patients diagnosed with LCIS, at a 12-year follow-up the onset of ipsilateral infiltrating breast cancer was observed in 5% of cases and contralateral breast cancer in 5.6% of cases.[29]
In the NSABP-P1 chemoprevention study, which included 13,388 women at increased risk of breast cancer, of whom 826 with LCIS, at a 7-year follow-up, a rate/year of 1.17% of new diagnoses of infiltrating breast cancer was observed in the placebo group, while this value was 0.63% in the group treated with tamoxifen.[30]
Data from the SEER (Surveillance, Epidemiology and End Results) database, which reported 4,853 cases of LCIS between 1973 and 1998, showed a 7.1% proportion of new diagnoses of infiltrating breast cancer at a median follow-up of 10 years.[31] More recent SEER data were published in 2017 on 19,562 patients with LCIS (mean age 53.7 years), which report a cumulative incidence of breast cancer at 10 and 20 years of 11.3% and 19.8%. At a median follow-up of 8.1 years (range 0-30.9), 1,837 primary breast cancers were diagnosed (55.2% ipsilateral: most were G1-G2, early-stage hormone-receptor positive). According to the multivariate analysis, the type of surgical treatment did not affect long-term survival. The 10- and 20-year breast cancer-specific survival for women with LCIS was 98.9% and 96.3%.[32]

Treatment

Following LCIS diagnosis, the available options are:
1. Surveillance
2. Chemoprevention
3. Multidisciplinary assessment for risk-reducing surgery (bilateral prophylactic mastectomy)

Surveillance: a clinical examination every 6-12 months and an annual mammogram. The use of breast MRI may be useful in young patients or patients with dense breast parenchyma or with a significant family history of breast cancer.
Chemoprevention: see chapter 2.3.
3. Multidisciplinary assessment for risk-reducing surgery (**bilateral prophylactic mastectomy**): in view of the limited data available in literature, the option of risk-reducing surgery should be considered in women who express such a desire or have severe carcinophobia, and should be thoroughly discussed in a multidisciplinary setting to assess risks and benefits and individualize the treatment. Bilateral prophylactic mastectomy should only be considered in women at high risk of developing invasive carcinoma, taking into account any other risk factors and after multidisciplinary evaluation in accredited breast centers. In these cases, nipple sparing mastectomy with immediate reconstruction should be offered and discussed with the plastic surgery team.
If LIN 1-2 is present at the margins of a surgical excision for carcinoma, there is no need for re-excision.

Pleomorphic LCIS

A histological variant called pleomorphic LCIS (PLCIS), with more aggressive biological behavior, has been identified in LCIS (see chapter 3.1).[33-38]

In these cases, post-surgical RT is not recommended. PLCIS consists of cells with marked pleomorphism, large and eccentric nuclei. There is often evidence of central necrosis and calcifications. Overexpression of HER2 is common.[39] Compared to classic LCIS, the pleomorphic variant appears to have a potential to evolve into infiltrating carcinoma similar to that of DCIS.[40] Although there are no studies on different therapeutic approaches, few cases were reported in literature and long-term follow-up data are missing, in view of the biological characteristics and potential problems of differential diagnosis with DCIS, some authors have suggested that PLCIS should be treated in the same way as high-grade DCIS[41], after informing the patient of available therapeutic options and the limited experience in this type of tumor.

4.1.4 Microinvasive carcinoma (T1 mic)

The American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) defines microinvasive breast cancer (pT1mic) as the presence of a microscopic infiltrating component ≤1 mm in size.[28] Microinvasive carcinoma is often associated with ductal carcinoma in situ (DCIS) and consists of small foci of tumor cells that infiltrate the stroma after crossing the basal membrane.

Morphologically, microinvasive carcinoma is often associated with high-grade DCIS foci and frequent presence of comedonecrosis.[42,43] In these cases, overstaging or understaging may arise in the presence of multiple foci of microinvasion; however, the rule according to which the major focus assessed for TNM staging must not be >1 mm also applies to these cases.

In about 49% of patients, microinvasive carcinoma shows overexpression of HER2, but this has not been associated with an increase in recurrences.

Prognosis is usually very good, with a 5-year survival of 97-100%.[44]

Treatment

In view of the low incidence (about 1% of all breast cancers) and the low number of reported cases, clinical treatment is still controversial.

Surgery

At the breast level, the extent of surgery (mastectomy or conservative surgery with complementary radiotherapy) is determined by extent of the disease, general clinical condition and the desire expressed by the patient.

The risk of recurrence after conservative surgery and radiation therapy is influenced by:
- positive surgical resection margins;[44]
- size of the DCIS component;[45]
- presence of unfavorable histological characteristics (e.g. high grade, comedonecrosis in DCIS).[43]

Mastectomy is indicated in the presence of an extended intraductal component, unfavorable histological characteristics and where it is not possible to achieve tumor invasion-free resection margins with conservative surgery.

The Nipple Sparing Mastectomy is commonly used in this setting if immediate reconstruction is foreseen in the absence of blood secretion, microcalcifications near the areola-nipple complex and disease at the histological examination of the retroareolar margin.

At the axillary node level, the percentage of metastases in the presence of microinvasive carcinoma varies from 0 to 20% in the various cases,[42,43,46-48] but in most studies it is less than 7%, and is almost exclusively associated with micrometastases with no multiple node disease. The probability of metastases in the axillary cavity would appear to be greater in the presence of stromal infiltration in the form of cancer cell clusters.[42] Sentinel lymph node assessment in the presence of microinvasive breast cancer is however recommended[46,48] and follows the

same indications for axillary surgery in the infiltrating form. In this regard, a recent study reported by the MSKCC in 414 patients showed that the number of microinvasive foci is not related to the incidence of lymph node metastases.[48]

Adjuvant systemic treatment

There is no data on the use of adjuvant systemic treatments in the presence of microinvasive carcinoma. One approach is to use endocrine treatment in the presence of pT1mic carcinoma with hormone-receptor expression. In all other cases, once the absence of involvement of the axillary lymph nodes has been confirmed, no adjuvant treatment is indicated.

Radiotherapy

Indications for radiation therapy of microinvasive carcinoma (T1mic) after conservative surgery do not differ from those for invasive carcinoma and DCIS, and conventional or hypofractionated RT is still necessary.
There is, however, no indication for complementary RT after radical surgery. Literature data are limited[44,46,50] and there is no prospective randomized study comparing conservative surgery followed by RT with mastectomy.

5 Treatment of operable infiltrating carcinoma

5.1 Local-regional treatments (Figure 2)

5.1.1 Breast Surgery

In patients with stage I-II invasive carcinoma (and in selected more advanced cases), whole breast irradiation or mastectomy should be considered as first-choice treatment.[1-3]

Randomized studies have shown that, in operable breast cancer, mastectomy with axillary dissection does not provide any advantage in overall survival compared to conservative surgery with axillary dissection associated with whole breast irradiation, even at a relatively long follow-up.[1-3]

The choice of the type of intervention at breast level (radical vs. conservative surgery) depends on the location of the tumor and the tumor/breast size ratio, on mammographic characteristics, on the patient's preference and on the presence or absence of contraindications to radiotherapy.
Whenever possible, conservative surgery is preferable, involving more extensive resection and reconstruction with oncoplastic techniques, if necessary, to ensure a good esthetic result. Oncoplastic surgery is oncologically safe even for tumors larger than 2 cm in diameter, if the preoperative consultation allows to evaluate its applicability.[4] In order to overcome the controversy over margin adequacy in the case of partial resection of invasive carcinoma, a multidisciplinary Consensus Panel examined a meta-analysis of 33 studies on 28,126 patients and concluded that a "NO INK on tumor" policy as adequacy standard in the present multidisciplinary era is associated with a low incidence of ipsilateral recurrence, has the potential to decrease the incidence of re-excision, and may contribute to improving the esthetic outcome and decreasing health costs.[5,6] This recommendation was jointly adopted by the Society of Surgical Oncology and the American Society for Radiation Oncology and is the policy applied by most centers.
General contraindications to the "conservative approach" include: inability to access a radiotherapy center due to logistical problems; compromised general physical or psychological condition of the patient; presence of diffuse, suspicious or malignant microcalcifications; multicentric tumors.
"Radiotherapy-specific" contraindications include:

    a. "Absolute" contraindications to radiotherapy:
      - pregnancy (in some cases, however, conservative surgery in the third trimester may be considered if radiation therapy is planned after delivery);
      - inability to maintain a correct treatment position for adequate irradiation;
      - some active autoimmune collagen diseases (lupus, scleroderma, dermatomyositis) are historically considered as treatment-limiting due to increased risk of toxicity. Recent data have demonstrated the possibility of irradiation in these patients without any apparent additional increase in toxicity.[7]

    b. "Relative" contraindications to radiotherapy:
      - prior local RT (including chest irradiation for Hodgkin's lymphoma);
      - breast volume not optimal for adequate irradiation (a problem that is today largely overcome by new RT techniques or by partial irradiation of the breast, where possible);
      - non-active collagen diseases.

If mastectomy is performed, immediate reconstruction is an option for every patient and therefore preoperative consultation should be guaranteed to jointly evaluate modalities and define risks and benefits.

Skin Sparing Mastectomy or Nipple Sparing Mastectomy are considered appropriate when immediate reconstruction is planned and has clear esthetic and psychological advantages.[8] Therefore, preoperative consultation by the plastic surgeon is indicated in most cases and should be offered as part of the patient's

multidisciplinary approach. Although there are no randomized studies, the results of retrospective studies did not show an increase in local recurrence compared to non-skin-sparing surgical procedures.[9-12] A meta-analysis of nine studies with 3,739 patients recently showed that local recurrences are comparable to those detectable after surgery with a traditional approach.[13]

Today, Nipple Sparing Mastectomy should be considered oncologically safe on the basis of multiple experiences of individual centers and a recent analysis that did not show a negative effect on OS, DFS and LR.[14] Recently, a study showed that, even in locally advanced disease cases or after neoadjuvant chemotherapy, Nipple Sparing Mastectomy may still be a therapeutic option, as it is not associated with a significant increase in local recurrence.[15]

This procedure should be performed in the presence of negative retroareolar margins at the intraoperative histological examination.

A national Consensus Conference presented in 2012 and the Expert Panel of the 2013 St. Gallen Meeting considered the Nipple Sparing approach acceptable, provided that resection margins close to the nipple are not involved. In addition, the results of a study in 1,006 patients from the analysis of an Italian Multicenter Registry showed that this procedure can be performed successfully and with a reasonable incidence rate of complications.[16] A systematic review of 12,358 Nipple Sparing Mastectomies also concluded that complications related to this approach are decreasing with increasing experience over time, and showed an incidence of local-regional recurrence of 2.3%.[17]

BREAST RECONSTRUCTION PROCEDURES

After mastectomy, immediate breast reconstruction is <u>desirable</u> because it improves the quality of life of women, is not associated with an increase in local-regional recurrence, and does not interfere with potential recurrence diagnosis. A preoperative consultation with the plastic surgeon is advisable, together with a multidisciplinary evaluation and a thorough discussion with the patient about the risk of sequelae if post-mastectomy radiotherapy is contemplated.

5.1.2 Ipsilateral axillary surgery

A- Axillary dissection

Axillary dissection (with removal of at least 10 lymph nodes for an accurate pathological evaluation of the axilla) is indicated:[18,19]

- in the presence of clinically pathological axillary lymph nodes confirmed by preoperative cytological and micro-histological testing;
- in the presence of positive sentinel lymph node with macrometastases at the histological examination:[20] according to the characteristics described in QUESTION No. 4 (see section B-1 and QUESTION 4); women candidates for mastectomy with positive SLN biopsy should undergo complete axillary dissection (ASCO Guideline Update March 2014).
- if the sentinel lymph node is not found;
- in T4 tumors and inflammatory carcinoma.[20,21]

Although complete axillary dissection (I-II-III levels) is considered standard practice,[22] it should be extended to level III in the presence of macroscopic level II disease.

B- Sentinel lymph node (SLN) biopsy

Sentinel lymph node (SLN) biopsy should be considered a therapeutic standard for patients with clinical stage I-II breast cancer and clinically negative lymph nodes or with clinically suspicious lymph nodes that are subsequently negative after needle aspiration.

- ASCO guidelines indicate that SLN biopsy is indicated for axillary cavity staging in women with early-stage breast cancer (clinical stage I-II) with clinically negative axillary lymph nodes,[23] and should therefore be preferred because it achieves a significant reduction in treatment-related morbidity.

This has been confirmed by the results of several randomized studies.[20,24-27]

SLN biopsy may be considered unnecessary in patients that are not candidates for systemic and/or radiation adjuvant therapy, patients with severe comorbidities[28,29] and elderly women, in particular with tumors that are especially favorable from a biological point of view.

B.1- Metastases in the sentinel lymph node

CLINICAL QUESTION No. 4 (Figure 2)

In patients with invasive cT1, estrogen-receptor positive and cN0 breast cancer with <u>macrometastases</u> in 1-2 sentinel lymph nodes, undergoing conservative surgery, is the omission of axillary dissection indicated?

The need to perform complete axillary dissection in the presence of a positive sentinel lymph node was evaluated by the ACOSOG Z0011 study.[30] In this trial, 856 patients with cT1-2 breast cancer and 1 or 2 histologically positive sentinel lymph nodes were randomized to subsequent standard axillary dissection or no additional axillary surgery. At 6.3 years of median follow-up, no significant differences were observed in overall survival and disease-free survival between the two treatment arms. It should be noted that all patients had undergone conservative surgery and subsequent radiotherapy, that 96%-97% had received adjuvant systemic therapy and that favorable disease characteristics prevailed (cT1 in 70% of cases, estrogen receptors positive in 83%). A certain criticism in Italy stems from the fact that the study was closed early for difficulties in recruiting patients: only 40% of patients were enrolled compared to the initial statistical design planned for the study, more than 80% of patients were at low risk (T1, hormone-responsive), and there was missing data on the radiotherapy performed[30] (**SIGN Level of Evidence: 1+**). Data from the ACOSOG Z0011 study have recently been updated up to a median follow-up of 9.5 years, which confirmed the absence of an increase in axillary and local-regional recurrences in the arm treated with sentinel lymph node biopsy alone.[31] The approach to the axillary cavity is constantly evolving and an important contribution could come from a multicenter Italian study currently under way, SINODAR ONE, which evaluates the omission of axillary dissection in the presence of metastases in the sentinel lymph node with any breast surgery (conservative or not).[32] In clinical practice, pending further data, the decision to perform axillary dissection after a positive sentinel lymph node in conservative surgery should be discussed and possibly recommended in a multidisciplinary setting.

SIGN Quality of Evidence	Clinical recommendation	Strength of clinical recommendation
B	In patients with cT1 invasive breast cancer, positive estrogen receptors and cN0 with macrometastases in 1-2 sentinel lymph nodes, undergoing conservative surgery, omission of axillary dissection could be considered.[30,31]	**Conditional Positive**

B.2- Micrometastases in the sentinel lymph node

CLINICAL QUESTION No. 5 (Figure 2)

In patients with invasive ≤ cT2 and cN0 breast cancer with micrometastases in the sentinel lymph node, is the omission of axillary dissection indicated?

In 2013, a multicenter phase III study (IBCSG 23-01) was published in which 934 patients diagnosed with ≤ cT2 and cN0 breast cancer with micrometastases in one or more sentinel lymph nodes were randomized to receive axillary dissection towards no axillary dissection. At a median follow-up of 5 years, disease-free survival was 87.7% (95% CI 84.4-91.2) in the no axillary dissection group and 84.4% (80.7-88.1) in the axillary dissection group (log-rank p=0.16; HR for no axillary dissection vs. dissection 0.78, 95% CI 0.55-

1.11, non-inferiority p=0.0042)[33] (**SIGN Level of Evidence: 1+**). There were 10 local recurrences (2%) in the axillary dissection group and 8 (2%) in the no axillary dissection group and 1 (<1%) and 5 (1%) regional recurrences, respectively. Grade 3-4 long-term adverse events were 1 sensory neuropathy (grade 3), 3 cases of lymphoedema (2 grade 3 and 1 grade 4) and 3 motor neuropathies (grade 3) in the dissection group and 1 motor neuropathy in the no dissection group. This non-inferiority study was under-powered (more than 1,960 patients were planned, while only 934 were enrolled) and therefore the risk of false positive results was high.

In the light of these data, in patients with characteristics similar to those of the study described above, in the presence of micrometastases in the sentinel lymph node, axillary dissection is not necessary regardless of the type of breast surgery.[34]

SIGN Quality of Evidence	Clinical recommendation	Strength of clinical recommendation
A	In patients with invasive ≤cT2 and cN0 breast cancer with micrometastases in the sentinel lymph node, omission of axillary dissection[33] should be indicated regardless of the type of breast surgery.	**Strong Positive**

B.3- Sentinel lymph node biopsy in patients with invasive breast cancer candidates for neoadjuvant chemotherapy

- **Patients with clinically negative axillary lymph nodes at baseline**

In patients with clinically negative lymph nodes at baseline, sentinel lymph node biopsy may be performed before or after neoadjuvant chemotherapy.[36]

- **Patients with clinically positive axillary lymph nodes at baseline**

In literature, it is reported that about 40%-70% of patients with clinically positive lymph nodes will have a complete axillary response after neoadjuvant chemotherapy. Axillary dissection exposes these patients to an increased rate of morbidities such as lymphoedema, and the potential benefit of removing pathologically negative lymph nodes it also unclear. This is the rationale that led to the evaluation of the feasibility of sentinel lymph node dissection <u>after</u> neoadjuvant chemotherapy in patients with clinically positive lymph nodes at diagnosis.[35]

Three large prospective studies were conducted to evaluate the accuracy of sentinel lymph node dissection after neoadjuvant chemotherapy in this subgroup of patients.

The SENTINA study (**SIGN 3 Level of Evidence**) is a prospective, multicenter, four-arm, cohort study designed to evaluate the optimal timing of sentinel lymph node biopsy in candidates for neoadjuvant chemotherapy.[36]

Patients with clinically negative lymph nodes (cN0) underwent sentinel lymph node biopsy before neoadjuvant chemotherapy (arm A): if positive (pN1), the sentinel biopsy was repeated after chemotherapy (arm B).

Patients with clinically positive lymph nodes (cN+) that became clinically negative after neoadjuvant chemotherapy (ycN0; C-arm) received sentinel lymph node biopsy and axillary dissection. Only patients with clinically positive lymph nodes at the end of neoadjuvant chemotherapy (ycN1) received axillary dissection without sentinel lymph node biopsy (arm D).

Of the 1,737 patients enrolled, 1,022 patients, those cN0, underwent sentinel lymph node biopsy before neoadjuvant chemotherapy (arms A and B), with a detection rate of 99.1% (95% CI 98.3 -99.6). In cN+ patients who became ycN0 after neoadjuvant chemotherapy (C-arm), the detection rate was 80.1% (95% CI 76.6 -83.2) and the false-negative rate was 14.2% (95% CI 9.9 -19.4). In cN0 patients with positive sentinel lymph node biopsy before neoadjuvant chemotherapy and who repeated the sentinel lymph node biopsy after neoadjuvant chemotherapy (arm B), the detection rate was very low, at 60.8% (95% CI 55.6 -65.9), and the rate of false-negative results was very high, at 51.6% (95% CI 38.7 -64.2). The authors concluded that sentinel lymph node biopsy before neoadjuvant chemotherapy is a reliable procedure; when performed at the end of neoadjuvant

chemotherapy the detection rate is lower and the false-negative rate higher than when performed before neoadjuvant chemotherapy.[36] The study has some important critical issues, such as the limited number of centers that have enrolled more than 20 patients in the study and the frequently excessive thickness of the sentinel lymph node sections, that has certainly made the detection of micrometastases impossible.

A literature review[37] conducted to assess the reliability of the sentinel lymph node assessment prior to neoadjuvant chemotherapy identified 10 studies conducted between 1993 and 2011 and showed an identification rate ranging from 97% to 100%, with false-negative rates of 0%.

The ACOSOG Z1071 study is a multicenter study designed to evaluate the false-negative rate resulting from sentinel lymph node dissection after neoadjuvant chemotherapy in patients with clinically positive basal lymph nodes.[38] From 2009 to 2011, 756 patients with cT0-4, cN1-2 breast cancer (lymph node positivity confirmed by biopsy) were enrolled. Of the 663 patients evaluated, 649 underwent sentinel lymph node biopsy and axillary cavity dissection after neoadjuvant chemotherapy. In 46 patients the sentinel lymph node was not identified (7.1%); in 78 patients only one sentinel lymph node was identified (12%); in 39 patients lymph node metastases were detected at the axillary dissection in the presence of a negative sentinel lymph node (false negative rate of 12.6%).[38] In cN1 patients with at least 2 sentinel lymph nodes removed, the false negative rate was 12.6%. This percentage was over 20% for patients with only 2 sentinel lymph nodes removed (n=90), and 9% for patients with at least 3 sentinel lymph nodes removed (n=220).

In the prospective multicenter study SN FNAC, 153 T0-3 N1-2 patients (lymph node positivity determined by biopsy) were enrolled.[39] After neoadjuvant chemotherapy, the detection rate of sentinel lymph node biopsy was 87.6% and the false-negative rate was 8.4%.

A meta-analysis of 15 studies examined the feasibility and diagnostic accuracy of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with clinically positive lymph nodes prior to chemotherapy and showed an identification rate of 89% and 14% false negatives.[40] Similarly, a second recently published meta-analysis of 72 studies showed an identification rate of 89.6% and a false-negative rate of 14.2%.[41] Some studies have reported an even lower incidence of false negatives (2-4%) when, in addition to the sentinel lymph node, the lymph node that tested positive to the pre-neoadjuvant chemotherapy biopsy and was marked with a clip[42-44] is also removed.

In a retrospective study, Galimberti et al evaluated the feasibility of sentinel lymph node testing after neoadjuvant chemotherapy: 396 cT1-4 cN0 or cN1-2 patients who received neoadjuvant chemotherapy were analyzed, who became cN0 post-therapy and were surgically treated with sentinel lymph node biopsy and axillary dissection in case of positive sentinel lymph node.[45] Of 147 patients who were initially cN1/2, , the sentinel lymph node was negative in 70 (47.6%) and positive in 77 (52.4%) after neoadjuvant chemotherapy; at a median follow-up of 61 months overall survival was 93.3% in cN0 patients and 86.3% in pre-chemotherapy cN1/2 patients. After 5 years, only one case (0.7%) of axillary recurrence was found in cN1/2 patients who became cN0 after neoadjuvant chemotherapy. These retrospective data would appear to show that the performance of sentinel lymph node biopsy alone in patients who, although cN1/2 at diagnosis, become cN0 after neoadjuvant chemotherapy, does not lead to differences in axillary recurrence. A prospective observational study conducted at MSKCC on 288 patients diagnosed with breast cancer and micro-histological confirmation of lymph node metastases, treated with neoadjuvant chemotherapy, showed that 68% of patients were eligible for sentinel lymph node biopsy and that this procedure allowed to avoid complete axillary dissection in 48% of cases. Complete lymph node response was evident in 97% of ER-negative/HER2+ cases, 70% of ER+/HER2+ cases, 47% of triple-negative tumors and 21% of ER+/HER2- cases.[46] Data analyzed from more than 20,000 patients in the National Cancer Database with stage cN1-3 at diagnosis and treated with neoadjuvant chemotherapy showed complete lymph node response in 61.3% of ER-negative/HER2-positive tumors, 47.3% of triple-negative tumors and 47.7 of ER-positive/HER2-positive tumours.[47]

A similar study with 528 patients showed that complete lymph node response is statistically more frequent in women with ER- tumors and in women with complete breast response.[48]

In patients with invasive carcinoma and clinically positive axillary lymph nodes who are candidates for neoadjuvant chemotherapy, the performance of sentinel lymph node biopsy after completion of neoadjuvant chemotherapy is associated with a variable false-negative rate in various studies.[36,38,40,41] The rate of false negatives is reduced to 8-10% by testing at least 3 sentinel lymph nodes.[38]

In patients with invasive carcinoma and clinically positive baseline axillary lymph nodes, who became cN0 after neoadjuvant chemotherapy, if the post-chemotherapy sentinel lymph node is negative, the omission of axillary dissection is still being investigated and may be discussed and evaluated in a multidisciplinary setting.[35]

In patients with invasive breast cancer and positive sentinel lymph node biopsy <u>after</u> neoadjuvant chemotherapy, treatment involves routine axillary dissection, as there is no data to support the omission of axillary dissection.
The surgical approach to patients with invasive carcinoma and clinically positive axillary lymph nodes at baseline, with a sentinel lymph node biopsy after neoadjuvant chemotherapy showing ITCs or micrometastases, remains controversial and needs to be defined.[49]
This is the subject of evaluation of new studies that were recently started. The ALLIANCE A11202 trial randomizes women with positive SLN after neoadjuvant chemotherapy to complete axillary dissection or RT of the breast/chest wall and lymph node stations including the axilla.

5.1.3 Radiotherapy

Radiation therapy over the entire residual breast should be considered in most patients with invasive breast cancer undergoing conservative surgery, because it reduces the risk of local recurrence and mortality (Figure 2).[50]

It is possible to offer partial breast irradiation (PBI), i.e. radiation therapy limited to the tumor bed only and to the breast tissue immediately adjacent to it, to selected (low-risk) patients. PBI may be considered an acceptable treatment option outside clinical trials, as specified in the GEC-ESTRO 2010[51] and ASTRO 2016[52] Recommendations, as reported in the chapter on Partial Breast Irradiation, in the following cases: patients aged ≥50 years with invasive ductal carcinoma or with favorable, unicentric, unifocal histology, pT1 pN0 for ASTRO and pT1-2 (≤30 mm) pN0 for GEC-ESTRO, without extensive intraductal component and lympho-vascular invasion and with free margins ≥2 mm. ASTRO also includes DCIS as long as it is not clinically detectable, is G1-2 and has diameter ≤2.5 cm and negative margins ≥3 mm, excluding IORT when performing PBI.[51]

Irradiation of regional lymph nodes (III-IV axillary level) is indicated in patients with pT3-T4 tumors and in pT1-2 tumors with 4 or more positive axillary lymph nodes. However, the indication is also being extended to patients with pT1-2 tumors with 1-3 positive axillary lymph nodes, especially in the presence of unfavorable biological parameters (this indication is not the standard of care and should be discussed on a case-by-case basis). After treatment with neoadjuvant chemotherapy, extended irradiation of lymph node stations (III-IV axillary level) is considered appropriate in case of locally advanced presentation or in the presence of pathological lymph nodes after chemotherapy, while in patients with complete lymph node disease response the rate of regional recurrences seems sufficiently low to warrant omission of radiation therapy of lymph node stations.

Locally advanced neoplasms represent a heterogeneous group of tumors including both T3-4 tumors with or without affected lymph nodes and N2-N3 (any T) tumors, all at high risk of recurrence. Therefore, radiation therapy after mastectomy of the chest wall and regional lymph node stations (III-IV axillary level) is indicated because it has a positive impact on local-regional and distant disease control, improving both overall survival and disease-free survival. In T3N0 tumors, in the presence of favorable risk factors, treatment may be given on the chest wall alone or may be omitted.

RADIOTHERAPY AFTER CONSERVATIVE SURGERY

CLINICAL QUESTION No. 6 (Figure 2)

Is radiotherapy of the residual breast tissue recommended in patients with invasive breast cancer treated with conservative surgery?

The results of the meta-analysis on the individual data of 10,801 patients by the Early Breast Cancer Trialists Collaborative Group (EBCTCG)[50] showed that adjuvant RT over the entire residual breast reduces the risk of any disease recurrence at 10 years from 35% to 19.3% (p<0.00001) (25% local-regional and 10% distant disease in the group that did not perform RT, 8% local-regional and 12% distant disease in the group that performed RT), with a proportional risk of recurrence reduced by about 50% and an absolute reduction of 15.7%. Furthermore, RT is associated with an absolute reduction of mortality at 15 years due to breast cancer by 3.8% (p=0.00005) and for any reason by 3% (p=0.03). In practice, RT allows to avoid one breast cancer-related death at 15 years every 4 recurrences avoided at 10 years. The relative benefit of RT varies little between patient risk subgroups. (**SIGN Level of Evidence 1++**).

In the presence of positive resection margins, it is reasonable to consider surgical re-excision or mastectomy, especially when margin involvement is not only focal. If re-intervention (always recommended) is not possible, it is common practice to administer a dose supplement on the tumor bed (15-20 Gy), even in the absence of studies that support non-inferiority in comparison with surgery.

To date, the possibility of omitting radiation therapy after conservative surgery is not confirmed, although some initial experiences show that this may be feasible. A recent Italian multicenter randomized study of 749 women between 55 to 75 years of age with unifocal tumors up to 2.5 cm in diameter without extended intraductal component suggested that radiotherapy may be omitted in selected patients, with only a modest increase in the incidence of local recurrences and no significant decrease in survival at 9 years of median follow-up.[53]

SIGN Quality of Evidence	Clinical recommendation	Strength of clinical recommendation
A	In patients with invasive breast cancer undergoing conservative surgery, radiotherapy should be considered and should include all the residual breast tissue.[50]	**Strong Positive**

Dose, fractionation and technique

- Although the "standard" fractionation type involves an administration of 50 Gy in 25-28 fractions/5 times per week (1.8/2 Gy/fraction), a Canadian study[54] has shown that, for selected patients (free resection margins and negative axillary lymph nodes), a hypofractionated scheme (42.5 Gy/16 fractions/22 days) can be an acceptable alternative both in terms of local disease control and in terms of cosmetic results. Two other randomized studies on 4,451 patients showed, at a median follow-up of over twelve years, comparable results in terms of local control between standard fractionation (50 Gy in 25 fractions) and hypofractionated schemes (42 Gy in 13 fractions[55] or 40 Gy in 15 fractions[56]). Recent ASTRO recommendations suggest that hypofractionated treatment should be used regardless of the age of the patient, although in young women (<50 years), in view of the follow-up of about 10 years of randomized trials on hypofractionation, standard fractionation may be preferred.[57] Standard treatment is preferable to hypofractionated treatment in rare histological types, in patients with DCIS, and in patients with autoimmune diseases. The addition of a dose supplement (10-16 Gy boost) on the tumor bed reduces the risk of local recurrence: the cumulative incidence at 20 years of local recurrence was 16.4% in the group without boost compared to 12% in the group with boost, without generally adding toxicity to the treatment, and with a modest impact on the esthetic result.[58] Absolute risk reduction was significant in all age groups, but particularly in the younger patient group: the risk at 20 years was 36.0% (99% CI 25.8-46.2) in the no boost group versus 24.4% (14.9-33.8) in the boost group for patients under 40 years of age; 19.4% (14.7-24.1%) versus 13.5% (9.5-17.5) for patients aged 41-50 years; 13.2% (9.8-16.7) versus 10.3% (6.3-1.3) for patients aged 51-60 years; and 12.7% (CI 7.4-18.0) versus 9.7% (5-14.4) for patients aged over 60 years.

▪ According to recent ASTRO recommendations, for infiltrating tumors, boost radiotherapy should be given in the following cases: age ≤50 years with disease of any grade, in patients aged 51-70 years with G3 disease and positive or <2 mm margins, in patients older than 70 years with G3 disease and/or margins <2 mm.[57] Boosting is an option that should be considered especially in relation to the risk of local recurrence and the technical possibility of limiting radiation to the tumor bed only. The most appropriate irradiation technique must be defined and planned individually, taking into account the morphology of the patient and the volumes to be irradiated, as well as the available resources (electron beams, photon beams, IORT or brachytherapy methods).

▪ A randomized study suggests that avoiding overdosed areas (≥2 cm^3 of breast tissue volume receiving > 107% of the prescription dose) within the target (breast) using appropriate and optimized technique improves the overall cosmetic outcome and reduces the risk of telangiectasia. It is therefore recommended to strive for dose homogeneity using the techniques available at the center and at all events to apply IMRT techniques to selected cases if the morphology of CTV or healthy organs requires it, as recently reported by ASTRO,[59] in order to reduce acute and delayed side effects.[60] *Recent ASTRO recommendations define the 3D field-in-field technique as the first approach to defining the radiotherapy plan required to achieve dose homogeneity; should the field-in-field technique not guarantee homogeneity, intensity modulation techniques can be used to ensure that healthy organs are spared, especially at cardiac level.*[57] Recently, the 10-year results of a randomized study that enrolled 358 patients and evaluated 241 patients receiving either conventional treatment or IMRT have been published. The authors claim that, although delayed side effects are related to acute ones and IMRT improves dose conformation to target and reduces acute side effects, this technique has not so far shown an advantage in terms of either risk of delayed effects or local disease control.[61]

PARTIAL BREAST IRRADIATION

Partial breast irradiation (PBI) indicates radiation therapy limited to the tumor bed alone and the breast tissue immediately surrounding it. PBI has been investigated in the last 15 years driven by scientific research on tumor radiobiology and by the needs of patients and radiotherapy centers, and its development has been facilitated by the diffusion and availability of technological innovations.
- The advantages offered by PBI are essentially represented by the reduction in the number of sessions and therefore in treatment duration (when accelerated), with logistical advantages for the patients; it also allows to shorten the waiting lists of radiotherapy centers, potentially optimizing access of patients to the treatment.
- PBI is not a simple technological evolution, but a different therapeutic strategy compared to traditional "*whole breast irradiation* (WBI)", with significant differences not only in treatment volumes but also in doses and fractionation;[62-64] as such, it requires adequate clinical evidence and phase III studies are underway to test its effectiveness compared to classic whole breast irradiation.
Partial breast irradiation can be performed using different methods: interstitial brachytherapy (*both low-dose rate* and *high-dose rate*), external beam radiotherapy, endoluminal brachytherapy, and intraoperative radiation therapy (IORT). The volume irradiated and the dose administered vary considerably from one technique to another, and each method has different advantages and problems.
- The Rapid Trial enrolled over 2,000 women aged >40 years with invasive or intraductal breast cancer ≤3 cm. After conservative surgery, patients underwent either PBI with external conformational RT (38.5 Gy in 10 fractions twice daily) or WBI (42.5 Gy in 16 or 50 Gy in 25 fractions ± boost). At a median follow-up of 36 months, the few local recurrence events (*ipsilateral breast tumor recurrence*, IBTR) have not yet allowed to perform the efficacy analysis. PBI has been significantly associated with a higher rate of toxicity (Grade 1 - 2).[65] Some possible causes of this unexpected adverse outcome could be the large breast volume that received 50% of the prescribed dose and the bi-daily treatment schedule that did not encourage cell recovery.[66]
Another way of performing PBI treatment is intensity-modulated radiotherapy (IMRT). This technique has the advantage of a better dose conformation than RT techniques using external conformational beams. To date, only one study has reported the results of PBI IMRT compared to WBI:[67] 520 women over 40 years of age with early-stage breast cancer with a maximum size <25 mm have been randomly assigned to receive WBI (50 Gy in 25 fractions followed by 10 Gy boost to the tumor bed in 5 fractions) or PBI IMRT (30 Gy to the tumor bed in 5 fractions daily). At a median follow-up of 5 years, no significant differences in terms of IBTR were

observed between the two groups (p=0.86). The PBI group had significantly better results in terms of acute toxicity (p=0.0001), delayed toxicity (p=0.004), and cosmetic result (p=0.045). The results of this study suggest that PBI IMRT has a better toxicity profile, but a longer follow-up and the enrolment of more patients are needed to confirm this hypothesis.

In a phase III randomized multicenter study (TARGIT-A), 3,451 women treated with conservative surgery were randomized between IORT (X-ray 50 Kv, 20 Gy in a single fraction) and standard breast radiotherapy. In 15.2% of randomized patients, external RT was also administered to the entire residual breast according to data available from histological examination.[68]

Approximately 1/3 of the patients received IORT after surgery (with consequent reopening of the surgical wound). The median follow-up of the study is short (29 months). The 5-year risk of local recurrence was found to be 3.3% in the TARGIT arm vs 1.3% after external radiotherapy over the entire breast (p=0.042), but within the predefined non-inferiority limit of 2.5%. No statistically significant differences in overall or specific cause survival were found between the two arms. Radiotherapy toxicity was lower in the group of patients treated with IORT. The results of this study suggest that partial irradiation is not inferior (in terms of local recurrences) to whole breast irradiation (1) in low-risk situations, (2) when intraoperative radiotherapy is administered during surgery, and (3) when external radiotherapy remains an option based on the results of the definitive anatomopathological examination. Patients were eligible if ≥ 45 years and eligible for conservative surgery for unifocal invasive ductal carcinoma; in particular, the median age of the patients was 63 years and in most cases T size was ≤ 2 cm (86%), axillary nodes were negative (83%) and estrogen receptors were positive (90%).[52,70] The short median follow-up (2.5 years) and the characteristics of the patients enrolled (generally low-risk) are important limitations of the study.

Recently, the results of the ELIOT study comparing IORT (21 Gy with electron beams in a single fraction) and external beam radiotherapy after conservative surgery[69] have been published (at a median follow-up of 5.8 years). 1,305 patients aged 48 to 75 years with primary tumor up to 2.5 cm in diameter, regardless of lymph node, receptor and molecular status were included in the study. The 5-year frequency of ipsilateral breast recurrences was 4.4% after IORT and 0.4% after external RT (HR 9.3, 95% CI 3.3-26.3, p<0.0001), but values were within the predefined margin of equivalence. Of patients who had received IORT, those with at least one of the following factors (T diameter >2 cm; pN+ ≥4; G3; triple-negative tumor) had a risk of intramammary recurrence of over 10% at 5 years, while in patients at low local recurrence risk the incidence of intramammary recurrence was around 1.5% at 5 years (BIB 98).

Both ELIOT and TARGIT seem to suggest that PBI is less effective than whole breast irradiation in patients not adequately selected according to the criteria suggested by ESTRO and ASTRO, but the incidence of local recurrences may be clinically negligible in patients at low risk of recurrence.

Another way to perform PBI is using multicatheter brachytherapy. The results of a randomized phase III trial have recently been published, enrolling 1,184 patients with low-risk breast cancer (age >40 years, pTis or pT1-2, with lesions less than 3 cm, pN0/pNmic, M0), undergoing conservative surgery (negative surgical margins <2 mm), who were randomized to receive PBI with multicatheter brachytherapy versus WBI. At 5 years follow-up, 9 patients treated with PBI and 5 patients treated with WBRT had a local recurrence: 1.44% (95% CI 0.51-2.38) with PBI and 0.92% (0.12-1.73) with WBI (difference 0.52% , 95% CI - 0.72-1.75; p=0.42). Local intramammary recurrence has not been shown to be age-related (<50 years, 50-60, 60-70, >70 years). The 5-year risk of Grade 2-3 side effects affecting the skin was 3.2% in the PBI group versus 5.7% in the WBI group (p=0.08), and 7.6% for subcutaneous tissue versus 6.3% (p=0.53).[70] Data on delayed side effects in this study are currently available. Only the cumulative incidence of delayed G2-3 skin toxicity was significantly higher in the whole breast radiotherapy group: 10.7% (95% CI 8.0-13.4) versus 6.9% (4.8-9.0) p=0.020. No differences were found between the two groups in terms of mastodynia, delayed subcutaneous tissue toxicity, and cosmetic results.[71]

A fundamental study in support of PBI, a multicenter, randomized, controlled, phase 3 non-inferiority trial (IMPORT LOW) has recently been published. Women aged 50 years or older who underwent conservative surgery for G1-3 unilocal invasive ductal carcinoma, with a tumor size of 3 cm or less (pT1-2), up to three positive axillary lymph nodes (pN0-1) and free surgical margins (>2 mm) were randomized (1:1:1) to receive 40 Gy RT over the entire mammary gland (control), 36 Gy RT over the entire mammary gland (reduced dose group) or 40 Gy PBI (PBI group) in 15 daily treatment fractions. 674 patients were evaluated in the control group, 673 in the reduced dose group and 669 in the PBI group. The results show non-inferiority of the PBI

treatment. The median follow-up was 72.2 months (IQR 61.7-83.2) and the 5-year estimates of cumulative incidence of local recurrence were 1.1% (95% CI 0.5-2.3) in the control group, 0.2% (0.02-1.2) in the low-dose group and 0.5% (0.2-1.4) in the PBI group.[72] The IMPORT LOW trial has shown that PBI can be the approach of choice for adequately selected patients.

Ultimately, in the light of the above data and of the limits and bias of randomized prospective studies, the most robust and mature scientific evidence for PBI in terms of method are significantly in favor of brachytherapy and radiotherapy with external beams.

In conclusion, PBI may be considered a treatment option in appropriately selected patients at low risk of local recurrence, who meet the criteria for inclusion in phase 3 studies IMPORT LOW[72] and GEC-ESTRO[70], as also specified in the GEC-ESTRO 2010[51] and ASTRO 2016[52] Recommendations (patients aged ≥50 years with invasive ductal, unicentric, unifocal, pT1 pN0 and RE positive carcinoma, no extensive intraductal component and lympho-vascular invasion, with free margins ≥2 mm, of any grade and in the absence of neoadjuvant chemotherapy and BRCA 1-2 mutation).
The patient should be adequately informed about the risk and implications of such a choice.

Outside of the inclusion criteria mentioned above, PBI is not yet a standard therapy, as studies have not yet provided definitive indications due to the number of patients enrolled, the small numbers of events detected and the still limited follow-up.

POSTMASTECTOMY CHEST WALL RADIATION THERAPY

After mastectomy, chest wall radiotherapy is indicated for primary tumors >5 cm (pT≥3), for tumors infiltrating the skin and/or pectoral muscle and/or chest wall, and for metastatic involvement of 4 or more axillary lymph nodes (Figure 2).[74] A recent consensus document from ASTRO, ASCO, and SSO has shown that, even for pT1-2 tumors with 1-3 positive lymph nodes, PMRT reduces recurrences and mortality from breast cancer. However, for some subsets of patients the risk is so low that risks and potential toxicities may discourage this approach, and therefore clinical judgment is needed in this setting. Patients with residual lymph node disease after neoadjuvant chemotherapy should receive PMRT.[75]

RADIATION THERAPY OF LYMPH NODE STATIONS

The rapid development and progressive application of sentinel lymph node biopsy, thanks to the confirmation of its diagnostic accuracy, has changed the surgical approach to the study and treatment of axillary nodes. Despite the help provided by the biological factors of the tumor, which play a pivotal role in therapeutic decisions, the number of lymph nodes involved is still unhelpful, especially for the radiation therapist. Moreover, it is not yet certain what role RT should play in the treatment of the axilla in the presence of unfavorable biological factors, if axillary dissection is omitted.

The administration of neoadjuvant chemotherapy is increasingly used in cases that are not locally advanced in order to facilitate surgical procedures, but some decision-making issues may arise, in the absence of data from randomized studies, on the role of RT after neoadjuvant chemotherapy, both in case of axillary dissection and sentinel lymph node biopsy.

Two recent Italian Consensus conferences (Senonetwork Consensus 2014 and AIRO Consensus on the treatment of breast lymph node stations 2016) and an update to American Guidelines[71] have addressed the above issues in order to standardize decision-making and treatment.

Therefore, after mastectomy and lymph node dissection, irradiation of regional lymph nodes (III-IV axillary level ± internal mammary chain) is indicated in patients with pT3-T4 tumors (regardless of lymph node status) and in pT1-2 tumors with 4 or more positive axillary lymph nodes.[75] In pT3 N0 tumors, depending on risk factors, treatment may be given on the chest wall alone or may be omitted. However, the indication is also being extended to patients with pT1-2 tumors with 1-3 positive axillary lymph nodes, especially in the presence of unfavorable biological parameters.[76] A recent meta-analysis of individual data on 8,135 patients enrolled in

22 studies between 1964 and 1986 shows that irradiation of the chest wall and lymph node stations provides an advantage in terms of local and regional control and specific cause mortality even in patients (N=1314) with 1-3 positive lymph nodes, and also in the presence of systemic therapy.[77]

After conservative surgery, generally irradiation of regional lymph nodes (in addition to breast irradiation) is always indicated in patients with 4 or more positive axillary lymph nodes, and can be considered in patients with 1-3 positive axillary lymph nodes based on risk factors. Recently, the results of the MA.20 study by the NCIC-CTG were presented, which randomized 1,832 patients with both negative but high-risk axillary nodes and positive axillary nodes after conservative surgery, with RT only of the breast or of the breast and regional lymph nodes (axillary apex, supraclavicular, internal breast nodes).[78]

At a 10-year follow-up, OS did not differ significantly between the two groups (82.8% in the group treated on regional lymph node stations and 81.8% in the control group; HR:0.91; 95% CI: 0.72-1.13; p = 0.38), while DFS was superior in the group that had received RT of lymph node stations (82.0% vs 77.0%; HR: 0.76; 95% CI:0.61-0.94; p = 0.01). In patients treated on lymph node stations, a higher incidence of acute pneumonia of grade ≥ 2 (1.2% vs. 0.2%, p = 0.01) and lymphedema (8.4% vs. 4.5%, p = 0.001) was observed.

On the basis of the available literature data, which are often sub-optimal (non prospective studies, which evaluate patients who have received chemotherapy protocols other than those employed more recently, designed to define the effectiveness of chemotherapy schemes and not the usefulness of RT), it is considered appropriate to perform extended irradiation of the lymph node stations (III-IV axillary level) that were not surgically treated in the case of locally advanced presentation or in the presence of pathological lymph nodes after adjuvant chemotherapy.

In patients with a complete lymph node disease response, the rate of regional recurrences seems sufficiently low to warrant omission of radiotherapy of the lymph node stations, but due to current uncertainties, different opinions, and the absence of randomized studies, a multidisciplinary joint discussion including an assessment of prognostic factors and adequate information of the patient is considered appropriate.

As regards the extent of irradiation and the volumes to be treated, the axillary region (level I and part of level II) does not require elective irradiation after axillary dissection except in selected cases (presence of residual disease or well-founded suspicion of residual disease after incomplete dissection). Therefore, after axillary dissection, irradiation of level III nodes and the supraclavicular region should be performed when indicated.

Irradiation of all axillary lymph node stations was performed in the multicenter phase III EORTC study (AMAROS), which compared the local-regional control achieved by axillary dissection with that achieved by direct radiotherapy of the 3 axillary levels and the medial part of the supraclavicular fossa in 1,425 T1-T2 patients with clinically negative lymph nodes, who underwent conservative surgery or mastectomy, but subsequently had a positive sentinel lymph node.[79]

At 6.1 years of follow-up, the frequency of 5-year axillary recurrence is extremely low in both arms (0.43% vs. 1.19%).[80] There was no statistically significant difference between the two groups for both disease-free and overall survival, but lymphadenectomy was found to be associated with a significantly higher rate of lymphoedema than radiotherapy. Unfortunately, data on tumor biology (e.g. receptor status, lymphovascular invasion, extranodal extension) have not been collected, which does not allow exploratory analysis of subgroups. Although the extremely limited number of events, according to some, reduces the reliability of statistical analysis, these results suggest that radiotherapy could be an alternative to axillary dissection with fewer side effects. These data will have to be confirmed over time.

- The indication for precautionary treatment of lymph nodes of the internal mammary chain (in the presence of positive axillary lymph nodes after histological testing for primary tumors of the central and/or internal quadrants, or regardless of the axillary lymph node status for primary tumors >5 cm) must be carefully evaluated based on benefits and potential toxicities (especially for the left breast), even if current radiotherapy techniques allow a personalized modulation of irradiation volumes and synchronization with respiratory acts (IMRT and IGRT). The indication is now debated, despite the recent result of the EORTC study that enrolled 4,004 randomized patients to receive RT only of the breast or chest wall versus RT of breast/chest wall and lymph nodes (axillary and internal breast nodes).[79] At 10 years, overall survival was 82.3% in the lymph node

RT group and 80.7% in the control group (HR for death with lymph node irradiation, 0.87; 95% confidence interval [CI], 0.76-1.00; p=0.06). The disease-free survival rate was 72.1% in the lymph node RT group and 69.1% in the control group (hazard ratio for disease progression or death, 0.89; 95 % CI, 0.80-1.00; p = 0.04), distant disease-free survival rate was 78.0 % versus 75.0 % (hazard ratio, 0.86; 95 % CI, 0.76-0.98; p=0.02), and specific cancer mortality was 12.5 % versus 14.4 % (hazard ratio, 0.82; 95 % CI, 0.70-0.97; p=0.02). Acute side effects of regional lymph node irradiation were modest.

- Incidental cardiac irradiation during radiation therapy for breast cancer increases the risk of ischemic heart disease. This increase in risk is proportional to the dose received by the heart, increases starting from a few years after exposure and continues for at least 20 years.[80] These recently published data showed that rates of major coronary events increase linearly with the average cardiac dose. It should be noted, however, that in this study, patients were treated from 1958 to 2001 with old RT techniques, and that the radiation dose delivered to the heart was roughly estimated and not calculated on the basis of the patient's anatomy.
The pre-existence of risk factors for heart disease amplifies the absolute risk of ischemic heart disease. The technology available today (IGRT, Breath-control, etc.) can allow a clear reduction of this risk and makes irradiation safer. It is therefore necessary that the planning of radiation therapy for breast cancer includes the estimation and possible minimization of radiation dose to cardiac tissue and coronary arteries, in particular to the left anterior descending artery (LAD), if necessary through the use of special radiotherapy techniques.

TIMING

An integrated plan shared between all the specialists involved in the therapeutic choices for each individual patient is desirable.

- In patients who are not candidates for chemotherapy treatment, even in the absence of reliable data from randomized trials, it is considered useful to start RT as soon as possible, since no threshold limit can be identified.[81,82] It is commonly believed that radiotherapy should begin after the surgical wound has healed, within 8-20 weeks. A delay beyond this period could lead to an increased risk of local recurrence.[82-85]

In patients receiving adjuvant chemotherapy, the preferred mode of chemoradiotherapy combination should be sequential, especially if anthracycline-containing regimens are used, due to the potential risk of increased cardiotoxicity. It is recommended that radiation therapy be initiated within one month of the end of chemotherapy.
- Radiotherapy should not be administered in conjunction with systemic treatments containing anthracyclines and/or taxanes because of the increased risk of side effects on skin and subcutaneous tissues, and on pulmonary and cardiac parenchyma.[86-88]
- Radiotherapy can be administered in conjunction with CMF.
- Radiotherapy can be administered in conjunction with trastuzumab: this does not seem to increase acute toxicity. There are no conclusive data for delayed toxicity.[89]

RADIATION THERAPY IN LOCALLY ADVANCED TUMORS

Locally advanced neoplasms represent a heterogeneous group of tumors including both T3-4 tumors with or without affected lymph nodes, and N2-N3 (any T), all at high risk of both local-regional and distant disease recurrence.[90] Patients with tumors that are potentially operable with mastectomy may be candidates for primary systemic treatment for cytoreductive purposes with the aim to make conservative surgery possible, while inoperable forms must still receive systemic therapy in order to allow surgery.
After completion of the primary therapy and based on its outcome and the type of initial presentation and surgery performed, radiation therapy is indicated. There is an indication for radiation therapy even if surgery cannot be performed. RT continues to be an important complement to systemic treatment and surgery.[90] However, it is difficult to provide evidence-based recommendations, as these are often derived from results of

retrospective studies, while prospective studies of primary therapies have not been designed to evaluate the role of radiotherapy.[91-93]

- RT has a positive impact on local-regional and distant disease control: it improves both overall survival and disease-free survival.[94,95]

- In case of conservative surgery, subsequent radiation therapy is always indicated both of the residual parenchyma and of regional lymph node stations.

- In case of mastectomy, the indication for radiotherapy follows the related guidelines.

- In stage III tumors, even if there is a complete pathological response to systemic therapy (likely to be a more favorable prognostic factor), RT of the chest wall and regional lymph node areas provides an additional clinical benefit in terms of local-regional control, compared to non radio-treated patients.[96,100]

Data from a cumulative study of 3,088 women enrolled in the NSABP B18 and B27 trials, where only 42 patients were cT3 and of these 25 were cT3 N1 (stage III), show that age, clinical stage before chemotherapy and pathological response obtained on T and N parameters can be used to predict the risk of local-regional recurrence and to optimize the use of adjuvant radiotherapy accordingly.[97]

On the other hand, some more recent analyses have shown reduced but not statistically significant local-regional recurrence rates in patients with complete clinical response (4% vs 8%).[98-100]

Therefore, there is currently no unanimous opinion on the need for radiotherapy of lymph node stations in patients with confirmed complete pathological response after ALND. An individualized assessment of each case in a multidisciplinary setting is therefore warranted in order to formulate the therapeutic strategy and provide adequate patient information.[99]

- In inflammatory carcinoma, RT of chest wall and local-regional lymph nodes should always be performed (according to many Authors this should also include internal mammary nodes). According to a recent Consensus, it is advisable to reach total doses above the standard dose (up to 66 Gy) in subgroups of patients at particularly high risk (age <45 years, close or positive margins, 4 or more residual positive lymph nodes after neoadjuvant chemotherapy, or non-responders).[101]

- With regard to the timing of radiotherapy and the choice of lymph node stations not otherwise specified, please refer to the relevant paragraphs.

For further details on indications in the various clinical settings and for the technical methods of radiation therapy, please refer to the documents issued by the Breast Pathology Study Group of the Italian Association of Oncological Radiotherapy (AIRO), which are periodically updated and are available on the Website www.radioterapiaitalia.it.

5.2 Adjuvant systemic treatments

5.2.1 Adjuvant systemic therapeutic strategy

Adjuvant systemic treatment should be considered after surgical treatment based on the significant reduction in the risk of recurrence and death achieved with polychemotherapy,[1] endocrine therapy[2] and biological therapy (trastuzumab).[3]

The decision of which therapy or therapies to use in each individual patient requires careful evaluation of:
- *Prognostic factors, which define the extent of the recurrence risk (Table 5.1);*
- *Predictive factors for response to specific treatments (ER, HER2) (Table 5.1);*
- *Expected benefits of treatment in terms of absolute benefit percentage and expected side effects;*
- *Patient's comorbidities;*
- *Patient preference.*

Table 5.1. Early-stage infiltrating breast cancer: prognostic and predictive factors

PROGNOSTIC FACTORS
- TUMOR DIAMETER
- STATUS AND NUMBER OF METASTATIC LYMPH NODES
- HISTOLOGY (NST; lobular; mucinous, tubular, papillary; medullary, adenoid-cystic, apocrine)
- HISTOLOGICAL GRADE
- PROLIFERATION INDEX (Ki67/MIB-1)
- HORMONE-RECEPTOR STATUS AND EXPRESSION LEVEL OF HORMONE RECEPTORS
- HER2 STATUS
- Vascular Invasion
- PATIENT'S AGE
- Gene expression profiles

PREDICTIVE FACTORS
- HORMONE-RECEPTOR STATUS AND EXPRESSION LEVEL OF HORMONE RECEPTORS
- HER2 STATUS

(NST = invasive carcinoma of no special type)

While the definition of risk is based on prognostic factors that should not be analyzed individually but integrated with each other, so far only two universally accepted predictive factors apply to the choice of treatment: the status of hormone receptors and of HER-2 (Figure No. 3).

Today, we must also consider the classification of breast cancer which, on the basis of gene expression profiles, allows to distinguish subgroups of Luminal A, Luminal B, HER2, and basal-like breast cancer, with different prognoses (see section 3.3).

The simple evaluation by immunohistochemistry of the status of estrogen and progesterone receptors, HER-2 (integrated by ISH where indicated) and Ki67 appears to be able to reproduce, in a surrogate manner, a classification corresponding to that of gene profiles, which can be used in the clinical setting, according to the criteria already described in paragraph 3.3.

In this way, on the basis of immunohistochemistry results, the following subgroups of breast cancer can be identified, with different adjuvant systemic therapy indications (Figures 4-7):

- ***Luminal A (Figure 4)**: Luminal A subtype generally includes low-grade tumors with good prognosis, high sensitivity to hormone therapy and lower sensitivity to chemotherapy. The key therapy is adjuvant hormone therapy, with the addition of chemotherapy in selected cases.*

- ***Luminal B** (HER2 negative, Figure 4): Luminal B tumors are characterized by a more aggressive phenotype than Luminal A, being more frequently high-grade tumors associated with a worse prognosis; the key treatment is chemotherapy in addition to hormone therapy, to be assessed on the basis of other recurrence risk factors (T and N), age of patients and comorbidities.*

Below are some considerations that apply to decisions on systemic adjuvant therapy in HER2-negative Luminal cases.

It may be decided not to administer any adjuvant treatment in microinvasive and in pT1a tumors provided they are pN0, based on associated favorable biological factors (G1, low Ki-67 levels and high ER levels), the (advanced) patient age and comorbidities. Histology is another factor to consider; tumors with tubular/cribriform, mucinous or papillary histology (better prognosis than ductal tumors),[5,6] especially if pN0, can be treated with hormone therapy alone and may also not receive any adjuvant treatment if pN0 and pT ≤ 1 cm. The addition of chemotherapy to adjuvant hormone therapy should be evaluated considering recurrence risk factors (pT, pN), associated biological factors (G3, high Ki-67 levels, low levels of ER and/or PgR), histology (ductal vs. lobular: see section 4.2.2.a), patient age and comorbidities. If available, the risk category based on gene expression profiles can be used as a prognostic factor to be integrated into the therapeutic decision. pN2-pN3 tumors should generally receive chemotherapy.

Chemotherapy in addition to hormone therapy should also be considered in lobular histology, when associated with a high risk of recurrence based on T (pT3/pT4) and N (pN2/pN3) parameters.

- *Luminal B (HER2 positive): (Figure 5) the key treatment consists of chemotherapy plus trastuzumab in addition to adjuvant hormone therapy; this treatment is generally indicated in tumors with T size over one centimeter or with positive axillary lymph nodes; in small tumors (pT1a and pT1b) and pN0/pN1mi, there are currently no prospective data from randomized studies about the benefit of adjuvant trastuzumab. The addition of chemotherapy and trastuzumab to hormone therapy can be considered, also taking into account Grade, Ki-67, age and comorbidities of the patient (see section 4.2.2.d).*
- *HER2 positive (non-luminal): (Figure 6) the key treatment is chemotherapy plus trastuzumab; this treatment is generally indicated for tumors with T size over one centimeter or with positive axillary lymph nodes. In small tumors (pT1a and pT1b) and pN0/pN1mi, there are no prospective data on the benefit of adjuvant trastuzumab. Chemotherapy and trastuzumab may be considered, taking into account Grade, Ki-67, age and comorbidities of the patient (see section 4.2.2.d).*
- *Triple-negative: (Figure 7) the key treatment is chemotherapy. In pT1a, pN0/pN1mi tumors, adjuvant chemotherapy may be considered if G3 or with elevated Ki-67. Some histological types of "triple-negative" tumors, such as medullary and adenoid-cystic carcinoma, have a favorable prognosis and if axillary lymph nodes are negative, they may not require systemic adjuvant treatments in the absence of additional risk factors. However, in view of the difficult diagnosis of medullary carcinomas and the possibility of aggressive variants of adenoid-cystic carcinoma, a careful evaluation of individual cases is warranted.[5-7] For tumors with diameter over one centimeter or for N+ tumors, adjuvant chemotherapy is indicated.*

NOTES
- Infiltrating lobular carcinoma, which accounts for 5-15% of all breast cancers, appears to be less responsive to chemotherapy than ductal infiltrating carcinoma, as reported in retrospective neoadjuvant chemotherapy studies where lower rates of pathological complete response and conservative surgery were obtained, although long-term prognosis was better.[8,9] Lobular carcinomas are often diagnosed at an advanced stage and frequently express hormone receptors. The rare pleomorphic variant of lobular carcinoma characterized by a low degree of differentiation (G3) has a more aggressive clinical course than the classical variant and should be treated, according to some authors, based on biological characteristics, comparably to infiltrating ductal carcinoma. [6,10,11]

5.2.2 Adjuvant hormone therapy

Hormone therapy is indicated in patients with hormone-responsive tumors, i.e. ER-positive (≥1%) and/or PgR-positive (≥1%) tumors; while there is no indication in hormone-receptor negative tumors (ER and PgR negative: <1%).
In the case of microinvasive tumors, hormone therapy prescription should be based on the determination of hormone receptors in the invasive component.

In the choice of type and duration of hormone therapy one should take into account menopausal status and patients recurrence risk.
Menopausal status should be defined by one of the following criteria:[12]
- *Bilateral annexectomy;*
- *Age > 60 years;*
- *Age < 60 years, FSH and estradiol values in the menopausal range, and amenorrhea for at least 12 months in the absence of chemotherapy, tamoxifen, and toremifene;*
- *If treated with tamoxifen or toremifene and age < 60 years, amenorrhea for at least 12 months, and FSH and estradiol values in the menopausal range;*
- *The menopausal status of patients treated with LHRHa cannot beassessed.*
Figure 8 shows adjuvant systemic therapies based on the patient's menopausal status.

Adjuvant hormone therapy in premenopausal women

TAMOXIFEN
In premenopausal or perimenopausal women diagnosed with ER-positive and/or PgR positive breast cancer, regardless of other tumor characteristics, adjuvant hormone therapy with 20 mg/day oral tamoxifen for 5 years should be considered as first-line treatment.[2]

TAMOXIFEN + OVARIAN SUPPRESSION
The addition of ovarian suppression (achievable in most cases with LHRHa, or with surgery or radiotherapy) to tamoxifen should be evaluated according to the individual disease recurrence risk, which depends on both patient's(age) and tumor charcteristics (pT, pN, histological grade, positive hormone-receptor levels, Ki-67 value):
- *In premenopausal or perimenopausal women with HER2 negative and hormone receptors positive tumors at low risk of recurrence, the addition of ovarian suppression to tamoxifen should not be considered (GRADE Question No. 1; Clinical recommendation: WEAK NEGATIVE),*
- *In premenopausal or perimenopausal women with HER2 negative and hormone receptors positive tumors at high risk of recurrence, the addition of ovarian suppression to tamoxifen should be considered (GRADE Question No 2; Clinical recommendation: STRONG POSITIVE).*

AROMATASE INHIBITOR + OVARIAN SUPPRESSION
In premenopausal or perimenopausal women with HER2 negative and hormone receptors tumors at high risk of recurrence and who are eligible for ovarian suppression, an aromatase inhibitor may be considered instead of tamoxifen (GRADE Question No. 3; Clinical recommendation: WEAK POSITIVE).

EXTENDED TAMOXIFEN THERAPY FOR 10 YEARS
On the basis of the results of the ATLAS[13] and aTToM[14] studies, continuation of tamoxifen for further 5 years at the completion of the first 5 years of therapy may be considered in women with ER-positive and/or PgR-positive tumorsthat are still premenopausal or perimenopausal, , after taking into consideration the benefit/harm ratio and the risk of recurrence in each individual patient (Clinical recommendation: WEAK POSITIVE).

EXTENDED AROMATASE INHIBITOR THERAPY FOR 5 YEARS AFTER 5 YEARS OF TAMOXIFEN
In women who were premenopausal when diagnosed with infiltrating breast cancer, have been treated with tamoxifen for 5 years and have entered menopause during the adjuvant treatment with chemotherapy or tamoxifen, treatment with letrozole after 5 years of tamoxifen could be evaluated after considering the benefit/harm ratio and the risk of recurrence of each individual patient.[15-18]

EXTENDED THERAPY AFTER OVARIAN SUPPRESSION IN ADDITION TO TAMOXIFEN OR AIs
There are no data supporting the continuation of hormone therapy beyond the fifth year in premenopausal patients treated with 5 years of ovarian suppression + tamoxifen or exemestane. In these patients, continuation of hormone therapy with tamoxifen or an AI may be considered based on the risk/benefit ratio and after confirmation of menopausal status. In patients who are candidates for hormone therapy with an AI, a complete evaluation of the menopausal status with repeated FSH and estradiol testing is necessary to confirm their postmenopausal status as accurately as possible.

Adjuvant hormone therapy in postmenopausal women

In postmenopausal women with resected ER-positive and/or PgR-positive infiltrating breast cancer who are eligible for adjuvant hormone therapy, a treatment including antiaromatase inhibitors should be considered (Clinical recommendation: STRONG POSITIVE).[3]

In women with contraindications to aromatase inhibitors or who develop severe toxicities (e.g. musculoskeletal), tamoxifen for 5 years, or tamoxifen for 2-3 years followed by an aromatase agent for 3-2 years, may be considered.

In postmenopausal women with resected ER-positive and/or PgR-positive infiltrating breast cancer who have completed 5 years of adjuvant tamoxifen, the use of aromatase inhibitors for 5 years should be considered, after evaluation of the benefit/risk ratio[15-18] (Clinical recommendation: STRONG POSITIVE).

In postmenopausal women with resected ER-positive and/or PgR-positive infiltrating breast cancer, the extension of aromatase inhibitor therapy after the fifth year may be considered, after an accurate risk/benefit assessment.[19]

5.2.2.1 Drugs used in adjuvant hormone therapy for breast cancer

1-TAMOXIFEN

In premenopausal or perimenopausal patients with resected ER-positive and/or PgR positive breast cancer, regardless of other tumor characteristics, tamoxifen 20 mg/day for 5 years should be considered as first-line treatment.[2] In premenopausal patients at high risk of recurrence, the addition of ovarian suppression to tamoxifen (see section on ovarian suppression) should be considered.[20-21]

Tamoxifen for 5 years significantly reduces the annual risk of recurrence by 39% and of breast cancer death by 30% regardless of chemotherapy use, age, menopausal status, lymph node status and progesterone receptor status. At a follow-up of 15 years, tamoxifen for 5 years led to an absolute reduction in the risk of recurrence and death of 13.2% and 9.2%, respectively.[2]

In postmenopausal women, tamoxifen may be administered upfront for 5 years, or for 2-3 years followed by third generation aromatase inhibitors (AIs) for 3-2 years[22-29]
In postmenopausal women, tamoxifen is an alternative to AIs:
1. **For patients who refuse AIs;**
2. **For patients for whom AIs are contraindicated or who develop severe toxicities (especially musculoskeletal).**

EXTENDED THERAPY WITH TAMOXIFEN
In patients with resected ER-positive and/or PgR positive breast cancer who are still premenopausal or perimenopausal after 5 years of adjuvant hormone therapy with tamoxifen, continuation of tamoxifen for a further 5 years can be considered[13-14] (Clinical recommendation: WEAK POSITIVE).

The continuation of tamoxifen beyond the fifth year for a total duration of 10 years significantly reduces the risk of recurrence, breast cancer mortality, and overall mortality.[13-14] The reduction in the risk of recurrence and death is time-dependent and becomes clinically significant after 10 years of diagnosis: the rate ratio [RR] for recurrence at 10 years is 0.75 in the ATLAS study and 0.86 in the aTTom study, while the RR at 10 years for mortality from breast cancer is 0.71 and 0.77, respectively. The continuation of tamoxifen leads to an increase in the cumulative risk of endometrial carcinoma, with an absolute increase in mortality from endometrial carcinoma ranging from 0.2% to 0.5%.

- PHARMACOGENOMICS: TAMOXIFEN AND CYP2D6 - CYP2C19
- SSRIs (selective serotonin reuptake inhibitors), also used for the treatment of hot flashes in patients taking tamoxifen or for depressive syndrome, may interfere with drug metabolism by inhibiting CYP2D6. In one study, a clinically significant interaction between tamoxifen and CYP2D6 inhibitors (paroxetine and fluoxetine) was demonstrated, leading to an increased risk of recurrence of breast cancer in patients using the two drugs concomitantly (HR=1.92; p<0.001).[30]

Therefore, pending further data, if the use of an SSRI is indicated in patients treated with tamoxifen, it would currently be preferable to prescribe citalopram, escitalopram, and venlafaxine.

2-AROMATASE INHIBITORS

In postmenopausal patients with resected ER-positive and/or PgR-positive breast cancer who are candidates for adjuvant hormone therapy, a treatment course including an aromatase inhibitors should be considered as first-line treatment[3] (strength of clinical recommendation: STRONG POSITIVE).

CLINICAL QUESTION No. 7 (Figure 8)

Several randomized studies have compared the efficacy of AIs vs. tamoxifen, with different schedules of administrations. An EBCTCG meta-analysis was performed on the individual data of the 31,920 postmenopausal patients enrolled in these studies: postmenopausal AIs reduce the risk of DFS events and breast cancer-related mortality, both when administered for 5 years (upfront strategy) and when administered for 3-2 years after 2-3 years of tamoxifen (switch strategy). 5 years of AIs reduce breast cancer mortality at 10 years by about 15% compared to 5 years of tamoxifen (12.1% vs 14.2%; RR 0.85; 0.75-0.96; 2p=0.009)[3], while switching to 3-2 years of AIs after 2-3 years of tamoxifen reduces breast cancer mortality at 10 years by 1.4% compared to 5 years of tamoxifen (8.7% vs 10.1%; 2p=0.015) **(SIGN Level of Evidence 1+)**.

SIGN Quality of Evidence	Clinical recommendation	Strength of clinical recommendation
A	In postmenopausal patients with resected ER-positive and/or PgR-positive breast cancer candidates for adjuvant hormone therapy, therapy including aromatase inhibitors should be considered as first-line treatment[125]	**Strong Positive**

- The treatment couldincludes a monotherapy with aromatase inhibitors for 5 years or a sequence of tamoxifen administered for 2-3 years followed by antiaromatase for 3-2 years. *Extension of aromatase inhibitor therapy after the fifth year was evaluated in the MA.17R study* (see section on EXTENDED STRATEGY).
- Based on data from the MA2731 and FATA32 studies, non-steroidal AIs (anastrozole, letrozole) and steroidal AIs (exemestane) should be considered comparablein terms of efficacy.

- In premenopausal women, the administration of AIs is unable to adequately suppress the ovarian synthesis of estrogen, and may be associated with the development of benign ovarian disease.
Amenorrhea developed during (neo)adjuvant chemotherapy by women who were premenopausal at the time of diagnosis cannot be considered aspostmenopausal status: the ovarian production of estrogen may actually persist despite the absence of menstruation.
In premenopausal patients who develop amenorrhea during chemotherapy, an evaluation of circulating levels of FSH, LH, and estradiol should be performed:
-   If these levels fall within the pre/perimenopausal range, hormone therapy with tamoxifen ± LHRHa or with exemestane + LHRHa should be administered (see related LHRH section and GRADE Recommendation);
-   If these levels fall within the postmenopausal range, hormone therapy with an antiaromatase can be administered, with periodic assessment of circulating levels of FSH, LH, and estradiol.
-   In male breast cancer, tamoxifen remains the standard adjuvant endocrine therapy (see section 11.2).

RESULTS OF STUDIES WITH AROMATASE INHIBITORS: UPFRONT STRATEGY

Two randomized phase III trials compared tamoxifen for 5 years vs AI for 5 years (anastrozole in the ATAC study, letrozole in the BIG 1-98 study).[33-35] The results of these studies have been combined in a meta-analysis: the upfront use of AIs for 5 years compared to 5 years of tamoxifen determines an absolute advantage in DFS of 2.9% at 5 years and 3.9% at 8 years (p<0.00001), without advantage in OS or mortality from breast cancer. The advantage in DFS is more evident in terms of of contralateral breast cancer (HR=0.59; p=0.0009) and local recurrence (HR=0.70; p=0.003), while is less evident for distant recurrence (HR=0.82; p=0.002)[36].

RESULTS OF STUDIES WITH AROMATASE INHIBITORS: SEQUENTIAL STRATEGY

Effectiveness of the switch strategy compared to upfront tamoxifen

Five randomized trials compared tamoxifen for 5 years with tamoxifen for 2-3 years followed by AIs for 3-2 years (IES, ABCSG-8, ARNO 95, N-SAS BC03, ITA).[22-27] A meta-analysis was conducted on the results of these studies: the sequential strategy vs upfront tamoxifen resulted in an advantage in 5-year and 8-year DFS of 3.1% and 3.6%, respectively, (p<0.00001), of 1.1% and 2.2% in OS (p=0.004) and in an absolute reduction of breast cancer specific mortality of 0.7% and 1.7%, respectively (p=0.02).

Effectiveness of switch strategy compared to upfront AIs

The direct comparison between upfront aromatase inhibitor therapy and switch therapy was evaluated in three randomized trials: the BIG 1-98 trial,[34,35] the TEAM trial,[37] and the FATA trial.[32] None of these studies showed statistically significant differences in DFS and OS. In addition, no significant differences in terms of adverse events emerged. In the FATA study, the incidence of pathological fractures was comparable between the group of patients receiving switch therapy (4%) and the group receiving upfront AIs (5%).[32]
The EBCTCG meta-analysis of individual data from patients enrolled in randomized trials comparing 5 years of AIs to 2-3 years of Tamoxifen followed by 3-2 years of AIs showed a statistically significant difference in DFS between upfront and switch strategy (HR=0.9; 95%CI 0.81-0.99; p=0.045), but with an absolute benefit of little clinical significance (1.1% at 5 years of follow-up, 0.7% at 7 years).[3] No significant differences were observed in OS.

RESULTS OF STUDIES WITH AROMATASE INHIBITORS: EXTENDED STRATEGY

The decision to extend hormone therapy beyond the fifth year must be taken after assessing the residual risk of recurrence. In postmenopausal women with ER-positive and/or PgR-positive infiltrating breast cancer who have completed 5 years of adjuvant tamoxifen, the use of antiaromatase or 5 years should be considered, as the MA-17 study showed a risk reduction for recurrence in the letrozole arm, and a [15,17] a reduction of the risk of death in women with positive lymph node tumors (Clinical recommendation: STRONG POSITIVE).

An unplanned subgroup analysis showed a significantly higher benefit in DFS, DDFS and OS for patients who were premenopausal at the time of diagnosis and entered menopause during the adjuvant treatment compared to patients who were already menopausal at diagnosis.[16]

AIs for 10 years

In postmenopausal women with ER-positive and/or PgR-positive infiltrating breast cancer, the extension of aromatase inhibitor therapy after the fifth year should be considered according to data from the MA.17R study, which showed an advantage in DFS with the extension of adjuvant letrozole for an additional 5 years, after 5 years of aromatase inhibitors administered upfront or preceded by tamoxifen.[19] No advantage was found in OS. It should be noted that about 70% of patients enrolled in both arms of the study had received tamoxifen for over 4.5 years, and therefore had already received extended adjuvant hormone therapy with tamoxifen for 5 years + AIs for a further 5 years.

3- OVARIAN SUPPRESSION

OVARIAN SUPPRESSION IN ADJUVANT HORMONE THERAPY IN PREMENOPAUSAL WOMEN.
The SOFT study and the TEXT study[20,21,38] are the two main randomized studies that evaluated the role of ovarian function suppression (OFS) in premenopausal women with hormone-responsive breast cancer. The SOFT study evaluated the role of OFS in addition to tamoxifen or exemestane vs tamoxifen therapy alone (randomization: 1) tamoxifen, 2) ovarian suppression + tamoxifen, 3) ovarian suppression + exemestane). The TEXT study randomized patients to OFS + tamoxifen vs OFS + exemestane.

In the SOFT study, at a median follow-up of 5.6 years, the addition of OFS to tamoxifen did not produce a significant advantage in DFS in the overall study population, while a trend in favor of ovarian suppression emerged in the group of patients at highest risk of recurrence: 1) patients who had received adjuvant chemotherapy (HR=.78; 95% CI, 0,60-1,02), 2) and patients under 35 years of age, 94% of whom had received adjuvant chemotherapy (DFS at 5 years 78,9%, 95% CI 69,8-85,5 vs 67,7%, 95% CI 57,3-76).[20]
The study update at a median follow-up of 7.4 years has recently been published:[21] the addition of ovarian suppression to tamoxifen resulted in a statistically significant advantage in DFS across the entire study population, with a reduction in the recurrence risk of 24% (HR=0.76; 95%CI 0.62-0.93; p=0.009), and an absolute benefit of 4.1% (83.2% vs 78.9%). Overall survival was also significantly better in women with ovarian suppression than in women treated with tamoxifen alone (HR = 0.67; 95% CI, 0.48 to 0.92; P=0.01). There is still no significant difference in DFS and OS in the subgroup of patients not previously treated with chemotherapy. Therefore, the vote on GRADE QUESTION No. 1 (CLINICAL QUESTION No. 8) was repeated in the light of the updated data, but the recommendation remained unchanged.

CLINICAL QUESTION No. 8 (Refer to GRADE Question No. 1) (Figure 8)

In low-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, is the addition of ovarian suppression to tamoxifen recommended?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Moderate	In low-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, the addition of ovarian suppression to tamoxifen should not be considered	**Conditional Negative**

See Chapter 14 - Recommendations according to GRADE methodology

CLINICAL QUESTION No. 9 (Refer to GRADE Question No. 2) (Figure 8)

In high-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, is the addition of ovarian suppression to tamoxifen recommended?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Moderate	In high-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, the addition of ovarian suppression to tamoxifen should be considered as first option	**Strong Positive**

See chapter 14 - Recommendations according to GRADE methodology

The combination of LHRHa + AIs was versus LHRHa + tamoxifen was evaluated in two randomized trials. In the Austrian study (ABCSG-12), 1,803 premenopausal women with stage I-II hormone-responsive tumors were randomized to receive goserelin and tamoxifen or goserelin and anastrozole for 3 years. At a median follow-up of 62 months there were no differences in DFS between the two arms of hormone therapy, while OS was significantly lower in patients treated with anastrozole, perhaps due to differences in the treatments administered at the onset of disease.[39,40]

A joint analysis of two randomized phase III studies, SOFT and TEXT, respectively, involving more than 5,700 women with ER and/or PgR positive breast cancer has been published to answer the question about the role of aromatase inhibitors in premenopausal women. In 2011, the Steering Committee decided to carry out a joint analysis of the two trials in order to encourage earlier maturation of the results.[38] This analysis included 4,690 patients. The TEXT and SOFT trials assigned patients to one of the following treatments: 1. tamoxifen with ovarian function suppression (T+OFS), 2. exemestane with ovarian function suppression (E+OFS). Ovarian function suppression was achieved by using one of the following approaches: analogue LHRH (tryptorelin), oophorectomy, ovarian irradiation.

At a median follow-up of 68 months, women who received E+OFS achieved a significant advantage in DFS (HR=0.72; 95% CI 0.60-0.85; p<0.001) compared to women treated with T+OFS. In particular, 5-year DFS was 91.1% vs 87.3% (E+OFS vs T+OFS). Areduction in the risk of local recurrence (HR=0.66, 95% CI 0.55-0.80; p<0.001) and in the risk of distant recurrence (HR=0.78, 95% CI 0.62- 0.97; p=0.02) were observed in patients who received E+OFS. No significant differences emerged in overall survival (HR=1.14, 95% CI 0.86-1.51) between the two treatments (5-year OS in E+OFS vs T+OFS: 95.9% vs 96.9%).

Data updated at a median follow-up of 9 years have recently been published:[21] showing the persistence of a statistically significant DFS advantage in women treated with exemestane + ovarian suppression (HR=0.77, 95% CI 0.67-0.90; p<0.001). The 8-year DFS was 86.8% in the exemestane arm + ovarian suppression vs 82.8% in the tamoxifen arm + ovarian suppression. Similarly, BCFI and DDFS were also significantly increased in the exemestane + OS arm, while overall survival continues to be comparable in the two treatment arms. In terms of side effects, a higher incidence of arthromyalgia, osteoporosis, bone fractures and menopausal symptoms (vaginal dryness, loss of libido, dyspareunia) were observed in the E+OFS group. On the other hand, among women treated with T+OFS, there was greater evidence of thromboembolic events, hot flashes, sweating and urinary incontinence.

Patients enrolled in the study completed a Quality of Life Questionnaire (QoL) comprising various global and symptom-related indicators at different intervals (at baseline, every 6 months for 24 months, and annually in years 3 to 6).[41] The differences in terms of variation of QoL from baseline between the two treatments were evaluated at 6, 24 and 60 months. At the time of analysis, the median follow-up was 5.7 years. Treatment with tamoxifen + ovarian suppression generated more *hot flushes* and sweating during the 5-year period than treatment with exemestane + ovarian suppression, although a progressive improvement of these symptoms was observed. Patients who received exemestane + ovarian suppression reported increased vaginal dryness, loss of sexual interest and difficulty in achieving excitement. These differences were maintained over time. A higher incidence of bone or joint pain was observed, especially in the short term, among patients who received exemestane + SFO. Changes from baseline in global QoL indicators were modest and similar between the two therapeutic regimens over the 5 years.

The conflicting results of the Austrian ABCSG-12 study and the combined analysis of the SOFT-TEXT studies are attributable to several factors: 1) different duration of the hormone therapy (hormone therapy in the ABCSG study was administered for only 3 years, while in TEXT and SOFT the duration of therapy was 5 years); 2) differences in study populations (patients enrolled in the ABCSG-12 were at low risk of recurrence: none had received adjuvant chemotherapy, and only 35% of them had an N+ disease); 3) the higher statistical power of SOFT-TEXT, which had a much higher number of DFS and OS events.

CLINICAL QUESTION No. 10 (Refer to GRADE Question No. 3) (Figure 8)

In high-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, candidates for ovarian suppression, is treatment with aromatase inhibitors recommended compared to treatment with tamoxifen?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Moderate	In high-risk premenopausal women with resected hormone-receptor positive, HER2 negative breast cancer, candidates for ovarian suppression, treatment with aromatase inhibitors could be considered.	**Conditional Positive**

See chapter 14 - Recommendations according to GRADE methodology

LHRH-ANALOGUES FOR PREVENTING CHEMOTHERAPY-INDUCED AMENORRHEA (SEE GUIDELINES FOR FERTILITY PRESERVATION IN CANCER PATIENTS, AIOM 2017)

The use of LHRH analogues to preserve ovarian fuction during chemotherapy has been investigated in several phase III studies, with conflicting results.[42-48] The mechanism by which analogues protect gonadal function is unknown.
Recently, a meta-analysis has been conducted on the individual data of patients enrolled in the main randomized phase III studies evaluating the protective effect of LHRHa during CT on ovarian function and fertility.[49] The meta-analysis included individual data of patients enrolled in the PROMISE, POEMS, OPTION, GBG-37 ZORO, and Moffitt-led studies. The primary endpoints were premature ovarian failure (as specifically defined in each trial) and the incidence of post-treatment pregnancies. The incidence of premature ovarian failure was significantly decreased in patients who received LHRHa (14.1% vs 30.9%; OR=0.38, 95% CI 0.26-0.57; p<0.001), and the incidence of pregnancies was significantly increased (10.3% vs 5.5%; incidence rate ratio=1.83; 95% CI, 1.06 to 3.15; P = 0.03).

In the light of current evidence, the use of LHRH-analogue during chemotherapy for the prevention of chemotherapy-induced menopause in younger patients who wish to preserve ovarian function can be considered.

5.2.3 Adjuvant chemotherapy

GENERAL CONSIDERATIONS: TIMING AND DURATION
Before describing the different adjuvant chemotherapy regimens, it is important to underline two general elements:

1- The optimal time interval between surgery and initiation of adjuvant chemotherapy has not been clearly established yet.[50-51] A recent analysis conducted on 24,843 patients shows that the interval between surgery and chemotherapy initiation influences the clinical outcome, with a significant detrimental effect for intervals of more than 90 days, especially for patients with triple-negative tumors.[52] The recommendation to start the adjuvant chemotherapy treatment as soon as the patient has recovered from surgery, and in any case no later than 90 days after surgery, remains valid.

2- The optimal duration of adjuvant chemotherapy is 4 to 8 cycles.

ADJUVANT CHEMOTHERAPY REGIMENS

In patients with resected breast cancer candidates for adjuvant chemotherapy, polychemotherapy should be considered, since data from meta-analyses and clinical studies show that polychemotherapy is superior to monochemotherapy in terms of DFS and OS.[1,53]

Table 5.2 shows the main adjuvant chemotherapy regimens.

Table 5.2. ADJUVANT SYSTEMIC THERAPY. MAIN CHEMOTHERAPY REGIMENS AND TRASTUZUMAB SCHEMES

Regimen	Drugs	Dose and schedule	Number of cycles	Notes
CMF-like regimens				
Classic CMF	Cyclophosphamide	100 mg/day oral, days 1➔14 - every 28 days	6	
	Methotrexate	40 mg/sqm iv, days 1, 8 - every 28 days		
	5-Fluorouracil	600 mg/sqm iv, days 1, 8 - every 28 days		
Intravenous CMF	Cyclophosphamide	600 mg/sqm iv, days 1, 8 - every 28 days	6	
	Methotrexate	40 mg/sqm iv, days 1, 8 - every 28 days		
	5-Fluorouracil	600 mg/sqm iv, days 1, 8 - every 28 days		
Anthracycline regimens without taxanes				
AC	Adriamycin or Epirubicin (for epirubicin dosage see row below)	60 mg/sqm day 1 - every 21 days	4	
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
A/E → CMF	Adriamycin or Epirubicin (for epirubicin dosage see row below)	75 mg/sqm day 1 - every 21 days	4	
	Epirubicin	90 mg/sqm day 1 - every 21 days		
	CMF	As classic or intravenous CMF	4	
CAF	Cyclophosphamide	100 mg/day oral, days 1➔14- every 28 days	6	
	Adriamycin	30 mg/sqm iv, days 1, 8 - every 28 days		
	5-fluorouracil	500 mg/sqm iv, days 1, 8 - every 28 days		
Canadian CEF	Cyclophosphamide	75 mg/day oral days 1➔14 - every 28 days	6	
	Epirubicin	60 mg/sqm iv, days 1, 8 - every 28 days		
	5-fluorouracil	600 mg/sqm iv, days 1, 8 - every 28 days		

Regimen	Drugs	Dose and schedule	Number of cycles	Notes
FAC	5-fluorouracil	500-600 mg/sqm iv, day 1 - every 21 days	6	
	Adriamycin	50-60 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	500-600 mg/sqm iv, day 1 - every 21 days		
FEC	5-fluorouracil	500-600 mg/sqm iv, day 1 - every 21 days	6	
	Epirubicin	75-100 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	500-600 mg/sqm iv, day 1 - every 21 days		
Taxane-containing regimens with or without anthracyclines				
AC/EC → weekly paclitaxel	Adriamycin or Epirubicin (for epirubicin dosage see row below)	60 mg/sqm iv, day 1 - every 21 days	4	
	Epiribicin	90 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
	Paclitaxel	80 mg/sqm/week iv	12 weeks	
FEC → weekly paclitaxel	5-fluorouracil	600 mg/sqm iv, day 1 - every 21 days	4	
	Epirubicin	90 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
	Paclitaxel	100 mg/sqm/week iv	8	
AC → docetaxel	Adriamycin	60 mg/sqm iv, day 1 - every 21 days	4	
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
	Docetaxel	100 mg/sqm iv, day 1 - every 21 days	4	
FEC 100 → docetaxel	5-fluorouracil	500 mg/sqm iv, day 1 - every 21 days	3	
	Epirubicin	100 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	500 mg/sqm iv, day 1 - every 21 days		
	Docetaxel	100 mg/sqm iv, day 1 - every 21 days	3	
TAC	Docetaxel	75 mg/sqm iv, day 1 - every 21 days	6	With the support of G-CSF as
	Adriamycin	50 mg/sqm iv, day 1 - every 21 days		

Regimen	Drugs	Dose and schedule	Number of cycles	Notes
	Cyclophosphamide	500 mg/sqm iv, day 1 - every 21 days		primary prophylaxis (for risk of febrile neutropenia >20 %).
TC	Docetaxel	75 mg/sqm iv, day 1 - every 21 days	4	
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
AC/EC → dose-dense paclitaxel	Adriamycin or Epirubicin (for epirubicin dosage see row below)	60 mg/sqm iv, day 1-every 15 days	4	G-CSF from day + 3 to day +10 or pegylated G-CSF 24 hours after chemotherapy
	Epirubicin	90 mg/sqm iv, day 1 - every 15 days		
	Cyclophosphamide	600 mg/sqm iv, days 1 - every 15 days		
	Paclitaxel	175 mg/sqm iv, day 1 - every 15 days	4	

Polychemotherapy schemes

Introductory note: A synthesis tool of all available scientific evidence on adjuvant chemotherapy in breast cancer is represented by periodic meta-analyses of data collected from randomized trials conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Unless otherwise specified, reference will be made in this section to meta-analyses by the EBCTCG.[1,53]

Available polychemotherapy regimens for breast cancer can be classified as first, second and third generation regimens.

1- *1st generation regimens: based on the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF), which, when administered x 6-12 cycles, reduce the 10-year risk of recurrence by 30% on average (RR=0.70; 95%:0.63-0.77) and overall mortality by 16% (RR=0.84; 95%:0.76-0.93). They are scarcely used today. For example, the CMF scheme may be used in patients with contraindications to anthracyclines (consider the docetaxel and cyclophosphamide x4 regimen as an alternative in such patients) or in patients who firmly refuse complete alopecia.*
CMF has low tolerability in elderly patients, as described in chapter 10.4.
In the adjuvant phase, administration on days 1 and 8 every 28 days is recommended, rather than every 21 days, since no study has compared these two different schedules in the adjuvant setting (in the metastatic setting, administration on days 1 and 8 every 28 days was superior to administration every 21 days).[54]

2- *2nd generation regimens: these are regimens containing anthracyclines, and on average they are more effective than CMF-like regimens. However, it is clear that not all regimens containing anthracyclines are equally effective. It is possible to distinguish between:*
- Low-efficacy regimens (AC/EC x 4 cycles). These regimens are substantially equivalent to CMF in terms of therapeutic efficacy but have different toxicity profiles, since gonadal toxicity is reduced but alopecia and cardiotoxicity are increased;
- High-efficacy regimens: FEC/CEF; FAC/CAF usually administered for 6 cycles.
These schemes are more effective than CMF, resulting in a further reduction of the risk of recurrence (RR=0.89) by 11% and mortality (RR=0.84) by 16%.[1]

However, these regimens are burdened by increased acute and delayed toxicity (which is rare but includes the development of congestive heart failure and acute myeloid leukemia).[55] The frequency of these toxic effects, however, although probably underestimated, does not significantly affect the reduction in overall mortality demonstrated with the use of treatments containing anthracyclines compared to CMF in the 2012 meta-analysis.[1]

3- *3rd generation regimens: these include regimens containing anthracyclines and taxanes administered sequentially (AC/EC/FEC x 3-4 cycles followed by taxane) or in combination (TAC/TEC).* The main randomized studies comparing taxane-containing to non-taxane-containing regimens in the adjuvant treatment of patients <u>at high risk of disease recurrence</u> (positive or negative axillary lymph nodes) were included in the latest EBCTCG meta-analysis[1] **(SIGN Level of Evidence 1++).**
These third-generation regimens are on average superior to second-generation regimens and lead to a further reduction in the risk of recurrence (RR=0.87) by 13% and death (RR=0.89) by 11%.
Sequential regimens are associated with a better toxicity profile than combination regimens. In addition, sequential regimens allow to reduce the total dose of anthracyclines (and therefore reduce the incidence of cardiotoxicity). These regimens are the most widely used treatment regimens in women at moderate to high risk.

Considerations for taxane-containing chemotherapy regimens

<u>The comparison between the concomitant or sequential use of taxanes with anthracyclines, between different administration schedules and between the two available taxanes was carried out in the context of so-called 2nd generation studies.</u>

- Sequential or concomitant use of anthracyclines and taxanes

The results of the BIG 2-98 study[56] show that the sequential association of anthracyclines and taxanes, but not the concomitant association, is superior to chemotherapy with anthracyclines without taxanes. The results of the BCIRG 005 study, which compared the concomitant TAC regimen (docetaxel, adriamycin, and cyclophosphamide every 21 days, for 6 cycles) to the AC➔T sequence (adriamycin and cyclophosphamide every 21 days for 4 cycles followed by docetaxel every 21 days for 4 cycles)[57] were also recently published. Unlike the BIG2-98 study, there were no significant differences in clinical outcomes. The TAC regimen was more often associated with febrile neutropenia and thrombocytopenia, while the AC➔T regimen resulted in a higher probability of sensory neuropathy, nail changes, myalgia and fluid retention. **Overall, these results support the preference for regimens where taxane is administered sequentially with anthracyclines**.

- Sequential schedules: weekly versus three-weekly schedule and comparison between paclitaxel and docetaxel

Regarding the choice of the best taxane and schedule, the American study North American Breast Cancer Intergroup Trial E1199 compared docetaxel with paclitaxel, both administered weekly or every 3 weeks, after four cycles of AC.[58]
The first analysis published in full, at a follow-up of 63.8 months, showed no statistically significant differences between the two taxanes or between the two schedules (weekly or every 3 weeks). However, considering the three-weekly paclitaxel as the standard treatment and comparing it with the other arms, an advantage in DFS with weekly paclitaxel and with docetaxel every 3 weeks and an advantage in OS with weekly paclitaxel were shown (HR=1.32; p=0.01). With regard to toxicity, a higher incidence of febrile neutropenia, neutropenia and infections was observed with docetaxel, while neurotoxicity was more frequent with weekly paclitaxel. An update of the R1199 study to over 12 years of median follow-up has recently been published.[59] While in general this analysis also shows the superiority of weekly paclitaxel or three-weekly docetaxel over three-weekly paclitaxel in terms of DFS (statistically significant) and OS (only marginal), a subgroup analysis shows a marked advantage of weekly paclitaxel in terms of both DFS and OS in patients with triple-negative cancer.

It is therefore preferable to administer paclitaxel according to a weekly schedule (80 mg/sqm/iv/week for 12 weeks or 100 mg/sqm/iv/week for 8 weeks) or docetaxel every three weeks (100 mg/sqm/iv/every 21 days, for 3-4 cycles). In case of triple-negative tumors, the paclitaxel schedule may be the preferred choice.

- Taxane-containing regimens without anthracyclines

In order to minimize the risk of cardiotoxicity, taxane-containing regimens without anthracyclines, have been developed. The US Oncology study[60] is the only one that compared a regimen containing anthracyclines (AC: adriamycin 60 mg/sqm, cyclophosphamide 600 mg/sqm every 21 days, for 4 cycles) with a taxane-containing regimen without anthracyclines (T-Cyclo: cyclophosphamide 600 mg/sqm, docetaxel 75 mg/sqm every 21 days for 4 cycles) in the adjuvant setting, showing an advantage in DFS and, at a follow-up of 5 years, also in OS for the regimen containing docetaxel. The T-Cyclo regimen can be considered in patients with contraindications that are not candidates for anthracycline therapy and as an alternative to the CMF regimen. A recent combined analysis of 3 adjuvant chemotherapy studies (USOR 06-090, NSABP B-46/USOR 07132 and NSABP B-49) comparing T-Cyclo x 6 vs. combination regimens containing AC and a taxane (TAC x 6 in two studies, various combination regimens in the NSABP B-49 study) in a total of 4,242 patients showed, at a median follow-up of 3.3 years, that T-Cyclo x 6 is inferior to regimens containing anthracyclines and taxanes. However, the difference in absolute terms is limited and exploratory analyses suggest that the greatest benefits of anthracycline inclusion are observed in hormone-receptor negative patients and hormone-receptor positive patients with positive lymph nodes.[61]

- Dose-dense adjuvant chemotherapy

In the systematic review and meta-analysis conducted by Bonilla et al., 10 randomized trials comparing dose-dense chemotherapy with standard schedule chemotherapy in the neoadjuvant or adjuvant setting were evaluated. Dose-dense chemotherapy was associated with a significant improvement in disease free survival and overall survival, most evident in the subgroup of patients with negative hormone receptors.[62]
The GIM 2 study compared a sequence of FEC or EC X4 and taxol 175 mg/sqm x 4 administered by conventional cycling (every 3 weeks) or accelerated cycling (every 2 weeks) with pegylated growth factor support in approximately 2,000 breast cancer patients with positive axillary lymph nodes. At a median follow-up of 7 years, dose-dense therapy was associated with improved DFS and OS regardless of hormone receptor status.[63]

CLINICAL QUESTION No. 11 (Refer to GRADE Question No. 4) (Figure 4, Figure 7)

In women with resected HER2 negative breast cancer and positive lymph nodes who are candidates for chemotherapy, are dose-dense anthracycline and taxane regimens recommended compared to conventional treatment methods?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Moderate	In women with resected HER2 negative breast cancer with positive lymph nodes who are candidates for chemotherapy, dose-dense anthracycline- and taxane-containing regimens should be considered as firstoption	**Strong Positive**

See chapter 14 - Recommendations according to GRADE methodology

- The role of antimetabolites in anthracycline and taxane regimens

A possible next step in enhancing adjuvant chemotherapy regimens is to add an antimetabolite to the anthracycline → taxane sequence. Several studies evaluated the addition of capecitabine to a regimen containing anthracyclines and taxanes.[64-68]

Overall, none of these studies demonstrated an advantage in favor of the capecitabine + taxane arm in terms of DFS, and in only one study a potential benefit was observed in the subgroup of patients with triple-negative tumors.[64] Moreover, the addition of capecitabine has led to an increase in treatment-related toxicities.

Not even the addition of gemcitabine to paclitaxel after dose-dense anthracycline and cyclophosphamide has shown an improvement in DFS and OS.[69]

Chemotherapy regimens containing anthracycline followed by capecitabine in addition to the taxane or gemcitabine in addition to the taxane CANNOT be considered a therapeutic standard.

The GIM2 study evaluated not only the role of dose density, but also that of fluorouracil in addition to epirubicin and cyclophosphamide (FEC vs. EC). At a median follow-up of 7 years, there were no significant differences between FEC and EC in terms of outcomes, while EC was associated with a reduction in the incidence of neutropenia, fever and vomiting.[63] **These results suggest the omission of 5-fluorouracil from FEC-type regimens when used in sequences containing paclitaxel**.

5.2.4 Adjuvant therapy with anti-HER2 agents

Table 5.3 shows the main adjuvant therapy regimens containing trastuzumab.

In patients with resected HER2 positive breast cancer who are candidates for adjuvant chemotherapy, trastuzumab, a monoclonal antibody for the extracellular domain of HER2, should be considered as first option in addition to chemotherapy for 1 year.[4,70-75]

In patients with resected HER2 positive breast cancer who are candidates for an anthracycline regimen followed by a taxane (e.g. AC→paclitaxel), trastuzumab should be started in conjunction with the taxane and then given as monotherapy until completion of one year of treatment.

In patients with resected HER2 positive breast cancer who are candidates for an adjuvant chemotherapy regimen such as regimens containing anthracyclines or regimens containing non-sequential anthracyclines and taxanes, trastuzumab should be administered after completion of chemotherapy.[72]

In patients with resected HER2 positive breast cancer who are not candidates for treatment with anthracyclines, a chemotherapy regimen containing docetaxel and carboplatin (every 21 days) with concomitant trastuzumab can be considered. (Trastuzumab should then be continued until completion of one year of treatment).[76]

In patients with resected HER2 positive breast cancer, trastuzumab can be administered at the same time as adjuvant radiotherapy.[77]

Table 5.3. Chemotherapy regimens associated with trastuzumab

Regimen	Drugs	Dose and schedule	Number of cycles	Notes
AC/EC → paclitaxel and trastuzumab	Adriamycin or Epirubicin (for epirubicin dosage see row below)	60 mg/sqm iv, day 1- every 21 days	4	
	Epirubicin	90 mg/sqm iv, day 1- every 21 days		
	Cyclophosphamide	600 mg/sqm iv, day 1- every 21 days		
	Paclitaxel	80 mg/sqm/week	12	

	Weekly <u>or</u> three-weekly trastuzumab (see below)	4 mg/kg loading dose, 2 mg/kg/week	For 1 year	Trastuzumab started in conjunction with taxol
	Three-weekly trastuzumab	8 mg/kg loading dose, 6 mg/kg every 3 weeks	For 1 year	
AC/EC → docetaxel and trastuzumab	Adriamycin <u>or</u> Epirubicin (for epirubicin dosage see row below)	60 mg/sqm iv, day 1- every 21 days	4	
	Epirubicin	90 mg/sqm iv, day 1 - every 21 days		
	Cyclophosphamide	600 mg/sqm iv, day 1 - every 21 days		
	Docetaxel	100 mg/sqm iv, day 1 - every 21 days	4	
	Trastuzumab	8 mg/kg loading dose, 6 mg/kg every 3 weeks	1 year	Trastuzumab started in conjunction with docetaxel
TCH	Docetaxel	75 mg/sqm iv, day 1 - every 21 days	6	
	Carboplatin	AUC 6, iv every 21 days		
	Trastuzumab	8 mg/kg loading dose, 6 mg/kg every 3 weeks	1 year	Trastuzumab started with chemotherapy
T-Cyclo H	Docetaxel	75 mg/sqm iv every 21 days	4	
	Cyclophosphamide	600 mg/sqm iv every 21 days		
	Trastuzumab	8 mg/kg loading dose, 6 mg/kg every 3 weeks	1 year	Trastuzumab started with chemotherapy
Paclitaxel-Trastuzumab	Paclitaxel	80 mg/sqm/week iv	12 weeks	
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg each week. From 13 weeks, possibility of switching to 6 mg/kg every 3 weeks	1 year	Trastuzumab started with chemotherapy
Anthracycline or anthracycline + non-sequential taxanes ➔ trastuzumab	After 4-6 courses of chemotherapy, start trastuzumab	8 mg/kg loading dose, 6 mg/kg every 3 weeks	1 year	Treatment started at the end of chemotherapy

Trastuzumab is a recombinant humanized monoclonal antibody with specificity for the extracellular domain of HER2.

Six randomized trials evaluated the use of trastuzumab administered sequentially or concomitantly with adjuvant chemotherapy compared to chemotherapy alone in patients with HER-2 positive tumors (IHC 3+ or amplified FISH/CISH).[70-76,78-80]

The Cochrane meta-analysis, which also included data from the NOAH study of preoperative chemotherapy +/- trastuzumab with or without subsequent adjuvant trastuzumab, confirmed that the inclusion of trastuzumab in chemotherapy regimens for early-stage HER2 positive breast cancer reduces the risk of recurrence by 40% (HR 0.60, 95% CI 0.50-0.71) and of death by 34% (HR 0.66, 95% CI 0.57-0.77).[4]

One of the pivotal studies of adjuvant trastuzumab, the NCCTG 9831 study, also allowed to establish the best administration schedule. The study compared 3 treatment arms: AC→paclitaxel, AC→paclitaxel + trastuzumab administered in conjunction with paclitaxel and continued for 1 year, AC→paclitaxel→ trastuzumab administered sequentially after chemotherapy. The comparison between the two arms containing trastuzumab showed an advantage with the concomitant schedule over the sequential one (5-year DFS rates 84.4% and 80.1%, absolute difference 4.3%).[72]

Data from the 9831 study indicate that concomitant administration of trastuzumab and radiotherapy does not increase the risk of acute adverse events.[77]

CARDIOTOXICITY OF TRASTUZUMAB

The Cochrane meta-analysis reported an increased risk of cardiotoxicity (congestive failure) for patients treated with trastuzumab, with a RR of 5.41 (95% CI 3.00-8.72) and an absolute incidence of 2.5% vs 0.4%.[4] A recent retrospective study conducted in 14 institutions in the United States involved about 12,500 women who had received adjuvant treatments.[81] The study reported a cumulative incidence of significant cardiotoxicity (heart failure and/or cardiomyopathy) at 5 years of 12.1% and 20.1% in women treated with trastuzumab without (0.9% of women in the sample) and with (3.5% of the sample) anthracyclines, respectively. Although it is unclear whetehr these high rates of cardiotoxicity are a faithful representation of reality, they highlight once again the need for a careful assessment of the benefit-risk ratio of treatment with trastuzumab, especially in patients with a lower risk of recurrence and/or a higher risk of cardiotoxicity. This is also one of the reasons that led to the design of clinical studies aimed at evaluating potentially less toxic treatments for these patients, especially if at low risk of recurrence.

POSSIBILITY OF DE-ESCALATION OF ADJUVANT TREATMENT IN PATIENTS WITH HER2 POSITIVE TUMOR

   1- Treatment of patients with HER2 positive T1a/b, N0 tumor

Most of the main studies evaluating the addition of trastuzumab to chemotherapy allowed the inclusion of patients with negative axillary lymph nodes (HERA[73] and BCIRG 006[76] and a limited group of patients in the NCCTG N98-31[72] and FinHer[78] studies), provided that the tumor diameter was >1 cm. In studies where this population was more widely represented (HERA trial and BCIRG 006), patients with stage I tumors (pT1c, N0) benefited from the addition of trastuzumab in a similar way as patients with higher stage tumors.[73,76] With regard to tumors with a diameter of one centimeter or less (pT1a and pT1b) and negative axillary lymph nodes (pN0), 6-10% of which show HER2overexpression and/or amplification, there are no prospective data from randomized studies on the possible benefit of adjuvant trastuzumab, but only retrospective data.[82-86]

CLINICAL QUESTION No. 12 (Figure 5, Figure 6)

In patients with operated HER2 positive breast cancer with a diameter of 1 cm or less and pN0, is adjuvant therapy including trastuzumab recommended rather than adjuvant therapy alone?

Retrospective studies have shown that these cancers have a worse prognosis than their HER2 negative counterparts.[87,88] In addition, 5 retrospective studies with a small sample size suggest that patients with small

HER2 positive tumors (pT $\leq$1 cm) and negative axillary lymph nodes can benefit from an adjuvant therapy including trastuzumab, although the estimate of this benefit varies from study to study and is not always significant (**SIGN Level of evidence 3**).[82-86]

On the basis of these considerations, although it is reasonable to consider the use of adjuvant trastuzumab in small tumors (pT1a/b), other factors such as degree of differentiation, proliferative activity, age of the patient and any comorbidities must also be carefully evaluated. The value of hormone receptor status is more controversial.[89]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
D	In patients with operated HER2 positive breast cancer with a diameter of 1 cm or less and pN0, adjuvant therapy including trastuzumab could be considered.[82-86]	**Conditional Positive**

One aspect of the treatment of HER2 positive tumors with a low risk of recurrence is the development of regimens in which the chemotherapy component is weakened, for example, by the omission of anthracyclines and by reducing the overall duration of treatment, without changing the duration of trastuzumab administration.

2- Chemotherapy regimens without anthracyclines + trastuzumab

One of the pivotal studies of adjuvant trastuzumab, the BCIRG 006 study, compared a regimen containing anthracyclines and docetaxel given sequentially versus the same regimen in association with trastuzumab administered concomitantly with docetaxel versus a regimen not containing anthracyclines (carboplatin and docetaxel) with trastuzumab administered concomitantly.[76] High-risk patients with negative axillary lymph nodes (about 30%) and positive lymph nodes were enrolled in the study. At a median follow-up of 65 months, a significant advantage in DFS and OS was observed with both regimens containing trastuzumab (with or without anthracycline) compared to chemotherapy alone, and a non-significant difference between the two arms containing trastuzumab. However, the study design did not include an assessment of non-inferiority of the regimen not containing anthracyclines to the regimen with anthracyclines. Moreover, the TCH regimen was better tolerated, with a lower incidence of both acute (heart failure) and chronic (acute leukemia, myelodysplastic syndrome) side effects.

Two phase II single-arm studies, described in CLINICAL QUESTION No. 13, were published more recently.

CLINICAL QUESTION No. 13 (Figure 5, Figure 6)

In women with operated HER2 positive breast cancer, tumor diameter <3 cm, with negative axillary lymph nodes or with maximum one micrometastatic axillary lymph node confirmed after complete axillary dissection, is a paclitaxel 80 mg/m²/week regimen with concomitant trastuzumab given for one year recommended rather than similar regimens including anthracyclines?

A phase II study recently presented by the US Oncology cooperative group enrolled a total of 493 women with operated HER2 positive stage <IIIA/B tumors. The chemotherapy regimen administered was T-Cyclo (docetaxel 75 mg/sqm and cyclophosphamide 600 mg every 3 weeks) + trastuzumab.[90] At a median follow-up of 3 years, 3y-DFS and 3y-OS were 96.9% and 98.7%, respectively. The non-randomized design and the short duration of follow-up do not allow to assign a high level of evidence to this study **(SIGN Level of evidence 3).** However, the T-Cyclo regimen with trastuzumab may be used in patients with low-risk breast cancer (T ≤2 cm, N0), who may or may not be eligible for treatment with anthracycline regimens or more toxic regimens.

Similar considerations apply to another phase II study, which enrolled 410 patients with HER2 positive tumors of less than 3 cm in diameter and negative axillary lymph nodes, or with a single micrometastatic lymph node confirmed after axillary dissection **(SIGN Level of evidence 3)**.[91] In this study, weekly paclitaxel at a dose of 80 mg/sqm/week was used concomitantly with weekly trastuzumab (4 mg/kg loading dose followed by weekly 2 mg/kg doses) for a total of 12 administrations. At the end of the combination treatment, the investigators were given the opportunity to continue to administer weekly trastuzumab or switch to the three-weekly schedule (6 mg/kg every 3 weeks) to complete one year of therapy with this monoclonal antibody. Although patients with a micrometastatic lymph node were eligible for this study, the majority were N0 (400 out of 406 evaluable patients). At a median follow-up of 4 years, only 12 patients had recurrence events or died. Invasive disease-free survival was 98.7%. It should be noted that about 50% of patients of this study had tumors with a diameter of ≤1 cm. However, the low number of events does not allow analysis by information subgroups. At a median follow-up of 6.5 years, the number of patients with recurrence or death events was 23, with a 7-year disease-free survival rate of 93.3%.[92]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
D	In women with operated HER2 positive breast cancer, with tumor diameter <3 cm and negative axillary lymph nodes or with maximum one micrometastatic axillary lymph node confirmed after complete axillary dissection, a regimen with paclitaxel 80 mg/sqm/week with concomitant trastuzumab for one year, could be considered.[91,92]	**Conditional Positive**

3- Treatment with trastuzumab for less than 1 year

The indication to administer trastuzumab for 1 year is based on the results of pivot studies which, in most cases, compared regimens without trastuzumab with regimens containing trastuzumab for the duration of 1 year.[70-73,76,80] To date, treatment with trastuzumab for 1 year remains the standard.

The HERA study[73] also included a third arm of trastuzumab treatment for a duration of 2 years. The final results of the comparison between the two different trastuzumab regimens at 11 years of median follow-up did not show any statistically significant difference in terms of DFS (HR 1.02, 95% CI 0.89-1.17). At 10 years, DFS rates were 69% for both arms receiving trastuzumab.[93]

In the FINHER study,[78,79] another pivot study of adjuvant trastuzumab, 1,010 high-risk patients with positive or negative lymph nodes were randomized to receive 3 cycles of vinorelbine or docetaxel, followed by 3 cycles of FEC (both groups).

The subgroup of 232 women with HER2 positive tumor was further randomized to receive or not receive trastuzumab concomitantly with vinorelbin or docetaxel for a total duration of only nine weeks. At a median follow-up of 62 months, in the subgroup of 232 patients with HER2 positive disease, a non-statistically-significant advantage in distant recurrence-free survival was shown, with HR of 0.65 (95% CI 0.38-1.12). In an exploratory analysis, the benefit was statistically significant in the subgroup of patients treated with docetaxel concomitantly with trastuzumab. In the exploratory subgroup of patients treated with docetaxel, the addition of trastuzumab for 9 weeks resulted in a significant reduction in the risk of distant recurrence (HR 0.32, p=0.029).

The equivalent efficacy of administering trastuzumab for one or two years and the potentially equal efficacy of a shorter duration of treatment suggested by the FINHER study make the evaluation of trastuzumab treatment for less than one year an important research objective. Of the studies conducted to assess this hypothesis, the first one that produced results was the PHARE study.[94] In this study, designed to evaluate the non-inferiority of 6 vs 12 months of treatment with trastuzumab added to chemotherapy (sequential or concomitant approach), the administration of trastuzumab for 6 months was associated with a 28% increase in the risk of recurrence (HR=1.28; 95% CI 1.05-1.56). Although not conclusive with respect to the hypothesis of non-inferiority, since the confidence interval includes the value 1.15 chosen by the authors as the limit below which 6 months could be considered non-inferior to 12 months, these results consolidate the choice of 12 months of trastuzumab as a therapeutic standard. Similar conclusions have been drawn from another recent study[95] in which 481 high-risk patients with operated breast cancer and positive or negative axillary lymph nodes were randomized to receive 12 or 6 months of adjuvant trastuzumab concomitantly with 4 cycles of dose-dense docetaxel (75 mg/sqm every 14 days) with GCSF support. All patients received 4 upfront cycles according to the FEC dose-dense scheme (5-fluorouracil 700 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 700 mg/m^2 every 14 days) with GCSF support. The primary endpoint of the study was 3-year disease-free survival. After 47 and 51 months of median follow-up, 17 (7.1%) and 28 (11.7%) recurrences were recorded in the 12- and 6-month group, respectively (P = 0.08). Three-year DFS was 95.7% versus 93.3% in favor of the 12 months group (hazard ratio = 1.57; 95% confidence interval 0.86-2.10; P = 0.137). No differences in overall survival and cardiac toxicity were observed between the two groups.[213]

At the ASCO 2017 Congress, the phase III Short-HER study[96] was presented, comparing a standard adjuvant treatment (AC or EC for 4 cycles followed by three-weekly docetaxel and trastuzumab for 4 cycles followed by three-weekly trastuzumab for 14 cycles) with a short treatment containing three-weekly docetaxel for 3 cycles plus weekly trastuzumab for 9 weeks followed by FEC for 3 cycles. The study was designed as a non-inferiority study. The statistical plan of the study was amended with a change to the statistical plan and sample size. From 2007 to 2013 the study enrolled 1,254 patients with median age 55 years and stage I (37.3%), IIA (40%), IIB (20.6%), and III (2.1%) disease; 30% of patients had 1 to 3 lymph nodes involved, 16% had ≥4 lymph nodes; 76% had hormone-receptor positive disease. At a median follow-up of 5.2 years, 5-yrs DFS was 87.5% in the standard arm and 85.4% in the control arm (HR 1.15; 90% CI, 0.91-1.46). The results showed that the upper limits of the confidence interval exceeded the preset non-inferiority limit (<1.29), and therefore the study has so far failed to demonstrate the non-inferiority of the short treatment (trastuzumab for 9 weeks) compared to standard treatment. A significant interaction between treatment arm and tumor stage was observed: there was a statistically significant benefit in favor of 1 year of trastuzumab for patients with 4 or more positive lymph nodes, whereas in the subgroup of patients with up to 3 positive lymph nodes, HR between treatments was 0.92 (95% CI 0.69-1.23), with comparable 5-year DFS rates. The incidence of cardiac toxicity was significantly lower in the short treatment arm (HR 0.32, 95% CI 0.21-0.50: p<0.0001).

The SOLD study[97] has recently been published, which randomized a total of 2,174 patients to receive three-weekly docetaxel + three-weekly trastuzumab for 9 weeks followed by concomitant FEC x 3 cycles or the same regimen followed by trastuzumab for 1 year. Even the SOLD study, while showing an absolute difference in 5-year DFS of only 2.5% between arms (90.5% 1 year, 88% 9 weeks), could not show the non-inferiority

of the short treatment, as the HR confidence interval included the non-inferiority limit (HR 1.39, 95% CI 1.12-1.72, non-inferiority limit 1.385). As in other studies, a shorter duration of trastuzumab treatment was associated with lower cardiac toxicity.

Finally, the results of the PERSEPHONE study,[98] another randomized non-inferiority study between chemotherapy + trastuzumab for 6 months or chemotherapy + trastuzumab for 12 months, were presented at the ASCO 2018 Congress. The study enrolled 4,088 patients and is the first study to demonstrate the statistically significant non-inferiority of trastuzumab administered for less than 1 year. At a median follow-up of 5.4 months, 4-year DFS rates were 89.8% in the 12-month treatment arm and 89.4% in the short treatment arm, HR 1.07 (95% CI 0.93-1.24, non-inferiority limit 1.29, p=0.01). The incidence of cardiac events was 4% in the short therapy arm versus 8% in the arm receiving trastuzumab for 1 year (p<0.0001).

ADJUVANT CHEMOTHERAPY AND DUAL ANTI-HER2 BLOCKADE

The international, open-label, randomized, phase III ALTTO study[99] compared the following treatment arms in patients with operated HER2+ breast cancer, all with duration of one year: trastuzumab (loading dose 4 mg/kg and then 2 mg/kg/week during chemotherapy or loading dose 8 mg/kg and then 6 mg/kg q21 when used alone), lapatinib (750 mg/day during chemotherapy and then 1500 mg/day when used alone), a sequential treatment with the two agents (trastuzumab → lapatinib) starting with 12 doses of trastuzumab followed, after 6 weeks of washout, by 34 weeks of lapatinib at a dose of 1500 mg/day, and a combination treatment with the two agents, with trastuzumab at the doses mentioned above and lapatinib at the dose of 750 mg/day during chemotherapy (reduced from the initial dose of 1000 mg/day as a result of the toxicity observed, especially in terms of diarrhea).[231] Investigators could adopt one of the following therapeutic strategies: initiation of anti-HER2 therapy upon completion of chemotherapy (design 1) or initiation of anti-HER2 therapy in conjunction with chemotherapy in the treatment phase with paclitaxel or docetaxel (design 2), or an anthracycline-free regimen with 6 cycles of docetaxel and carboplatin and anti-HER2 therapy administered in conjunction with chemotherapy (design 2B, introduced towards the end of the enrolment period in North American Centers). Between June 2007 and July 2011, 8,381 patients were enrolled. In 2011, due to the futility of demonstrating that lapatinib was not inferior to trastuzumab, the arm with lapatinib alone was closed and disease-free patients were offered the opportunity to receive trastuzumab. In accordance with the protocol, the analysis carried out after a median follow-up of 4.5 years showed a 16% reduction in the risk of recurrence with lapatinib+trastuzumab compared to trastuzumab (555 DFS events; HR 0.84; 97.5% IC, 0.70-1.02; P = 0.048, not significant according to the statistical design, which predicted a p value ≤0.025). A 4% reduction was observed when comparing trastuzumab→lapatinib to trastuzumab (HR 0.96; 97.5% IC 0.80-1.15; p = 0.61). Patients treated with lapatinib experienced more side effects, in terms of diarrhea, skin rash and liver toxicity. The incidence of cardiotoxicity was low in all treatment arms. Lapatinib is not approved for use in the adjuvant setting.

The phase III APHINITY study[100] evaluated the role of the addition of pertuzumab to standard adjuvant treatment with chemotherapy and trastuzumab in women with operated HER2 positive breast cancer.[232] Patients with positive axillary lymph nodes or with negative axillary lymph nodes with tumor diameter of 1 cm or more, or with tumor between 0.5 and 1 cm and at least one of the following risk factors were eligible: G3, negative hormone receptors, age less than 35 years. The primary endpoint of the study was invasive disease-free survival (IDFS) at 3 years. About 40% of the patients enrolled had negative axillary lymph nodes and more than 60% had a hormone-receptor positive tumor. The study reached the predefined endpoint, with a statistically significant 3-year difference in favor of the group treated with pertuzumab in addition to standard treatment (HR 0.81; 95% CI, 0.66-1.00; p=0.045), but with an absolute difference in 3-year IDFS of 0.9% (94.1% and 93.2% with pertuzumab and placebo respectively). The difference at 3 years was most evident in the group of patients with positive axillary lymph nodes (HR 1.13; 95% CI, 0-68-1.86; p=0.02), although in

absolute terms the difference did not reach 2% (DFS at 3 years 92% with pertuzumab vs 90.2% without pertuzumab). No differences in cardiotoxicity were found. Treatment with pertuzumab resulted in a higher incidence of diarrhea.

Adjuvant pertuzumab in combination with chemotherapy and trastuzumab has been approved by the EMA for patients with HER2 positive breast cancer at high risk of recurrence (positive lymph nodes or negative for hormone receptors); in Italy it is currently a Cnn class drug.

5.2.5 Role of bisphosphonates and denosumab

The role of bisphosphonates in the adjuvant treatment of breast cancer is still under investigation and includes two important aspects:

- The prevention and treatment of bone loss induced by adjuvant treatments;

- The prevention of recurrences and the improvement of survival.

As far as the prevention of bone mineral loss is concerned, three studies (Z-FAST n= 602, ZO-FAST n=1065, E-ZO-FAST n=527) compared the efficacy of zoledronic acid 4 mg iv every 6 months, administered from the start of adjuvant treatment with AIs or when BMD <-2 or a spontaneous fracture occurs.[101] The 61-month update of the Z-FAST study showed that delaying the start of treatment with bisphosphonates results in a BMD loss in the lumbar spine and femur compared to baseline (p < 0.0003), while immediate initiation leads to a BMD gain that lasts for the duration of treatment (p < 0.0003). Similar results were achieved by the 36-month analysis of the ZO-FAST and E-ZO-FAST studies. The ability of bisphosphonates to reduce the incidence of non-traumatic fractures was investigated as a secondary endpoint or as part of exploratory analyses of studies that did not have the power required to demonstrate differences. The ABCSG study[18] is a double-blind, multicenter, prospective phase III trial where 3,425 postmenopausal patients with operated HR+ breast cancer candidate for treatment with AIs were randomized 1:1 to receive sc denosumab 60 mg or placebo every 6 months.[102] The primary endpoint was the time to the first fracture. Denosumab showed a significant reduction in time to first fracture compared to placebo (HR = 0.5, 95% CI 0.39-0.65, p < 0.0001). The updated results of DFS at a 72-month median follow-up were presented at the ASCO 2018 Congress and showed a 5-year DFS rate of 89.2% with denosumab and 87.3% in the control arm (HR0.823, 95% CI 0.69-0.98, p=0.026).[103]

An additional study (D-CARE) randomized 4,509 patients with early-stage breast cancer at high risk (positive lymph nodes, 93.5%, positive estrogen receptors 77%, chemotherapy with anthracyclines and/or taxanes 95.9%) to receive standard treatment associated with denosumab or not. No difference was observed in terms of bone metastasis-free survival, DFS or OS.[104]

Two phase III randomized studies, the results of which have been published in full, evaluated the efficacy of zoledronic acid in terms of disease-free survival and overall survival. In the ABCSG-12 study, the drug was administered at a dose of 4 mg every 6 months for 5 years in premenopausal patients with endocrine-sensitive breast cancer who received tamoxifen or anastrozole associated with LHRH-analogue (treatment administered for 3 years). At a follow-up of about 48 months, this study showed a relative benefit of 35% (absolute: 3.2%) in disease-free survival in favor of the group of patients who also received zoledronic acid.[105] A recent update of this study also shows a benefit in OS only in the subgroup of women aged >40 years, with a proportional reduction of 43% in death risk.[106] The AZURE study[107] randomized over 3,000 patients to receive or not to receive zoledronic acid at a dose of 4 mg every 3-4 weeks for the first six doses, followed by 8 doses every 3 months and finally 5 doses every 6 months for a total of 5 years of treatment.

Results at a median follow-up of 59 months did not show any benefit in terms of event-free survival (primary objective of the study). The unscheduled subgroup analysis did not reveal any benefit of zoledronic acid in the group of patients with ER-positive breast cancer in premenopausal women. The study showed an advantage in event-free and overall survival in the subgroup of postmenopausal patients aged >60 years or in patients who had been postmenopausal for at least 5 years.

In addition to these studies, the results of the NSABP study B-34[108] (clodronate vs placebo, pre- and postmenopausal patients), of the Zo-FAST study[109] (zoledronate vs zoledronate at the onset of confirmed osteoporosis, menopausal patients), and of the GAIN study[110] (ibandronate vs observation, chemotherapy-exposed patients) were also added. Subgroup analyses of these studies provide results that, in line with the observations made in the ABSCG 12 study and the AZURE study, suggest a potential benefit of bisphosphonates on the outcome of operated breast cancer dependent on the patient's hormonal milieu.

A meta-analysis collected individual data from about 18,000 of the 23,000 women enrolled in randomized trials with bisphosphonates vs control in women operated for breast cancer.[111] In this study, the use of bisphosphonates was associated with a 34% reduction in the risk of developing bone metastases in postmenopausal women, equal to an approximately 3% increase in bone metastasis-free survival at 10 years. This effect has not been observed in premenopausal women and for exclusively non-bone metastatic recurrences. In the same postmenopausal setting, bisphosphonates were associated with a 17% reduction in the risk of death from breast cancer, corresponding to an absolute 10-year reduction of 3.1%, and a 2.3% reduction in mortality from all causes. The effect was observed both with aminobisphosphonates such as zoledronic acid and with clodronate, and for both "metastatic disease" and "osteoporosis/osteopenia prevention" regimens.

The SWOG S0307 study compared the efficacy of 3 bisphosphonates; 6,097 patients with operated stage I-III breast cancer were randomized to receive clodronate (1600 mg oral qd), ibandronate (50 mg oral qd) or zoledronic acid (4 mg IV monthly x 6, then q3 months x 2.5 years) for a total duration of 3 years. The study showed no differences in the primary endpoint, with a 5-year DFS of 88% for clodronate and zoledronic acid and 87% for ibandronate.[112] The incidence of ONJ was higher with zoledronic acid (1.2%) compared to ibandronate (0.6%) and clodronate (0.3%). Fractures did not differ between study arms.

According to note 79 (Determination no. 589 of Gazzetta Ufficiale no. 115 of 20-05-2015), alendronate (± vitD), risedronate, zoledronate and denosumab are reimbursed by the National Health System as first choice drugs in the primary prevention of osteoporotic fractures in menopausal women at high risk due to adjuvant hormone-blocking therapy for breast cancer. Zoledronate can only be prescribed and administered in public or National Health System -affiliated hospitals. For denosumab, the note applies in the presence of a diagnosis and a renewable 12-month therapeutic plan by medical specialists, universities or health agencies.

According to Determination no. 1490 of Gazzetta Ufficiale No. 279 of 30-11-2015, it is noted that oncologists are included among the specialists who can prescribe denosumab 60 mg every 6 months.

6. Neoadjuvant systemic therapy in operable breast cancer and non-operable locally advanced breast cancer

(Figure 9)

Neoadjuvant systemic therapy refers to the systemic treatment of breast cancer prior to a potentially radical surgical procedure. Typically, neoadjuvant treatment has taken the form of chemotherapy (possibly associated with biological drugs), although there is increasing interest in expanding the role of neoadjuvant endocrine therapy in some subgroups of patients with endocrine-sensitive disease.

OBJECTIVES

Operable tumors - While the primary goal of adjuvant systemic therapy is to reduce the risk of distant recurrence and mortality from breast cancer, the administration of the same therapy in a neoadjuvant setting also aims to reduce the tumor, allowing for less extensive surgery, better aesthetic results and fewer postoperative complications.[1-5] In addition, neoadjuvant therapy also allows an early evaluation of the effectiveness of systemic therapy; in particular, the presence or absence of residual invasive disease after neoadjuvant therapy is an important prognostic factor.

Although an improvement in overall survival (OS) of patients after neoadjuvant chemotherapy (NACT) was hypothesized, randomized trials have not been able to demonstrate such benefit, and the pre- and postoperative strategies appear to be equivalent in terms of overall survival.[1,3,6-12,18] A single patient meta-analysis compared the outcomes of neoadjuvant vs. adjuvant chemotherapy based on data from 4,756 women participating in 10 studies started between 1983 and 2002:[18] NACT was associated with increased rates of conservative surgery (65 vs. 49%); NACT was associated with increased risk of local recurrence (21.4% vs. 15.9%, HR: 1.37, IC 95% 1.17-1.61), attributable at least in part to the increased use of conservative surgery; NACT was not associated with any survival advantage, since no difference was observed between neoadjuvant vs. adjuvant chemotherapy in rates of distant recurrence (38.2% vs. 38%) or breast cancer mortality (34.4 vs. 33.7%).

Non-operable locally advanced tumors and inflammatory carcinoma - In these cases, the patient not considered a candidate for an up-front surgery, since the tumor cannot be resected with a radical approach (due to its size and/or the presence of clinical N2/N3), and therefore the neoadjuvant systemic treatment is intended to allow subsequent surgery. Conservative surgery can be offered to patients who achieve a good response after the neoadjuvant treatment, except in patients with mastitis carcinomatosa, where surgery (if feasible) should always considermastectomy associated with axillary dissection.

PATIENT SELECTION - Although originally developed for patients with non-operable locally advanced breast cancer, NACT is now frequently administered to patients with operable tumors in an effort to improve cosmetic outcome and reduce surgical complications. The indications are listed below:

Locally advanced breast cancer - Patients with locally advanced breast cancer (stage IIB-IIIC), regardless of breast cancer subtype, are ideal candidates for neoadjuvant chemotherapy, because in most cases they are not suitable for conservative surgery and because the risk of recurrence justifies systemic chemotherapy.

Early-stage breast cancer - Patients with early-stage breast cancer (including stage I or IIA) are suitable candidates for neoadjuvant chemotherapy if conservative surgery is not feasible (e.g. due to a high tumor/breast ratio or if the expected cosmetic outcome is suboptimal due to tumor location). In cases of patients with triple-negative (TNBC) or HER2+ cancer, NACT is strongly encouraged because these patients are usually candidates for postoperative chemotherapy and because these tumor subtypes are particularly sensitive to the systemic treatment.[13] In contrast, the role of NACT in patients with HR+/HER2- breast cancer is less clear;[14-17] in particular, it is still debated whether these patients should be offered NACT or neoadjuvant endocrine therapy (NET).

PATHOLOGIC COMPLETE RESPONSE - In addition to clinical goals, neoadjuvant therapy represents an extraordinary model for translational and clinical research, thanks to the availability of pre- and post-therapy tissue samples and to the early evidence of treatment efficacy, evaluated on the basis of tumor response, and in particular the achievement of pathologic complete response (pCR). In this regard, it should be noted that **the most widely accepted definition of pCR observed after neoadjuvant therapy requires the absence of residual invasive breast disease and of measurable disease in any axillary lymph node (ypT0ypN0). Since persistence of carcinoma *in situ* does not affect the risk of distant recurrence, residual intraductal disease is still defined as pCR (ypT0/is ypN0).**

The documented pCR after NACT has a significant prognostic relevance.[19-21] In 2014, a single-patient data meta-analysis evaluated 11.955 patients included in 12 randomized clinical trials of neoadjuvant therapy (CTneoBC): eradication of tumor from the breast and lymph nodes (ypT0ypN0 or ypT0/is ypN0) was

associated with improved EFS (ypT0ypN0: HR 0.44, 85%CI 0.39-0.51; ypT0/is ypN0: HR 0.48, 95% CI 0.43-0.54) and OS (HR 0.48, 95% CI 0.33-0.69) compared to the eradication of invasive tumor from the breast alone. The association between pCR (ypT0/is ypN0) and long-term outcome was strongest in patients with rapidly growing tumors, including TNBC (EFS: HR 0.24, 95% CI 0.18-0.33; OS: HR 0.16, 95% CI 0.11-0.25) and HER2 positive (EFS: HR 0.39, 95% CI 0.31-0.50; OS: HR 0.34, 95% CI 0.24-0.47) subtypes.[19] The meta-analysis confirmed this prognostic effect at the individual level ("per patient"), but not at the chemotherapy protocol level ("per trial").

PRE-TREATMENT EVALUATION

Tumor assessment - Before starting neoadjuvant treatment, biopsy with an adequate histopathologic diagnosis of the disease is required, with determination of hormone-receptor and HER2 status. In patients who will receive NACT, the placement of intratumoral radiopaque clips or surface markings should always be encouraged to facilitate subsequent surgery, especially when a significant reduction/eradication of the tumor mass is expected.

Imaging evaluation - In most cases, mammography and breast ultrasound are considered sufficient to accurately document the extent of disease prior to neoadjuvant therapy. It has been demonstrated that breast magnetic resonance imaging (MRI) is the most accurate tool for the evaluation of disease response both ongoing and at the end of neoadjuvant therapy, and therefore can be considered in all patients receiving NACT. In addition, MRI can provide relevant information about the tumor extent in the presence of: (1) suspected multicentric disease, (2) in the case of dense breast at the X-ray examination, (3) in the presence of internal and/or deep breast adenopathy or (4) even in the case of suspected invasion of muscles and underlying chest wall. For more details on the role of MRI, see the chapter on disease staging (Chapter 3.6).

Lymph node evaluation - Physical examination of the axilla is recommended in all patients with newly diagnosed breast cancer. When axillary adenopathy is identified on physical examination, needle aspiration or needle biopsy is suggested for cytological and histological confirmation. In patients where an objective axillary assessment is not possible, ultrasound is recommended. As described elsewhere, in the absence of lymph node involvement on physical examination or instrumental imaging, a sentinel lymph node biopsy (SLNB) can be performed after neoadjuvant treatment. This avoids a new surgical procedure and preserves the prognostic information that can be obtained from lymph node response.[22]

Disease staging - In patients with clinical stage I or II disease, instrumental staging to look for distant lesions is not required, while further assessment is suggested in patients with clinical stage III disease or inflammatory carcinoma, or in patients with suspicious symptoms (including abnormal laboratory values) that could be related to the presence of occult metastases.

TREATMENT OPTIONS

Chemotherapy

The chemotherapy regimens commonly used in the adjuvant setting are also effective as neoadjuvant treatments. The regimens commonly used in patients with HER2 negative disease include regimens based on anthracyclines (A) and cyclophosphamide (C) followed or preceded by a taxane (docetaxel or paclitaxel), and regimens without anthracyclines, such as the combination of docetaxel and cyclophosphamide (TC), reasonably offered to patients with contraindications to the use of anthracyclines.

Anthracycline regimens - In HER2 negative patients, 4 cycles of anthracycline and cyclophosphamide are typically offered, possibly according to a "dose-dense" schedule (EC or AC every two weeks), followed by taxanes in a schedule including weekly paclitaxel for 12 cycles or two/three-weekly paclitaxel or docetaxel for 4 cycles. Other less used regimens include concomitant combinations of anthracyclines and taxanes (TAC).

The preference for combination regimens with anthracyclines and a taxane (sequential or concomitant) derives primarily from the Oxford meta-analysis conducted on adjuvant chemotherapy data.[23]

In addition, several neoadjuvant studies have shown that the addition of a taxane to an anthracycline regimen, given concomitantly or sequentially, is associated with higher response rates.[12,24-29] For example, in the NSABP-B27 study, 2,411 patients received 4 cycles of neoadjuvant AC and were subsequently randomized to stop chemotherapy or receive 4 more cycles of neoadjuvant docetaxel (100 mg/m2 q3w) or receive surgery followed by 4 cycles of adjuvant docetaxel.[12] At a follow-up of 8 years, compared to AC alone, the addition of docetaxel in the neoadjuvant setting led to higher rates of clinical response (91% versus 86%) and pCR (26% versus 13%), with no difference in survival (OS: 75% versus 74%; DFS: 62% and 59%).

Anthracycline-free regimens - As in the adjuvant setting, also in the neoadjuvant setting, an anthracycline-free regimen may be a reasonable option in selected patients, particularly in the presence of heart disease, advanced age, cardiac risk factors (i.e. hypertension and diabetes mellitus). The TC combination (docetaxel and cyclophosphamide) is widely used in the adjuvant setting for HER2 negative disease, and the use of this regimen in the neoadjuvant setting is acceptable, even if there is limited experience.[32,33]

Addition of other chemotherapeutic agents - The role of the addition of other chemotherapeutic agents to regimens containing anthracyclines and taxane is still being investigated. In the GBG GeparQuattro study, no benefits were observed from adding capecitabine to the standard A-T treatment, either in terms of increasing the rate of conservative surgery or increasing the rate of pCR.[34] Similarly, in the NSABP B-40 study, no benefit was observed from the addition of gemcitabine or capecitabine to docetaxel (T) followed by doxorubicin and cyclophosphamide (AC), either in terms of complete clinical response (cCR), or pCR, or conservative surgery. Similarly, survival (OS and DFS) was not affected by the addition of capecitabine or gemcitabine.[35,36]

Platinum-containing regimens - The addition of carboplatin to neoadjuvant anthracycline- and taxane-based chemotherapy regimens for triple-negative breast cancer has been evaluated in several studies.

CLINICAL QUESTION No. 14 (Refer to GRADE Question No. 5) (Figure 9)

In women with TRIPLE-NEGATIVE breast cancer (hormone-receptor and HER2 negative) who are candidates for primary/neoadjuvant chemotherapy, is the addition of platinum to a standard regimen with anthracyclines and taxanes recommended rather than anthracyclines and taxanes alone?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Moderate	In women with triple-negative breast cancer (hormone-receptor and HER2 negative) who are candidates for primary/neoadjuvant chemotherapy, the addition of platinum to	**Conditional Positive**

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
	a standard regimen with anthracyclines and taxanes could be considered.	

See chapter 14 - Recommendations according to GRADE methodology

A recent systematic review and meta-analysis included 9 randomized trials (n=2,109) comparing platinum-containing neoadjuvant chemotherapy regimens to platinum-free regimens in patients with triple-negative breast cancer.[37] Of the 9 studies included, 7 compared carboplatin + anthracyclines and taxanes vs anthracyclines and taxanes, of which 5 (GEICAM/2006-3, GeparSixto GBG66, CALGB 40603 Alliance, UMIN000003355 and BrighTNess) used the same backbone chemotherapy with anthracyclines and taxanes in the two randomization arms. The meta-analysis of these 5 studies showed that the addition of platinum is associated with an increased probability of obtaining a complete pathological response (54.2% vs 37.1% OR 2.04; 95% CI 1.39-3.00). However, the use of platinum has not been associated with significantly improved survival, both in terms of event-free survival and overall survival.

In CALGB 40603, the addition of carboplatin every three weeks to weekly paclitaxel followed by "dose-dense" AC did not show any benefit in EFS after 3 years;[38] on the contrary, in the GeparSixto study the addition of carboplatin to an unconventional chemotherapy regimen produced an absolute improvement of 10% in survival (EFS).[39] Finally, from the analysis of all 9 studies included included in the meta-analysis, treatment with platinum was associated with an increased risk of grade 3-4hematological toxicity.

Biological therapy

Addition of anti-HER2 drugs - In patients with HER2+ breast cancer who are candidates for primary systemic therapy, trastuzumab associated with chemotherapy should be considered as first-line treatment.

In patients with operable HER2 positive tumors (stage II-IIIA), a randomized phase II trial evaluated the concomitant addition of trastuzumab to paclitaxel chemotherapy for 4 cycles and FE(75)C for 4 cycles.[40,41] The study, which planned to enroll 164 patients, was prematurely closed with only 42 randomized patients due to a significant increase in pCR rate with the use of trastuzumab (65% vs 26%). Cardiotoxicity was modest with the doses administered. The updated analysis (including a further 22 patients) confirmed the high proportion of pCR, the absence of disease recurrence and the absence of significant toxicities. In patients with locally advanced or inflammatory HER2+ tumors, a randomized study (NOAH study) compared chemotherapy alone (doxorubicin-paclitaxel x 3 cycles followed by paclitaxel x 4 cycles followed by CMF x 3 cycles) with the same chemotherapy in combination with trastuzumab, prior to surgical treatment. The addition of trastuzumab significantly increased the percentage of pCR in both the overall population and the subgroup of patients with mastitis carcinomatosa (38% vs 20%). The study also showed an absolute advantage of 15% in 5-year EFS in favor of trastuzumab.[42,43] Overall, from a meta-analysis of 5 studies, the addition of trastuzumab to neoadjuvant chemotherapy was associated with a higher probability of obtaining a pCR (38% vs 21%, RR 1.85, 95% CI 1.39-2.46, p<0.001).[44] Although no clinically significant risk of cardiotoxicity emerged with regimens containing trastuzumab given concomitantly with anthracyclines in the neoadjuvant treatment of HER2+ cancer,[40-43,45] the most common regimen remains a sequence of anthracyclines and taxanes with

trastuzumab administered concomitantly with taxanes.

Recent studies have evaluated the role of other anti-HER2 drugs (lapatinib and pertuzumab) in the neoadjuvant treatment of HER2+ cancer, showing that the combination of chemotherapy with two anti-HER2 agents (double block) produces the highest pCR rates ever observed (up to 65%).[46-49] Evidence of the efficacy of pertuzumab in the neoadjuvant setting comes mainly from the Neosphere and Tryphaena studies.[48,49]

The use of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting is authorized but not reimbursed in Italy for locally advanced, inflammatory or early stage HER2+ carcinoma at high risk of recurrence (Cnn drug class). As stated in the technical data sheet updated on 28 June 2018: "In the neoadjuvant setting, locally advanced and inflammatory breast cancer is considered to be at high risk regardless of hormone-receptor status. In early breast cancer, tumor size, grade, hormone-receptor status and lymph node metastases should be considered in the risk assessment." The regulatory procedure for drug reimbursement is underway.

The use of lapatinib in combination with trastuzumab and neoadjuvant chemotherapy is not approved.

Endocrine therapy

Early neoadjuvant endocrine therapy (NET) studies evaluated the role of tamoxifen as the treatment of choice for elderly women diagnosed with breast cancer, showing clinical response rates above 30% and overall survival similar to that achieved with the surgery-tamoxifen sequence, although with a worse local-regional disease control.[50] The IMPACT study compared the efficacy of anastrozole vs tamoxifen vs the combination of anastrozole and tamoxifen in the neoadjuvant setting.[51] The conversion to conservative surgery for mastectomy candidates was greater in the anastrozole arm than in the tamoxifen arm and compared to the combination regimen (46%, 22%, and 26%, respectively). Similarly, in the PROACT study, which evaluated 3 months of preoperative treatment with anastrozole vs. tamoxifen, the conversion to conservative surgery for patients who were not immediately operable was greater in the arm with anastrozole (44% vs. 31%)[52]. Similar results were obtained with letrozole vs tamoxifen (PO24study).[53] In 2016, a meta-analysis of individual patient data[54] evaluated the impact of neoadjuvant endocrine therapy in 20 randomized trials (3,490 patients), observing that in HR positive disease, preoperative endocrine treatment obtains similar results for clinical, radiological and pathological responses, as well as for conversions to conservative surgery, compared to neoadjuvant chemotherapy in the same setting, but with clear advantages in terms of tolerability. Although no standard has been set for the duration of neoadjuvant endocrine therapy, the available studies suggest a duration of at least 3-4 months, regularly monitoring the clinical response and considering the surgical approach in the presence of signs of progression.[50-55] In patients undergoing neoadjuvant endocrine therapy, the pCR rate is very low, mostly around 1%:[56] therefore, the evaluation of pCR as a predictive factor of therapeutic benefit is not useful in this setting. Several studies have examined the role of Ki67 with the aim of identifying a biological surrogate endpoint that can provide information on the clinical impact. In particular, the POETIC study evaluated, in 4,350 postmenopausal patients with HR positive breast cancer, the impact of perioperative endocrine treatment, with particular regard to reducing the level of Ki67 after 2 weeks of hormone therapy with anti-aromatase agents. The effect of reducing Ki67 below the 10% threshold (from a higher starting value) was a consistent predictor of survival and a possible tool for selecting the optimal postoperative therapy.[57]

POST-TREATMENT EVALUATION

Patients receiving neoadjuvant treatment should undergo regular clinical evaluations during the treatment period in order to evaluate the response and ensure that the tumor does not progress. For patients with operable tumors who progress during the neoadjuvant therapy, it is recommended to move up the surgery. Patients with inoperable tumors should be offered a new line of chemotherapy with non-cross resistant drugs, with the aim of allowing subsequent breast surgery and/or radiation therapy.

Breast Surgery - Definitive surgical treatment should be planned after recovery from any toxicity of the neoadjuvant treatment, generally within 3-8 weeks of the end of systemic therapy. Once the patient has completed neoadjuvant chemotherapy (NACT), in most cases a physical examination, possibly associated with breast and ipsilateral axilla ultrasound examination, is considered a sufficient clinical assessment. Magnetic resonance imaging (MRI) is recommended at the end of NACT in all patients where a MRI-baseline assessment is available. In addition, MRI may be useful in cases where the tumor has not been visualized adequately or if a better definition of the extent of post-NACT disease would change the surgical approach. Otherwise, FDG-PET is not adequate for the detection of residual disease post-NACT.[58] Despite the accuracy of the detection, it should be noted that the correlation between tumor measurements obtained at the physical examination and/or with imaging (mammography, US or MRI) and tumor size at the final pathological assessment remains rather modest.[59-61] Typically, the size of the residual neoplasm guides the extent of surgical resection, and the complete resection of the entire initial tumor bed is unnecessary. Although the "NO INK ON TUMOR" margin recommendation may also be adopted after neoadjuvant chemotherapy, a recent panel of experts suggests larger margins in the case of residual multifocal disease.[62]

Axillary surgery - Patients without clinical and/or radiological evidence of lymph node involvement before or during NACT, who have not already undergone SLNB, may have a post-NACT SLNB that can guide the optimal surgical approach.

It should be borne in mind that, compared to cases of upfront surgery, the rate of false negatives (FN) at post-NACT SLNB assessment appears higher and can be reduced by analyzing more than one sentinel lymph node (at least 3), as described above (see Chapter 5.1.2).

For patients who had a SLNB assessment before receiving NACT, decisions about the axillary surgery option will be based on the results of the biopsy. These patients should not be subjected to an additional SLNB at the end of NACT.

In patients with clinical and/or radiological evidence of pre-NACT (baseline) axillary involvement, confirmed by a needle aspiration/needle biopsy or in case of evident extensive clinical involvement of lymph nodes (cN2-N3), the optimal definitive surgery should consider ipsilateral axillary dissection. In selected cases, for patients who become cN0 after NACT, SLNB may be an option, especially using procedures that reduce the risk of false-negatives (i.e. >2 SLNB). For patients who become cN0 post-NACT and are SLNB-negative, the option of omitting the axillary dissection is still under investigation and represents an opportunity to be discussed in a multidisciplinary setting on a case-by-case basis. For details about the optimal surgical approach for axillary lymph nodes, see Chapter 5.1.2.

Post-surgical therapy - Normally, there is no need for further adjuvant chemotherapy if 6-8 cycles of chemotherapy have previously been completed. In the case of neoadjuvant chemotherapy failure, the post-surgical strategy must be personalized. In particular, if the patient has not received anthracyclines and/or taxanes in the pre-surgical phase, she may receive these agents in the adjuvant setting. A phase 3 study showed that adjuvant treatment with capecitabine in patients who had not obtained pCR after NACT containing anthracyclines and taxanes, improved disease-free survival (74.1% vs 67.6%, p=0.01) and overall 5-year

survival compared to the control group without capecitabine (89.2% vs 83.6% p=0.01). In the sub-group analysis, the benefit was highest in the sub-group of hormone-receptor negative BCs.[63]

Adjuvant endocrine therapy is indicated in the presence of hormone-receptor expression (HR+) in the pre-treatment biopsy sample.

In HER2 positive cases, if trastuzumab was not administered in the preoperative treatment plan, it should be administered for one year after surgery; if trastuzumab was administered during the preoperative phase, it should be administered as monotherapy in the post-surgical phase until completing one year of treatment.

Radiotherapy is indicated after breast surgery depending on the initial clinical characteristics of the tumor (cT and cN) and the information acquired after surgery (ypT and ypN).

7. Follow-up management

Clinical examination	Patient history and objective examination should be obtained every 3-6 months in the first three years after the primary treatment, every 6-12 months in the following 2 years and then annually[1]
Mammography	Mammography should be performed within one year of the mammogram that allowed to diagnose the tumor (in women undergoing conservative surgery, a mammogram at least 6 months after the end of radiotherapy), then once a year[2-3]
Monitoring of side effects of treatments	In the case of *aromatase inhibitor* therapy, periodic monitoring of blood levels of cholesterol and triglycerides, as well as bone densitometry, is recommended. In the case of therapy with *tamoxifen*, an annual gynecological evaluation (examination and possible pelvic ultrasound) may be considered, even in the absence of evidence supporting its clinical utility[4] In asymptomatic patients at risk of cardiotoxicity, an echocardiogram 6-12 months after completion of treatment with anthracyclines and/or trastuzumab is recommended[5]
Promotion of correct lifestyles	All patients should be encouraged to adopt a healthy lifestyle (limitation of alcohol consumption, smoking cessation if they smoke, regular physical activity, reduction of body weight with appropriate nutritional program if obese or overweight)[4]
Non-recommended procedures	In the absence of clinical indications, the following tests are not recommended: breast MRI; brain-chest-abdomen CT; CT-PET with FDG; blood tests; chest X-ray; abdominal ultrasound, bone scintigraphy; determination of tumor markers (CEA, CA 15.3, CA 125, etc.)[6-10]

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INTRODUCTION - According to the AIRTUM 2017 report, a total of 767,000 women in Italy have been diagnosed with breast cancer, equal to 43% of all women living with a prior cancer diagnosis and to 23% of all prevalent cases. These data are in line with the epidemiology of the disease recorded in other Western countries (1-3). Patients who live for decades after the diagnosis of breast cancer experience the common problems related to aging, which are often exacerbated by the delayed effects of the disease and of any cancer therapies received. For this reason, patients deserve special attention and post-treatment surveillance. There is no clear evidence of what constitutes the best practice in patient follow-up management, and this contributes to a certain degree of variability in post-treatment care and surveillance options [4,5].

OBJECTIVES - In 2015, the ACS/ASCO guidelines on patient follow-up management after breast cancer [5-6] were published. The main objective of surveillance after the primary treatment of breast cancer is the early recognition of disease recurrence that may potentially obtain a radical treatment, in particular local-regional recurrence or second breast cancer events. In addition, the follow-up should be aimed at identifying and treating any physical and/or psychosocial sequelae induced by the tumor and/or by cancer treatments, assessing adherence to anti-hormone therapy, promoting and maintaining a healthy lifestyle, defining hereditary-familial risk, and secondary prevention of other cancers.

FOLLOW-UP MANAGEMENT

Breast cancer must be considered a chronic condition, even in patients who remain disease-free, and therefore must receive the care and attention reserved for all other medical chronic conditions. At the end of the follow-up by the oncology specialist (usually after 5 years), the patient can be referred to her General Practitioner (GP), with indication to receive annual mammographic checks and clinical examinations. In fact, the guidelines of the American Society of Clinical Oncology (ASCO) suggest that patients with early-stage breast cancer (tumor <5 cm and <4 positive lymph nodes) may switch early to an oncology surveillance program performed exclusively by the GP, possibly after the first year of specialist surveillance [6]. This approach must be agreed between the GP and the patient and must be placed in the context of network surveillance, with the possibility of specialist intervention whenever necessary.

EXAMINATIONS USEFUL FOR FOLLOW-UP

History and physical examination

History - History collection and physical examination are two relevant tools for detecting a breast cancer recurrence [6-10]. It is suggested that patients be examined every 3-6 months during the first three years after the end of therapy, every 6-12 months for the next two years, and then every year according to the recommendations of international scientific societies [11]. However, this program is arbitrary; no study

evaluated the benefit of less frequent clinical visits in patients with low-risk disease or more frequent visits in patients with high-risk disease [12].

Breast Imaging

Mammography - Although evidence is limited, mammography surveillance seems to be associated with a reduction in mortality among women with previous breast cancer, regardless of age [13-18]. This observation was best confirmed in a case-control study comparing the use of mammography in women over 65 years of age surviving for over 30 months after a breast cancer diagnosis [17], demonstrating a survival advantage in favor of mammographic surveillance (odds ratio [OR] 0.83, 95% CI 0.72-0.95). Given the 4% local recurrence rate [19], one of the aims of post-treatment mammography surveillance is precisely to detect local disease recurrences after conservative surgery in a timely manner. In addition, mammographic surveillance can help in the early diagnosis of second breast tumors. It should be noted that there is no sound evidence on optimal mammography surveillance timing in operated women [16,20], although an annual frequency is usually suggested. Despite established practice, it should be noted that for both local recurrence and contralateral cancer, there is a lack of robust controlled studies that can define with certainty the impact of mammography surveillance in terms of survival in the entire population of patients operated for breast cancer [21-27].

MRI - MRI is not recommended as a routine examination in the follow-up of breast cancer. A systematic review of the literature included 10 studies (n = 494) investigating the role of MRI in the detection of recurrences [28], without demonstrating any advantage over mammography. If necessary, breast MRI can be considered in case of clinical suspicion of recurrence when mammography is inconclusive [29]. Otherwise, breast MRI is indicated in the follow-up of women at high risk of disease in the presence of a known BRCA mutation or a strongly suggestive family history.

Breast ultrasound - Routine use of breast ultrasound as an integral part of post-surgical surveillance is not recommended. The addition of breast ultrasound to screening mammography was evaluated in a study with 2,809 women at high risk of breast cancer without showing any diagnostic advantage with ultrasound (8 to 12 per 1,000 women, CI 95% 1.1-7.2), versus an increased rate of false positives (4.4 vs 10.4%) [30].

Interruption of breast imaging - There is no age limit for patients to suggest that breast imaging surveillance should be discontinued. On the contrary, screening mammography is recommended for all surviving patients with a reasonable life expectancy [31]. In fact, the available data suggest that mammography can reduce the risk of death even among elderly patients with previous diagnosis of breast cancer [16,17].

Other imaging examinations

Bone density test (see also Chapter 5.2.5) - Women with a history of breast cancer may have an increased risk of osteoporosis as a result of the cancer treatments received. Therefore, international guidelines include a basic screening assessment (i.e. dual energy X-ray absorptiometry), to be typically performed in the following patients [32]:

- women over 65 years of age
- women aged 60 to 64 years if with family history of osteoporosis, or body weight <70 kg, or history of a non-traumatic fracture or other risk factors for osteoporosis (e.g. smoking, sedentary lifestyle, alcohol use)
- postmenopausal women taking aromatase inhibitors (AI)
- premenopausal women with iatrogenic premature menopause.
In this context, it is not clear what role vitamin D supplementation could play in women treated for breast cancer, nor whether blood levels should be monitored regularly. In the absence of evidence, the assessment of vitamin D levels and the role of vitamin D supplementation should be performed according to the principles applied to general population.

Genetic counseling - Breast cancer survivors who have not already had genetic tests should be prescribed such tests if they meet previously defined eligibility criteria. In particular, BRCA tests should always be considered for men and women who were diagnosed before 40 years of age or with a family history of breast or ovarian

cancer [31]. Before performing the test, it is important that patients are informed about the potential implications (medical and psychosocial) of test results for themselves and their families.

Intensive follow-up - Intensive follow-up (laboratory testing and/or radiological examinations) is not indicated in the post-treatment surveillance program. This evidence emerges from some past-prospective studies, and in particular from a 2005 meta-analysis [33], which demonstrated the absence of any survival advantage in favor of intensive follow-up compared to a standard approach (OS: hazard ratio [HR] 0.96, IC 95% 0.80-1.15). EFS: HR 0,84, IC 95% 0,71-1,00). In addition, it should be noted that laboratory and imaging tests employed for surveillance produce significant rates of false positives and false negatives, along with increased costs [34-37]. This also applies to serum tumor markers (38-41), which are known to be of low sensitivity/specificity and should not be used in the follow-up phase [41,42-44]. The measurement of serum tumor markers should only be used to monitor the response to treatment in patients with metastatic cancer without easily measurable disease [45].

Chest imaging - Neither chest X-ray nor computed tomography (CT) is recommended for lung screening in asymptomatic patients [46-49]. In a series of 416 patients who underwent routine chest imaging surveillance after completing primary treatment for breast cancer, only nine patients had isolated lung metastases [50].

Bone scintigraphy - There is no evidence that early identification of bone metastases can change the clinical course of the disease. Bone metastases are usually diagnosed when specific symptoms appear, even when patients are routinely monitored with bone scintigraphy [51-54].

Abdominal & pelvic imaging - Neither liver ultrasound nor abdominal & pelvic CT scans are recommended in post-treatment surveillance [56-58]. In a wide range of more than 2,400 patients observed over a nine-year period, pelvic metastases were the site of metastatic disease in only 13 patients (0.5%) [57]. However, the radiological results led to more than 200 additional interventional radiology procedures and 50 surgical procedures, 84% of which had negative results.

PET scanning - There is no role for positron emission tomography (PET) in post-treatment follow-up. In retrospective cohort studies and a meta-analysis of 16 studies, while PET was consistently more sensitive than traditional imaging tools for early diagnosis of disease recurrence [59-61], the impact on survival and quality of life remained elusive.

Promotion of a healthy lifestyle - Some observations suggest that exercising, controlling obesity, and reducing alcohol use are conditions associated with a reduced risk of recurrence and death in breast cancer patients [62-65]. In addition, exercise seems to improve the quality of life of patients, who should therefore be encouraged to adopt a physically active lifestyle after cancer treatment.

Management of symptoms and side effects of treatments

At follow-up visits, it is strongly recommended that the patient adherence to any adjuvant hormone treatment be monitored, with the identification and management of any side effects of the therapy, both in the short and long term.

Cardiac toxicity
Chemotherapy regimens containing anthracyclines are associated with an increased risk of dose-dependent cardiac toxicity. Acute toxicity during or at the end of infusion, generally reversible, occurs in <1% of cases; chronic toxicity may emerge early (during or within 12 months after the end of chemotherapy) in 1.6%-2.1% of cases, or later on (more than 12 months after the end of treatment) in 1.6%-5.1% of cases [66]. Data from US registers (SEER) indicate that 38% of patients aged 65 years and treated with anthracyclines experience a heart failure event in their life-time, compared to 32% and 29% of patients who never received anthracycline-containing regimens or any kind of chemotherapy [67]. Recently, a Canadian case-control study has been published involving about 99,000 women diagnosed with early-stage breast cancer: in women aged >66 years, surviving more than 5 years after diagnosis, cardiovascular mortality was the leading cause of death, surpassing breast cancer [68], which emphasizes the importance of cardiological surveillance in these patients.
In 2017, ASCO published guidelines on the prevention and monitoring of cardiotoxicity in patients who received cardiotoxic treatments in adulthood [60].
In particular, patients at high risk of cardiotoxicity have been defined as those treated with:

- Anthracyclines at moderate doses (i.e., doxorubicin at a cumulative dose <250 mg/m^2, epirubicin <600 mg/m^2), in combination with radiotherapy at doses <30 Gy (if the cardiac area is included in the treatment fields).
- Trastuzumab, given sequentially after anthracyclines at moderate doses
- Moderate-dose anthracyclines or trastuzumab, in the presence of cardiovascular risk factors (≥2 of the following: smoking, hypertension, diabetes, dyslipidemia, obesity); age ≥60 years; impaired cardiac function (during or after treatment: borderline left ventricular ejection fraction between 50-55%; history of myocardial infarction; valvular disease).

The ASCO guidelines recommend that attention be paid to the cardiological aspects of history collection and physical examination during the follow-up of these patients. Asymptomatic subjects should have an ECG in the 6-12 months following completion of treatment. In the absence of clear evidence, the guidelines do not make recommendations on the frequency and duration of the ECG surveillance of asymptomatic subjects with negative echocardiogram at follow-up.

The guidelines of the European Society of Oncology [70] suggest, in the absence of specific indications, a cardiological evaluation 6 months after the end of chemotherapy, to be repeated annually for 2 or 3 years and then every 3-5 years. Patients at high risk, those who have received high cumulative doses of anthracyclines and elderly patients may be monitored more frequently.

The NCCN guidelines stress the importance of and ECG evaluation within 12 months of the last dose of anthracyclines in patients >65 years with risk factors (hypertension, dyslipidemia, diabetes, reduced baseline LVEF), and the potential early initiation of cardiological therapy in the presence of prodromal symptoms.

As regards cardiotoxicity in patients who received chemotherapy and trastuzumab in the adjuvant setting, the incidence of severe events (NYHA class III/IV - death) differs in the various studies from 0.6% to 4.1%, also depending on the type of associated chemotherapy.

The guidelines of the European Society suggest a cardiological evaluation at 3, 6, and 9 months during treatment and then at 12 and 18 months or when clinically indicated [70]. The risk of cardiovascular disease increases with age, so premenopausal women who enter menopause early because of cancer treatments may be at greater risk for events. Therapy with aromatase inhibitors may promote increased levels of cholesterol and serum lipids [71-72] and increase the risk of diabetes: these patients should therefore be monitored due to increased cardiovascular risk.

Gynecological Toxicity

Menopausal symptoms - Climacteric syndrome, with hot flashes, vaginal dryness and atrophy, can result from chemotherapy-induced menopause as well as from the hormone therapies that patients have received or receive in the post-surgical phase.

Hot flashes - In case of hot flashes related to the anti-cancer treatments received, patients may benefit from non-hormonal drug therapy, such as gabapentin or selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors (SSRIs/NSRIs). For the latter, caution is required in patients treated with tamoxifen, as SSRIs may interfere with tamoxifen metabolism due to CYP2D6. Acupuncture is a non-pharmacological alternative for hot flash control, with encouraging results obtained in the context of controlled clinical trials [73,74].

Sexual dysfunction - Dyspareunia and decreased libido are events that often accompany the oncological treatments received by patients for breast cancer. The consequences of a breast cancer diagnosis can produce changes in the female body image, induce tensions in the couple's relationship and affect sex life [75]. It has been observed that sexual dysfunction is associated with phases of depression in patients being followed-up

for breast cancer. [76]. It is important that doctors do not underestimate sexual disorders and possibly report patients and/or couples to experienced psychologists/sexologists. In general, the treatment of clinical symptoms of vaginal atrophy and dyspareunia is based on the use of vaginal lubricants and non-hormonal moisturizers. While no topical estrogen-progestin therapy is recommended in patients at high risk of recurrence, the use of low-dose vaginal estrogens in women with low-risk breast cancer is considered acceptable [77-79].

Fertility and pregnancy after breast cancer - While some experts recommend that patients wait at least 2 years after diagnosis before considering conception, in order to avoid pregnancy when the risk of recurrence is highest, others suggest that pregnancy is safe even before 2 years of diagnosis [80-81]. Moreover, previous treatments for breast cancer do not seem to increase the risk of congenital malformations [82]. However, due to the risk of tamoxifen-related teratogenicity, patients should wait at least 3 months after cessation of the drug before attempting to conceive.

Contraception after breast cancer - In the absence of prospective data, the World Health Organization (WHO) guidelines suggest that hormone contraception should be avoided in women with a current or past history of breast cancer (particularly in patients with hormone-receptor positive tumors). Doctors should discuss with the patient the use of non-hormonal barrier birth control methods (condom, diaphragm, copper IUD), to help the woman to choose the method that is most consistent with her lifestyle and beliefs.

8. Treatment of local-regional recurrence

According to cases reported from the 1980s onward, between 10% and 30% of women treated for breast cancer develop local-regional recurrence.[1] Significant differences and variations between the various molecular subtypes are reported, and the incidence is lower in women with luminal tumors and higher in women with triple-negative tumors.[2]

However, although the pattern of recurrence remains unchanged, a significant reduction in local-regional recurrences has been reported in recent years, as a result of early detection and improvement of integrated treatments.[3] About 80% of these recurrences occur in the first two years after precautionary therapy. Local-regional recurrences may or may not be accompanied by distant recurrences.

In case of local-regional recurrence, the determination of the biological characteristics of the tumor (hormone receptors, HER2, Ki67) must always be repeated, since these factors can change.

The estimated 10-year survival of patients with local-regional recurrence is above 80%.[4-6]

Patients with regional recurrence have on average a more unfavorable disease course than those with only local recurrence, especially if the recurrence is delayed. Compared to the local treatment performed, local recurrence has a worse prognosis if it occurs after mastectomy than after conservative surgery.

In five NSABP studies, patients with negative lymph nodes undergoing tumorectomy and radiotherapy, with or without adjuvant chemotherapy, had a low incidence of local-regional recurrence, but patients with local-regional recurrence had worse distant metastasis-free survival and overall survival.[7]

The probability of developing local-regional recurrence seems to be higher in patients with triple-negative or HER2 positive breast cancer, with a less favorable clinical course in these subgroups.[9,10]

Local-regional treatment with curative intent should always be considered in non-metastatic patients.

Patients with local recurrence who initially had mastectomy, should undergo surgical excision of the lesion, with the aim of obtaining clear resection margins. After removal of the local recurrence in a patient who previously had mastectomy but not radiotherapy, radiotherapy of the chest wall is recommended. Treatment

with adjuvant radiotherapy or treatment of lymph node stations only, on the other hand, has not provided clear results and must be individualized.

Patients with local recurrence after initial conservative surgery should undergo mastectomy with axillary staging if no level I/II axillary cavity dissection has been previously performed. There is limited data to support sentinel lymph node biopsy repetition in patients with local recurrence who were initially treated with conservative surgery and sentinel lymph node removal.[11]

In selected situations, however, it is possible to consider a second conservative surgery, particularly if the patient had not received breast radiotherapy. The diameter of the recurrence (<2 cm) and the time from primary surgery (>4 years) are the two factors that allow to identify women who may be candidates for conservative re-intervention with a good chance of success.[12,13]

After a second conservative surgery, *in patients who have already undergone radiotherapy,* the possibility of **re-irradiation of the chest wall or partial irradiation of the breast** with external beam radiotherapy or brachytherapy may be considered. Although this method is not free from complications, with about 10% of delayed toxicity, re-irradiation of the chest wall was feasible and shows satisfactory percentages of complete response, although not long-lasting according to isolated reports.[13,14]

Systemic treatment should consider the biological characteristics of the recurrence (hormone receptors, HER2, Ki67) and be adjusted accordingly. In patients with hormone-receptor positive disease, the use of hormone therapy after local treatment is recommended, while in patients with HER2 positive cancer a new treatment with anti-HER2 agents should be considered, in combination with chemotherapy or hormone therapy.[15]

The CALOR study evaluated the efficacy of chemotherapy after local therapy for isolated local-regional recurrence in patients with ER-negative and ER-positive breast cancer.[16] In this study, 162 patients were randomized to receive or not receive chemotherapy; stratification factors were prior chemotherapy, hormone-receptor status and site of local-regional recurrence. Patients with ER-positive cancer received endocrine therapy. At a nine-year median follow-up, 27 DFS events were observed in the ER-negative group (HR 0.29, 95% CI, 0.13 - 0.67; 10-year DFS, 70% v 34%, chemotherapy vs no chemotherapy, respectively) and 40 in the ER-positive group (HR 1.07, 95% CI, 0.57 - 2.00; 10-year DFS, 50% vs 59%, respectively); interaction test p = .013. HR for breast cancer-free interval was 0.29 (95% CI, 0.13 - 0.67) in the ER-negative group and 0.94 (95% CI, 0.47 - 1.85) in the ER-positive group, interaction test p=.034. For OS, HR 0.48 (95% CI, 0.19 - 1.20) in the ER-negative group and 0.70 (95% CI, 0.32 - 1.55) in the ER-positive group, interaction test p = .53). These results confirm a benefit from the administration of chemotherapy limited to patients with operated ER-negative local-regional recurrence, while they do not support the use of chemotherapy in patients operated for ER-positive local-regional recurrence.

9. Treatment of metastatic disease (Stage IV)

Only about 5% of breast cancers are *de novo* metastatic tumors, and most diagnoses of metastatic disease are made during follow-up after treatment for local disease. The risk of recurrence over time depends mainly on the stage at diagnosis and the molecular subtype. The latter is also usually associated with a different *pattern* of metastatic sites (greater risk of bone metastases in ER+/HER2- neoplasms, greater risk of visceral metastases in *triple-negative* tumors, greater risk of brain metastases in HER2 positive tumors)[1]. After a recurrence of the disease is documented, complete restaging should be performed.

METASTATIC breast cancer: Initial diagnostic evaluation
Initial stage
Objective examination
Laboratory tests
Whole body imaging (e.g. CT, PET, bone scintigraphy)
"Targeted" radiological examinations (e.g. regional CT, MRI)
Metastatic lesion biopsy*

* Consider the following factors (one or more): single metastasis, incompatibility between clinical course and biological characteristics of the initial tumor, biological structure of the primary tumor, subsequent oncological treatments and clinical course during therapy, metastatic site and accessibility, general condition of the patient.

The definition of potential objectives in the treatment of metastatic disease and the selection of the most adequate systemic therapy should take into account several factors, including disease burden, biological characteristics of the tumor, presence of any symptoms and/or visceral crisis, disease-free interval, treatments previously received, general clinical condition of the patient, as well as patient preferences. Based on this global assessment, the metastatic disease can be classified into situations at a low risk of short-term mortality (indolent disease) and at intermediate/high risk (aggressive disease). Indolent disease is defined as follows: long disease-free interval (>24 months from the end of adjuvant therapy), a mainly bone and/or soft tissue metastatic involvement, a limited number of metastatic lesions (such as small-volume lung metastases of limited number or limited liver involvement, in any case less than 30%). "Aggressive" disease, on the other hand, usually emerges either as a visceral crisis or with a high number of metastases in multiple organs or as functional organ impairment, or after a short disease-free interval (appearance of metastases during adjuvant therapy or within 12 months of the end of therapy). The definition of "visceral crisis" identifies a status of severe organ dysfunction (defined by laboratory testing and clinical symptoms), with the possibility of rapid evolution and risk of imminent death, which requires treatment with rapid effect (since further treatment upon progression may not be feasible). Typical conditions include diffuse pulmonary lymphangiomatosis, liver or respiratory failure, or neoplastic meningosis. The visceral crisis should not, therefore, be confused with situations of visceral involvement accompanied by minor symptoms. The treatment of metastatic breast cancer essentially aims to prolong survival, reduce or delay the appearance of symptoms, and improve the quality of life.

The choice of systemic therapy takes all these factors into consideration, but *primarily* the biological characteristics of the disease, in particular the status of hormone receptors and HER2: these are the only two predictive factors validated in breast cancer.

Chemotherapy alone or in combination with anti-HER2 biological agents is the first treatment option in *triple-negative* or HER2+ tumors, respectively. If the tumor expresses hormone receptors (luminal subgroups), the first-choice treatment is represented by endocrine therapy +/- biological drugs; only in patients with visceral crisis chemotherapy is indicated *d'emblée*.

Although the goal of treatment in most cases of metastatic breast cancer is to control the disease, there is a limited number of selected patients (2-3%) who can achieve long survival or even recovery. This is the case with oligometastatic disease (1-10% of cases), where it may be appropriate to adopt aggressive and integrated treatment strategies (systemic therapy and local-regional therapy) (Figure 10).

Biopsy of the metastatic lesion – when feasible – should be considered, as it may help to confirm the diagnosis of metastatic disease (especially in the case of a single metastasis), and it may identify non-malignant lesions or a new primitive tumor. In addition, since one in eight cases show an overall variation in the receptor status of metastases compared to primary tumors, the biopsy of the metastatic site can provide useful elements for the selection of the optimal systemic treatment.[2]

9.1   Therapeutic strategy according to subgroup

9.1.1   HER2 positive, hormone-receptor negative tumors (Figure 12)

In patients with hormone-receptor positive and HER2 negative tumors, in the absence of visceral crisis or significant organ function impairment, endocrine therapy – alone or in combination with biological drugs (CDK4/6 inhibitors or everolimus) – should be considered as first treatment option. Endocrine therapy can ensure survival comparable to that obtained with chemotherapy, with fewer side effects and a better quality of life. The use of endocrine therapies should continue (including with subsequent treatment lines) as long as the disease can be considered hormone-responsive.

9.1.2   HER2 positive tumors (Figure 11)

In HER2 positive tumors, treatment with combinations of anti-HER2 agents should be considered as first choice, mainly in combination with chemotherapy.

In postmenopausal women with tumors that also express hormone receptors, a combination of an anti-HER2 agent (lapatinib or trastuzumab) and an aromatase inhibitor may also represent a therapeutic option in selected cases (patient with contraindications to chemotherapy).

9.1.3   Triple-negative tumors (Figure 12)

In tumors without expression of HER2 or hormone receptors, chemotherapy currently appears to be the only treatment option, possibly in combination with biological (anti-angiogenic) agents.

9.2   Types of systemic therapy: hormone therapy (Figure 13, Figure 14)

When hormone treatment is indicated (according to the above principles), the choice of therapy, both as first-line and subsequent lines of treatment, is based mainly on the patient's menopausal status and hormone sensitivity/resistance, estimated according to the therapies previously administered in the adjuvant or metastatic setting and their duration and effect.

A- <u>THERAPEUTIC OPTIONS FOR PREMENOPAUSAL PATIENTS</u>

In premenopausal patients with metastatic ER-positive/HER2 negative breast cancer, candidates for hormone therapy for metastatic disease, treatment should include ovarian suppression with LHRH-analogue.[3-5] Therefore, premenopausal endocrine therapy options also include those described for postmenopausal women. In women who were never exposed to hormone therapy, tamoxifen added to the LHRH-analogue is a reasonable option.

In patients who already received an adjuvant or first-line metastatic treatment with tamoxifen +/- LHRH-analogue, the association of an aromatase inhibitor and the LHRH-analogue may be considered.[6,7]

The addition of a CDK4/6 inhibitor (palbociclib) to first-line hormone therapy (aromatase inhibitor + LHRH-analogue) has recently been approved and is reimbursed by the NHS in Italy.

In patients who have already received adjuvant or first-line metastatic treatment with tamoxifen or an aromatase inhibitor and who have progressed, the preferred hormone therapy option is fulvestrant + LHRH-analogue.

In these patients, the addition of palbociclib to fulvestrant should be considered, unless they have previously received a CDK4/6 inhibitor.

In the Paloma 3 study, about 20% of women were pre/perimenopausal with disease progression during a previous line of therapy with an aromatase inhibitor and received the fulvestrant+LHRH-analogue combination with palbociclib.[8] In this study, the addition of palbociclib to endocrine therapy increased median PFS from 4.6 months to 9.5 months (HR 0.46, 95% CI 0.36-0.59, p<0.0001). Specifically, in the subgroup of premenopausal women, median PFS increased from 5.6 to 9.5 months with the addition of palbociclib (HR 0.50, 95% CI 0.29-0.87).

<u>AIFA has approved palbociclib in this patient population.</u>

B- <u>THERAPEUTIC OPTIONS FOR POSTMENOPAUSAL PATIENTS</u>

There is no evidence on the best hormone treatment sequence in postmenopausal patients with metastatic hormone-receptor positive HER2 negative breast cancer.

Figure 14 shows some treatment options and therapeutic sequences that can be considered based on the results of several clinical studies available in the literature, which were mainly conducted in patients with different exposure to various hormone therapies. On the contrary, the clinical questions described below refer to the population identified in the single question expressed according to P.I.C.O.

DRUGS USED IN POSTMENOPAUSAL WOMEN WITH ER+/HER2- TUMORS

B.1-Aromatase inhibitors

Aromatase inhibitors are usually preferred to tamoxifen as first-line treatment, thanks to an advantage in TTP/PFS; however, these drugs have never shown an advantage over tamoxifen in terms of OS. More recently, fulvestrant has proven to be more effective than an aromatase inhibitor as first-line therapy in treatment-naïve patients. The addition of a CDK4/6 inhibitor to an aromatase inhibitor was shown to be more effective than the aromatase inhibitor alone; therefore, this combination seems to be the current therapy of choice. Two of the three CDK4/6 inhibitors (palbociclib and ribociclib) are currently approved and reimbursed by the NHS in Italy. The combination with m-TOR inhibitors, on the other hand, has not produced similar benefits in this population of patients who were never previously exposed to hormone therapies.

As second-line treatment, for patients already exposed to a non-steroidal aromatase inhibitor, the combination of a steroidal aromatase inhibitor with m-TOR inhibitors or the combination of fulvestrant and palbociclib was more effective than monotherapy with a steroidal aromatase inhibitor or fulvestrant, respectively.

B.2 - m-TOR inhibitors in combination with aromatase inhibitors

Patients who showed resistance to prior treatment with a non-steroidal aromatase inhibitor (defined as progression during or within 12 months of the end of the adjuvant treatment or progression during or within one month of the end of treatment for advanced disease) were treated with a combination of everolimus and exemestane (compared with exemestane alone)[9] (**SIGN Level of evidence 1++**). This association produced a relative reduction in progression risk of 56% compared to treatment with exemestane alone (64% according to the central evaluation), providing consistent benefit in all the subgroups analyzed. Despite the significant improvement in PFS, no significant differences in overall survival were observed (30.9 vs 26.5 months, HR 0.89, p=0.14)[10] (**SIGN Level of evidence 1++**). Objective responses were reported in 9.5% of cases and a clinical benefit in 33%, accompanied by grade 3-4 toxicities such as stomatitis 8%, anemia 6%, hypoglycemia 4%, fatigue 4%, non-infectious pneumonia 4%. A relative reduction in the risk of bone disease progression of 47% and a relative reduction in the risk of QoL deterioration of 26% were also observed.[11-13]

In the phase 2 BOLERO-4 study, everolimus was combined with letrozole as first-line metastatic treatment in 202 patients not previously treated for metastatic disease (adjuvant therapy was allowed, completed more than 12 months before). At 29.5 months of follow-up, the median PFS was 22 months (CI 95% 18.1-25.1), with an objective response rate of 42.6%.[14]

The combination of exemestane and everolimus is approved by **AIFA** "for the treatment of advanced hormone-receptor positive, HER2/neu negative breast cancer, in combination with exemestane, in postmenopausal women in the absence of symptomatic visceral disease after recurrence or progression following treatment with a non-steroidal aromatase inhibitor." In the BOLERO-2 study, patients treated with everolimus + exemestane in the first-line setting must have had a recurrence during or within 12 months of the end of adjuvant treatment with non-steroidal AIs.[9]

B.3-Fulvestrant

Fulvestrant is a selective estrogen-receptor down-regulator (SERD) currently registered for clinical use at a dose of 500 mg every 28 days, with an additional 500 mg dose 14 days after the first administration.

Recently, the randomized phase III trial FALCON, conducted in a population naïve to hormone therapy, enrolled 462 postmenopausal patients with advanced hormone-receptor positive breast cancer, never treated with hormone therapy before (neither in the adjuvant nor in the metastatic setting).[19] Fifty-five percent of patients had visceral disease. PFS (primary endpoint) was statistically significantly superior in the fulvestrant 500 vs anastrozole group (16.6 months vs 13.8 months; HR=0.797, CI 95%, 0.637-0.999; p=0.0486).[19] At the predefined subgroup analysis, the effects of treatment were reported in all prespecified subgroups, except in the subgroup of patients with visceral metastases where no PFS advantage was shown with fulvestrant 500. Instead, in the subgroup without visceral metastases, a PFS of 22.3 months with fulvestrant 500 vs. 13.8 months with anastrozole was reported.[19]

The duration of the response reported in the fulvestrant group was 20 months vs 13.2 months in the anastrozole group. Side effects were similar to those already observed in previous studies.

Based on these results, in August 2017 the indication extension for fulvestrant was approved, and today in Italy fulvestrant (500 mg) is authorized by AIFA for the treatment of locally advanced or metastatic estrogen-receptor positive breast cancer in postmenopausal women:

• not previously treated with endocrine therapy, or

• with disease recurrence during or after adjuvant anti-estrogenic therapy, or disease progression during anti-estrogenic therapy.

B.4-Cyclin-dependent kinase 4/6 inhibitors with hormone agents

Three different drugs have been developed so far that can selectively block CDK4/6: palbociclib, ribociclib and abemaciclib. Although they are considered similar, these drugs have a different chemical function, a different potency against CDK4/6, and a different spectrum of toxicity. At present, solid and consistent data on the use of CDK4/6 inhibitors are available from several randomized clinical trials conducted in the metastatic setting in patients with HR positive/HER2 negative breast cancer.

B.4.1 Palbociclib

The first CDK4/6 inhibitor to be studied is palbociclib.

The Phase II trial PALOMA-1/TRIO-18 trial randomized 165 postmenopausal women with metastatic HR positive/HER2 negative breast cancer to receive letrozole or letrozole and palbociclib as first-line therapy.[34] The addition of palbociclib to letrozole led to a statistically significant increase of PFS compared to letrozole alone (20.2 versus 10.2 months, HR, respectively, 0.488; p = 0.0004).[34] The most frequently observed adverse event was neutropenia G3-4 (54% in the experimental arm vs 1% in the control arm).[34]

The phase III study PALOMA-2 confirmed the superiority of palbociclib and letrozole over letrozole alone in treatment-naïve patients with metastatic HR positive/HER2 negative breast cancer.[35] Six hundred and sixty-six postmenopausal patients were randomized 2:1 to receive letrozole with palbociclib or placebo, respectively. The median PFS was 24.8 months in the palbociclib arm versus 14.5 months in the placebo arm (HR 0.58; p < 0.001).[22] Again, G3-4 neutropenia was the most frequent adverse event (66.4% in the palbociclib arm versus 1.4% in the placebo arm), with a febrile neutropenia rate of 1.8% in the experimental arm and no events in the control arm.[35]

The phase III study PALOMA-3 randomized 521 pretreated women with metastatic HR positive/HER2 negative breast cancer – regardless of their menopausal status – to receive fulvestrant plus palbociclib or fulvestrant plus placebo.[22] The combination of palbociclib and fulvestrant significantly increased PFS (9.2 versus 3.8 months, HR 0.42; p < 0.001). The most common adverse event was again neutropenia G3/4 (62.0%

with palbociclib versus 0.6% with placebo) [22]. Febrile neutropenia, however, occurred only in 0.6% of patients treated with palbociclib and 0.6% of patients who received placebo. At the final analysis of PALOMA-3, the median PFS was 9.5 months in the palbociclib arm and 4.6 months in the placebo arm (HR 0.46, p < 0.0001). The addition of palbociclib was superior in all subgroups.[36] PALOMA-3 includes the largest population of premenopausal women in the setting of endocrine-resistant disease. A recent analysis conducted specifically in premenopausal women treated in the PALOMA-3 study with palbociclib plus fulvestrant and goserelin (luteinizing hormone-releasing hormone [LHRH] agonist) showed a doubled median PFS and a significantly increased ORR rate compared to endocrine therapy alone.[37]

In Italy, palbociclib is indicated for the treatment of locally advanced or metastatic hormone-receptor (HR) positive and human epidermal growth factor 2 receptor (HER2) negative breast cancer in association with an aromatase inhibitor; in association with fulvestrant in women who have received previous endocrine therapy. In pre - or perimenopausal women, endocrine therapy should be associated with a luteinizing hormone-releasing hormone (LHRH) agonist.

B.4.2 Ribociclib

Ribociclib is another selective inhibitor of CDK4/6 in the breast cancer treatments' armamentarium.

The MONALEESA-2 phase III trial randomized 668 postmenopausal women newly diagnosed with HR positive/HER2 negative metastatic breast cancer to receive letrozole plus ribociclib or placebo. The experimental treatment led to a statistically significant increase in PFS: at a median follow-up of 18 months, PFS was 63.0% in the ribociclib arm and 42.2% in the placebo arm.[26] Median PFS was 14.7 months (95% CI, 13.0 - 16.5) in the placebo group (HR, 0.56; 95% CI, 0.43 - 0.72; P = 3.29×10^{-6} for superiority), while this endpoint was not reached in the ribociclib group (95% CI, 19.3 - unreached). In addition, ribociclib led to a higher ORR compared to letrozole/placebo (52.7% versus 37.1%, p < 0.001). The most frequent adverse event was neutropenia G3/4 (59.3% in the ribociclib arm versus 0.9% in the placebo arm).[26]

The phase III study MONALEESA-7 was the first study designed to evaluate a CDK4/6 inhibitor as first-line treatment in pre- and perimenopausal women with HR positive/HER2 negative metastatic breast cancer.[27] In this study, the addition of ribociclib to tamoxifen or to a non-steroidal aromatase inhibitor (NSAI) plus goserelin significantly improved PFS compared to placebo plus tamoxifen/NSAI plus goserelin (23.8 versus 13.0 months, respectively, HR=0.553, p=0.0000000983).[27] The benefit of treatment was consistent across all subgroups and independent of the endocrine agent used.[27]

In Italy ribociclib is currently approved and reimbursed by the NHS in combination with an aromatase inhibitor as initial endocrine therapy for the treatment of postmenopausal women with HR positive/HER2 negative locally advanced or metastatic breast cancer.

B.4.3 Abemaciclib

Abemaciclib is another powerful selective CDK4/6 inhibitor that leads to a more pronounced CDK4 inhibition.[29] As with the other CDK4/6 inhibitors, the greatest benefit was observed in patients with HR positive/HER2 negative breast cancer, with a disease control rate of 81% compared to 33% in patients with HR negative cancer. Highly pretreated patients with HR positive/HER2 positive and HR positive/HER2 negative metastatic breast cancer had a clinical benefit rate (CBR) of 54.5% and 64%, respectively.[30] In the HR positive subgroup, the median PFS was 8.8 months (95% CI, 4.2-16.0) [30]. Based on these results, abemaciclib received the FDA's "breakthrough therapy" designation for pretreated patients with HR positive metastatic breast cancer.

Monotherapy with abemaciclib was evaluated in the single-arm phase II study MONARCH 1, which included 132 women with HR positive/HER2 negative metastatic breast cancer, whose disease progressed during or after endocrine therapy and chemotherapy.[31] Abemaciclib led to an ORR of 17.4%, a CBR of 42.4% and a median PFS of 5.7 months. The most common adverse event was diarrhea (90.2%), followed by fatigue (65.2%), nausea (64.4%), appetite loss (45.5%), and abdominalgia (38.6%).

The MONARCH 2 study evaluated abemaciclib and fulvestrant in 669 women with HR positive/HER2 negative metastatic breast cancer pretreated with endocrine therapy. These patients were randomized 2:1 to receive either fulvestrant/abemaciclib or fulvestrant/placebo.[32] The combination of fulvestrant/abemaciclib resulted in a statistically significant prolongation of PFS compared to fulvestrant/placebo (16.4 versus 9.3 months; HR, 0.553; p < 0.001). Higher ORR rates were obtained in the abemaciclib/fulvestrant arm (48.1%) compared to the placebo arm (21.3%).[32] The double-blind phase III trial MONARCH 3 randomized 493 postmenopausal women with HR positive/HER2 negative metastatic breast cancer not previously treated in the metastatic setting to receive abemaciclib or placebo with an NSAI. Median PFS was significantly longer with abemaciclib (HR, 0.54; 95% CI, 0.41 - 0.72; p = .000021; median: not reached in the arm with abemaciclib, 14.7 months in the placebo arm). In patients with measurable disease, the ORR was 59% in the arm with abemaciclib versus 44% in the placebo arm (p = .004). In the abemaciclib arm, diarrhea was the most frequent adverse event (81.3%), although it was a predominantly grade 1 event (44.6%). The most common grade 3 or 4 adverse events with abemaciclib were neutropenia (21.1% v 1.2%), diarrhea (9.5% v 1.2%), and leukopenia (7.6% v 0.6%) [33].

In Europe abemaciclib is not currently approved.

THE CHOICE OF POSTMENOPAUSAL TREATMENT

Since clinical studies have not been conducted in homogeneous populations with respect to endocrine therapy exposure and endocrine sensitivity/resistance conditions, it is difficult to extrapolate a unique recommendation on the choice of therapy.

However, the following suggestions appear reasonable:

- Population never exposed to endocrine agents: Falcon was the only randomized study that exclusively enrolled patients with metastatic disease never exposed to hormone treatments before. Based on this study, fulvestrant represents a valid alternative to aromatase inhibitors, which have been the cornerstone of first-line hormone treatment of postmenopausal metastatic disease for many years. In registration studies, the combination of NSAI and CDK4/6 inhibitors (palbociclib and ribociclib, authorized by AIFA) was associated with a 42-44% reduction in the risk of progression, corresponding to an increase of about 10 months in median PFS compared to endocrine therapy alone. In these studies, the hormone therapy naïve population was between 44% and 48% of the enrolled patients, and subgroup analyses showed a similar benefit of the combined treatment also in these patients. Therefore, in endocrine therapy naïve patients, the combination of an NSAI and CDK4/6 inhibitors should be considered as a first-line option.

- Population exposed to hormone agents in the adjuvant setting: in the absence of predictive biomarkers, the type of drug already used and the recurrence-free interval appear to be valid criteria for therapy selection. After tamoxifen, aromatase inhibitors are a well-established indication, but based on the benefits observed in the FIRST study, fulvestrant may also be an alternative. For the above reasons, therapy with aromatase inhibitors and CDK4/6 inhibitors should be considered as a first-line option. For recurrences during the adjuvant endocrine therapy or within one year of completion, combinations of fulvestrant and palbociclib or exemestane and everolimus should be considered.

- Population exposed to hormone agents in the metastatic setting: after progression during the first-line therapy, for patients who did not receive a CDK4/6 inhibitor in the first-line setting, the use of fulvestrant in association with palbociclib is indicated, or everolimus associated with exemestane; in case of contraindications to biological drugs and/or if the patient received a CDK4/6 inhibitor in the first-line setting, monotherapy with fulvestrant may be considered. The choice should be based on the evaluation of the benefit/risk ratio of treatments and the characteristics of the patient and the disease. The transition to chemotherapy should also be considered, particularly in patients with early and massive disease progression with impaired organ function.

There are no studies that have explored the different hormone sequences in the metastatic setting; however, it should be remembered that the choice of treatment can significantly influence subsequent lines, and therefore a therapeutic algorithm for the potential sequence should be defined.

Retrospective data indicate that at each line change the probability of response to the next hormone therapy line tends to decrease by 25-30%, as does the duration of the PFS. Therefore, if hormone therapy is still indicated based on the clinical characteristics of the disease and the patient's response to previous therapies, treatment options that have not yet been used may be attempted, in compliance with registered indications.

CLINICAL QUESTION No. 15 (Figure 14)

In postmenopausal patients with advanced hormone-receptor positive and HER2 negative breast cancer, not candidates for chemotherapy, pretreated with a non-steroidal aromatase inhibitor and recurring during or within 12 months of the adjuvant hormone therapy, is the combination of fulvestrant and palbociclib recommended rather than the combination of exemestane and everolimus?

724 patients who showed resistance to previous treatment with a non-steroidal aromatase inhibitor (defined as progression during or within 12 months of the end of adjuvant treatment or progression during or within 1 month of the end of treatment for advanced disease) were randomized (2:1) to a combination of everolimus and exemestane or to exemestane only in the BOLERO-2 study.[9] The combination of everolimus and exemestane produced a relative reduction of 57% in the risk of progression compared to treatment with exemestane alone (HR 0.43; 95% CI 0.35-0.54; p<0.001), with a median PFS (investigator-assessed: primary endpoint of the study) of 6.9 months vs 2.8 months. Centrally assessed median PFS (considered only a complementary analysis) showed values of 10.6 months vs 4.1 months; HR 0.36; 95% CI 0.27-0.47; p<0.001). The benefit in PFS was consistent in all the subgroups analyzed (in particular for age, visceral involvement, exclusive bone disease, and sensitivity to previous hormone therapy), and in the exploratory analysis carried out in the subgroup of 137 patients (19% of the 724 patients enrolled in BOLERO 2) treated for advanced disease in the first-line setting, a PFS of 11.5 months vs 4.1 months was reported (HR 0.39; 95% CI 0.25-0.62)[13].

Despite the significant improvement in PFS, no significant differences in overall survival were observed (30.9 vs 26.5 months; HR 0.89; p=0.14), a result that is possibly related, according to investigators, to the low power of the study for the analysis of this effect, to an imbalance in the therapies administered at progression, and to possible biological resistance triggered by everolimus itself.[10] Objective responses were reported in 9.5% of cases, and a clinical benefit in 33%, compared to grade 3-4 toxicities such as stomatitis 8%, anemia 6%, hyperglycemia 4%, fatigue 4%, non-infectious pneumonia 4%. A relative reduction in the risk of bone progression of 47% and a relative reduction in the risk of QoL deterioration of 26% were also observed.[11-13] A population similar to that of the BOLERO-2 study was the subject of the phase III study PALOMA-3, where 521 patients with ER+ metastatic breast cancer (with no visceral crisis), recurrence or progression during hormone therapy, regardless of their menopausal status, were randomized (2:1) to receive fulvestrant 500 mg in association or not with palbociclib (125 mg/day 3 weeks out of 4), up to progression.[8,34] About 40% had

received only one line of treatment in the advanced setting. The average age of patients was 57 years and about 60% of cases had visceral disease. According to the definition adopted, about 80% of cases had shown prior sensitivity to hormone treatments (aromatase inhibitors). Approximately 25% (=129) of the patients enrolled (84 in the palbociclib group and fulvestrant vs 45 in the fulvestrant group) were receiving their first-line metastatic treatment. PFS (primary endpoint of the study) was significantly longer with the combination of fulvestrant and palbociclib (9.5 vs 4.6 months; HR 0.46; 95% CI 0.36-0.59; p<0.0001), a result confirmed by an independent evaluation of the radiological documentation of responses (performed randomly in 40% of cases). Subgroup analysis based on stratification criteria did not show significant differences between the presence or absence of visceral disease, nor for hormone-sensitivity status. Even menopausal status did not lead to any differences. The effect of palbociclib was independent of the presence or absence of PIK3CA mutations (present in 33% of the patients tested), determined by liquid biopsy. The rate of objective responses was 10.4% with the combination, compared to 6.3% for fulvestrant alone (with a clinical benefit in 34% and 19% of cases, respectively). Survival data are not available at present. The most frequent and significant side effects of the combination of fulvestrant and palbociclib were neutropenia, leukopenia, fatigue and nausea; the incidence of grade 3-4 toxicities was 62% for neutropenia (vs 0.6 in the fulvestrant group), 25.5% for leucopenia (vs 0.6%), 2.6% for anemia (vs 1.7%), 2.3% for platelet disease (vs 0%) and 2% for fatigue (vs 1.2%). Febrile neutropenia was also rare (0.6%), although overall a higher number of infections was observed in the combination group, but were grade 1-2. Serious adverse events were not significantly different in the two treatment arms.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
VERY LOW	In postmenopausal patients with hormone-receptor positive, HER2 negative advanced breast cancer, who are not candidates for chemotherapy, have been pretreated with a non-steroidal aromatase inhibitor and have recurred during or within 12 months of the end of adjuvant hormone therapy or during or within one month of the end of hormone therapy for advanced disease, the combination of fulvestrant and palbociclib could be considered compared to the combination of exemestane and everolimus.	**Conditional Positive**

9.3   Types of systemic therapy: chemotherapy

Patients with hormone-receptor negative or hormone-receptor positive metastatic breast cancer should receive chemotherapy if they have endocrine-resistant disease or if they have a visceral crisis or highly symptomatic visceral metastases. Polychemotherapy usually produces an increase in the rate of objective responses and lengthens the time to progression compared to monochemotherapy. However, polychemotherapy is associated with increased toxicity and only minimal survival benefit.[35-38] In addition, the administration of single chemotherapy agents in sequence reduces the need for dose reduction. Therefore, the advantage of polychemotherapy is marginal and debated. In clinical practice, chemotherapy is continued until progression. Adverse events may require dose reduction or discontinuation of chemotherapy prior to progression. Some available data seem to suggest that protracted use of chemotherapy may increase PFS compared to shorter chemotherapy courses.[39,40] However, as there are no substantial differences in OS, the use of prolonged chemotherapy compared to shorter chemotherapy must be balanced against side effects that adversely affect

quality of life. Sequential responses are often observed and support the use of sequential monochemotherapy or polychemotherapy. Failure of three different lines of chemotherapy or a performance status of 3 or more are indications for supportive therapy alone.

POLYCHEMOTHERAPY

The most frequently used polychemotherapy regimens are: CAF/FAC, FEC, AC/EC, CMF, doxorubicin/docetaxel, epirubicin/docetaxel, doxorubicin/paclitaxel, epirubicin/paclitaxel, docetaxel/capecitabine, paclitaxel/gemcitabine, carboplatin/gemcitabine. Recently, data from the phase II study tnAcity have been published, which evaluated efficacy and safety – as first-line metastatic treatment for patients with triple-negative breast cancer – nab-paclitaxel + carboplatin, nab-paclitaxel + gemcitabine, and gemcitabine + carboplatin. The study, which enrolled 191 patients, showed that the combination of nab-paclitaxel and carboplatin significantly prolongs PFS compared to nab-paclitaxel + gemcitabine (median PFS, 8.3 vs 5.5 months; HR, 0.59 [95% CI, 0.38-0.92]; p = .02) and gemcitabine + carboplatin (median PFS, 8.3 vs 6.0 months; HR, 0.58 [95% CI, 0.37-0.90]; P = .02).[41]

MONOCHEMOTHERAPY

The choice of treatment should also consider which drugs were administered in the adjuvant setting, the doses achieved, the duration of the disease-free interval and the patient's performance status. For paclitaxel and nab-paclitaxel, weekly treatment was more active and less toxic than treatment with docetaxel every three weeks.

There is no gold standard treatment in the second-line setting, too. A recent systematic review assessed the chemotherapy regimens used after first-line therapy in terms of the relationship between activity and safety.[42] The median survival observed in most studies is between 8 and 13 months. However, heterogeneity of the populations and regimens studied, lack of data on quality of life and the difficulty of comparing different treatments are frequently observed.

Among the drugs that can be considered most active, we include:
- Anthracyclines: adriamycin, epirubicin, liposomal doxorubicin
- Taxanes: paclitaxel, docetaxel, Nab-paclitaxel
- Anti-metabolites: capecitabine
- Vinca alkaloids: vinorelbine
- Microtubule inhibitors other than taxanes: vinorelbine and eribulin**

Other medications that can be considered moderately active are:
- Cyclophosphamide
- Gemcitabine
- Fluorouracil
- Methotrexate
- Mitoxantrone
- Mitomycin C
- Cisplatin (higher activity was observed in tumors in women with BRCA1 mutation)***
- Carboplatin ***
- Others.

* Nab-paclitaxel, a formulation of paclitaxel bound to albumin nanoparticles and free of chemical solvents and therefore not requiring premedication, significantly improved the percentage of objective responses (33% vs 19%; p = 0.001) and TTP (23 vs 16.9 weeks; p = 0.006) compared to three-weekly paclitaxel in a phase III study conducted in patients with metastatic breast cancer receiving first-line and further-line treatment. In this study, a significant OS advantage was reported with nab-paclitaxel in patients treated in the second-line and further-line settings (56.4 *v* 46.7 weeks; HR = 0.73; p=0.024)[43].

A randomized phase II study evaluated the anticancer activity and safety of three different nab-paclitaxel schedules (300 mg/m^2 every three weeks versus weekly administration of 100 mg/m^2/week or 150 mg/m^2/week) and studied the differences in activity and safety between these nab-paclitaxel schedules and three-weekly docetaxel (100 mg/m^2).[44] The 150mg/m^2/week dose of nab-paclitaxel significantly improved progression-free survival (PFS >5 months) compared to docetaxel, both according to the investigator assessment and the independent radiological evaluation. Based on the independent radiological review, the rate of objective responses (RC+RP) was higher with both weekly doses of nab-paclitaxel compared to docetaxel, but this difference did not reach statistical significance. Disease control (RC+RP+SD ≥16 weeks) was statistically better with both weekly doses of nab-paclitaxel than with docetaxel. No differences were reported in terms of objective responses and PFS between nab-paclitaxel every three weeks and docetaxel. Neutropenia, grade 3 and 4 febrile neutropenia and asthenia were more frequent with docetaxel, while peripheral neuropathy of any grade were similar in all arms, but was more rapidly reversible with nab-paclitaxel. The indication authorized to date by AIFA for nab-paclitaxel is as follows: "monotherapy in the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard therapy containing anthracycline is not indicated." The treatment is approved for three-weekly administration, although the weekly schedule has shown a good profile of activity and safety.

** Eribulin is a drug derived from a substance extracted from sponges that is part of a new class of microtubule inhibitors, which destroy the mitotic spindle in a different way than agents such as taxanes, vinca alkaloids and others. A randomized phase III trial was conducted in patients with metastatic breast cancer who were pretreated with ≥2 lines of chemotherapy including anthracyclines and taxanes unless contraindicated. Patients were randomized 2:1 to receive eribulin or a treatment selected by the investigator. Eribulin significantly improved overall survival (about 2.5 months), the main objective of the study, and the percentage of objective responses. It improved – although not significantly – TTP with an acceptable toxicity profile. The grade 3-4 side effects reported included neutropenia (44%), asthenia/fatigue (7.6%), and peripheral neuropathy (8.4%). About 10% of all patients had serious treatment-related side effects.[45]

This drug is currently approved in Italy for the treatment of adult patients with locally advanced or metastatic breast cancer, who have progressed after at least one chemotherapy regimen for advanced disease. Previous treatment should have included the use of an anthracycline and a taxane, in an adjuvant or metastatic setting, unless patients were not eligible to receive these treatments.

In another phase III study, eribulin was compared with capecitabine in 1,102 women with metastatic or locally advanced breast cancer. Patients should have received anthracyclines and taxanes, but eribulin could be administered in the first, second or third-line setting.[46]

No significant differences were observed in terms of PFS (4.1 vs 4.2 months) and OS (15.9 vs 14.5 months). In a preplanned subgroup analysis, patients with triple-negative tumors still showed a more favorable outcome with eribulin (14.4 vs 9.4 months; HR=0.7), which warrants further evaluation in this subgroup.

A pooled analysis of the two phase III studies with eribulin was requested by EMA to evaluate the effect of the drug in specific subgroups. Median overall survival was 15.2 months for eribulin and 12.8 months for the control treatment (HR 0.85, p=0.003). A particular benefit was confirmed especially in the triple-negative cancer subgroup (HR 0.74).[47] A further retrospective analysis conducted on phase II and III studies evaluated

the effect in elderly patients. Age did not influence the efficacy of the drug, which was comparable in patients > 50 years and > 70 years, although in the latter group side effects were more frequent.[48]

*** The use of **platinum salts** in the triple-negative population has been the subject of numerous studies. In populations not selected according to BRCA status, responses were obtained in about 30% of cases, with a median PFS of about 15 months. The randomized phase III study TNT evaluated carboplatin and docetaxel activity (with crossover upon progression) as first-line therapy in patients with TNBC not selected according to BRCA status.[49] The primary endpoint was the objective response rate (ORR). In the unselected population (376 patients; 188 carboplatin, 188 docetaxel), carboplatin was no more active than docetaxel (ORR, 31.4% versus 34.0%, respectively; $P = 0.66$). In contrast, in subjects with the BRCA mutation, carboplatin doubled the ORR rate compared to docetaxel (68% versus 33%, respectively; interaction test, $P = 0.01$). This benefit was not observed in patients with BRCA1 methylation, low levels of BRCA1 mRNA or a high score in the HRD Myriad test.

Similar results were also reported in the phase II study TBCRC009, with 54.5% objective responses in the group of patients with germinal BRCA mutation (vs 25.6% in the unselected population).[50]

Although these data do not support the indiscriminate use of platinum salts in the TN population, they indicate that knowledge of BRCA status for these patients may allow better selection of therapy.

9.4   Types of systemic therapy: biological therapies

Anti-HER2 drugs in the treatment of HER2 positive metastatic disease
Indications: Patients with metastatic tumor HER2 positive are candidates for therapy with anti-HER2 drugs.

Treatment with anti-HER2 drugs should be started as early as possible, but – if not used as a first-line therapy – should still be considered during the course of the disease.

9.4.1 Monoclonal antibodies

First-line treatment with trastuzumab-containing combinations

Dual HER2 blockade with two biological agents + monochemotherapy

CLINICAL QUESTION No. 16 (Figure 11)

In women with HER2 positive advanced breast cancer who are candidates for first-line chemotherapy, is the combination of pertuzumab, trastuzumab and chemotherapy recommended rather than chemotherapy combined with trastuzumab?

The randomized clinical trial CLEOPATRA evaluated the addition of the monoclonal antibody pertuzumab to the combination of docetaxel and trastuzumab.[51] By binding to a different epitope from the one recognized by trastuzumab on the extracellular portion of HER2, pertuzumab inhibits its dimerization with other members of the epidermal growth factor receptor (EGFR) family. One of the eligibility criteria required that >12 months had elapsed since the end of adjuvant therapy with trastuzumab. In this study, which enrolled 808 patients (only 10% of which treated with trastuzumab in the adjuvant setting), the combination of the two biological agents with docetaxel was associated with a significant increase in objective responses, PFS (18.5 months vs

12.4 months; HR=0.62; 95% CI 0.51-0.75; p < 0.001) and OS (56.5 months vs 40.8 months; HR=0.68; 95% CI, 0.56-0.84; P<0.001).[52]

These benefits in terms of effectiveness were obtained at the price of a modest worsening of the safety profile, with an increase in diarrhea and febrile neutropenia in the arm treated with pertuzumab and trastuzumab.

Pertuzumab is currently reimbursed by the NHS in Italy and indicated in association with trastuzumab and docetaxel in adult patients with HER2 positive inoperable, metastatic or locally recurred breast cancer, not previously treated with anti-HER2 therapy or chemotherapy for the metastatic disease.

With regard to the association of pertuzumab, trastuzumab and paclitaxel, a phase II study was conducted in 69 patients with HER2 positive metastatic breast cancer treated with pertuzumab, trastuzumab, and weekly paclitaxel in the first-line (n=51) and second-line (n=18) settings, achieving a six-month PFS of 86% (95% CI, 75%-92%) and a median PFS of 19.5 months (95% CI, 14-26 months); this regimen was well tolerated and no episodes of febrile neutropenia or symptomatic left ventricular dysfunction were recorded.[53] According to AIFA's prescribing information, paclitaxel can be used in association with pertuzumab and trastuzumab.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
High	In women with HER2 positive advanced breast cancer who are candidates for first-line chemotherapy, the association of pertuzumab, trastuzumab and chemotherapy should be considered compared to the association of trastuzumab and chemotherapy.	**Strong Positive**

Treatment with trastuzumab in the first-line metastatic setting <u>after</u> adjuvant treatment with trastuzumab.

Data on the efficacy of trastuzumab in previously exposed and recurred patients come from a retrospective study of 164 patients and a small prospective study.[54] These data suggest the potential efficacy of re-treatment with trastuzumab, in addition to chemotherapy, compared to chemotherapy alone (**SIGN Level of evidence 3**).

Analyzing the CLEOPATRA study, where only 88 patients (about 10% of the enrolled population) received trastuzumab in the (neo)adjuvant setting, it can be observed that, also in this subgroup of patients, PFS was higher for the group treated with pertuzumab/trastuzumab (16.9 months) than for the control group treated with trastuzumab alone (10.4 months).[51]

CLINICAL QUESTION No. 17 (Figure 11)

In patients with HER2 positive breast cancer with first metastatic recurrence, pretreated with trastuzumab in the adjuvant setting and recurred during or within 6 months after completion of treatment, is T-DM1 recommended rather than capecitabine and lapatinib in terms of PFS and survival and tolerance?

The EMILIA randomized clinical trial compared the combination of lapatinib and capecitabine with trastuzumab-DM1 (T-DM1) in women with metastatic disease previously treated with trastuzumab and taxanes, enrolling both first-line metastatic patients whose recurrence occurred during or within six months of adjuvant treatment with trastuzumab, and second-line or further-line metastatic patients who failed the HER2

treatment, provided they had never received lapatinib and/or capecitabine before.[55] Compared to the control arm, T-DM1 led to an increase in objective responses, median PFS (9.6 months vs 6.4 months; HR=0.65; 95% CI 0.55-0.77; p<0.001) and median overall survival (30.9 months vs 25.1 months; HR=0.68; 95 CI 0.55-0.85; p<0.001). T-DM1 was associated with a lower incidence of grade 3 and 4 side effects (41% vs 57%) (**SIGN Evidence Level 1+).**[67]

T-DM1 is approved and reimbursed by the NHS in Italy for patients with HER2 positive metastatic disease who were previously exposed to a taxane and trastuzumab (in combination or separately) with disease progression during or within six months of adjuvant treatment with trastuzumab or during trastuzumab therapy for the treatment of inoperable metastatic or locally advanced disease.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
A	In patients with HER2 positive breast cancer with first metastatic recurrence, pretreated with trastuzumab in the adjuvant setting and recurred during or within 6 months of completion of treatment, T-DM1 should be considered as a first-choice option.[74]	**Strong Positive**

Monoclonal antibodies + first-line hormone therapy

Trastuzumab in combination with anastrozole was compared with anastrozole alone in a randomized phase III trial in postmenopausal patients with hormone-receptor and HER-2 positive tumors, never treated with chemotherapy for the metastatic disease.[56] The combination therapy significantly improved PFS, TTP, the percentage of objective responses (only partial responses) and clinical benefit. There were no significant differences in OS, but it should be noted that 70% of patients progressing with anastrozole had subsequently received trastuzumab (**SIGN Level of evidence 1+).**

A second randomized phase III study evaluated the addition of trastuzumab to letrozole to letrozole alone in 57 postmenopausal women who had not previously been treated for HER2 and ER positive metastatic disease. Although limited by the low number of patients enrolled (the study was discontinued due to low accrual), this study shows a significant increase in median progression time in favor of the combination arm (3.3 months vs. 14.1 months).[57]

Treatment with an aromatase inhibitor in addition to trastuzumab can be selected for:

1) Postmenopausal patients with extremely indolent ER-positive and HER2 positive breast cancer as an alternative to trastuzumab/chemotherapy or pertuzumab/trastuzumab/chemotherapy;

2) Patients with contraindications to chemotherapy.

Maintenance therapy with anti-HER2 drugs after first-line treatment

Trastuzumab is indicated as monotherapy or in association with pertuzumab as maintenance therapy after obtaining an objective response or stable disease with trastuzumab/chemotherapy or trastuzumab/pertuzumab/chemotherapy, respectively. In case of HER2 positive and hormone-receptor positive disease, after treatment with trastuzumab +/- pertuzumab/chemotherapy, anti-HER2 maintenance therapy should be associated with maintenance hormone therapy.

Treatment of patients resistant to trastuzumab or trastuzumab/pertuzumab

If progression occurs during or within 6-12 months of completion of the adjuvant treatment with trastuzumab, the patient may be considered eligible for further treatment with anti-HER2 agents (Figure 11).

In patients resistant to a therapeutic line containing an anti-HER2 drug, it is important to maintain the continuous pharmacological inhibition of this molecular target in subsequent therapy lines.

CLINICAL QUESTION No. 18 (Figure 11):

In patients with HER2 positive breast cancer with metastatic disease progression after previous treatment with anti-HER2 drugs (trastuzumab, lapatinib), is T-DM1 recommended rather than capecitabine and lapatinib in terms of PFS, survival and tolerability?

The EMILIA randomized clinical trial compared the combination of lapatinib and capecitabine with T-DM1 in women with metastatic disease previously treated with trastuzumab and taxanes.[55] T-DM1 is an immunoconjugate consisting of the monoclonal antibody trastuzumab and emtansine, a microtubule toxin.

Following the binding of T-DM1 with the HER2 receptor, the complex is internalized in the cell and, following cleavage, the toxoid is released and exerts its antitumor activity.

In this randomized phase III trial, first-line metastatic patients with recurrence during or within six months of adjuvant treatment with trastuzumab, or second-line or further-line metastatic patients with recurrence after failure of HER2 treatment, were eligible for enrolment, provided they had never received lapatinib and/or capecitabine before. Compared to the control arm, T-DM1 led to an increase in objective responses, median PFS (9.6 months vs 6.4 months; HR=0.65; 95% CI 0.55-0.77; p<0.001) and median overall survival (30.9 months vs 25.1 months; HR=0.68; 95 CI 0.55-0.85; p<0.001). In addition, overall, T-DM1 was associated with a lower incidence of grade 3 and 4 side effects (41% vs 57%). In patients with HER2 positive metastatic disease who had previously received treatment with a taxane and trastuzumab, T-DM1 was superior to treatment with lapatinib/capecitabine in terms of PFS and OS (**SIGN Level of evidence 1**+).

T-DM1 was also used in the experimental arm of the phase III study TH3RESA, which enrolled 602 patients with HER2 positive metastatic disease who had already received two or more prior anti-HER2 treatments, of which at least one with lapatinib. Patients enrolled in the control arm received a treatment selected by the investigator.[58] 83% of the patients in the control arm received a regimen containing an anti-HER2 drug, while 17% received chemotherapy alone. T-DM1 was associated with a significant increase in median TTP (6.2 vs 3.3 months), objective responses (31% vs 9% in patients with measurable disease), and OS (HR=0.552), although this last endpoint did not reach the prespecified level of significance.

T-DM1 is approved and reimbursed by the NHS in Italy: as monotherapy, for the treatment of adult patients with HER2 positive, inoperable, locally advanced or metastatic breast cancer, previously treated with trastuzumab and a taxane, administered separately or in combination. Patients must have been previously treated for locally advanced or metastatic disease or have developed recurrence during or within six months of completion of adjuvant therapy.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
A	In patients with HER2 positive breast cancer with metastatic disease progression after prior treatment with anti-HER2 drugs (trastuzumab, lapatinib), T-DM1 should be considered as a first-choice option.[74]	**Strong Positive**

9.4.2   *Lapatinib*

The results of three phase III randomized trials are available.

- A randomized phase III study compared the combination of lapatinib and capecitabine with capecitabine alone in patients with HER-2 positive breast cancer pretreated with regimens containing anthracyclines, taxanes and trastuzumab.[59,60] Combination therapy significantly improved TTP (8.4 months vs 4.4 months) and the rate of objective responses and clinical benefit, and caused a non-statistically significant improvement in OS. The frequency of side effects was similar in both arms except for diarrhea, dyspepsia and rash, which were observed most frequently with the combination therapy (**Evidence level SIGN 1**+). There was also a reduction in the first brain progression in patients treated with lapatinib and capecitabine (4 months vs 11 months). Lapatinib is currently authorized in Italy "in association with capecitabine in patients with HER2 positive advanced or metastatic breast cancer progressing after treatment containing anthracyclines and taxanes and treatment with trastuzumab for the metastatic disease.

In another randomized, multicenter, open-label phase III trial, 296 patients with HER2 positive metastatic breast cancer progressing during a trastuzumab regimen were randomized to receive lapatinib as monotherapy or a combination of lapatinib and trastuzumab.[61] The combination therapy significantly improved PFS (11.1 weeks vs 8.1 weeks; HR=0.74, 95% CI 0.58-0.94; p=0.011) and OS (median advantage of 4.5 months) even if over 50% of patients randomized in the lapatinib arm had crossed over. The incidence of side effects (mainly grade 1 and 2) was similar in the two arms, with only a significant increase in diarrhea in the combination arm. The incidence of symptomatic and asymptomatic cardiac events was low. The association of lapatinib and trastuzumab (without chemotherapy) has been approved by EMA in patients with HER2 positive and hormone-receptor negative metastatic breast cancer, progressing despite prior therapy with trastuzumab and chemotherapy.
This association is authorized by AIFA, but is not reimbursed by the NHS.

In addition to this evidence on lapatinib, the randomized study CEREBEL, comparing trastuzumab and capecitabine to lapatinib and capecitabine with the primary objective of assessing the incidence of brain metastases in the two treatment groups, is worth mentioning.[62] The rationale was to observe whether lapatinib, a small molecule capable of crossing the blood-brain barrier, could prevent the development of brain metastases in a group of patients known to be at high risk for this type of event. The study failed to show any differences in the incidence of brain metastases in the two treatment arms. Moreover, in patients with first

metastatic recurrence, trastuzumab was superior to lapatinib in terms of both PFS and OS. On the contrary, in patients previously treated with trastuzumab, no differences in terms of PFS between trastuzumab/capecitabine and trastuzumab/lapatinib were found.

NOTE: In patients receiving HER2 treatment, it is advisable, regardless of the treatment line, to monitor the left ventricular ejection fraction (LVEF) with MUGA or echocardiogram every three months. Due to the high incidence of brain metastases, a brain CT or MRI is recommended in the presence of neurological symptoms, however mild.

In a randomized phase III study, the association of lapatinib and letrozole was compared to letrozole and placebo in the first-line treatment of patients with hormone-receptor positive metastatic or locally advanced breast cancer. Therapy containing lapatinib significantly improved PFS, objective response rates and clinical benefit in the subgroup of patients with HER-2 positive tumors (**SIGN Level of evidence 1+**).[63]

Lapatinib is currently registered in Italy "in association with an aromatase inhibitor in postmenopausal women with HER2 positive and hormone-receptor positive metastatic disease, for whom chemotherapy is not currently indicated. The patients in the registration study had not previously been treated with trastuzumab or an aromatase inhibitor."

9.4.3 Biological drugs in the treatment of HER2 negative metastatic disease

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against VEGF (vascular endothelial growth factor) that inhibits tumor angiogenesis.

Bevacizumab has been tested in phase III randomized clinical trials in the first-line metastatic setting or in subsequent lines of treatment in HER2 negative breast cancer.

A randomized phase III trial in patients with metastatic disease compared paclitaxel with paclitaxel and bevacizumab as first-line breast cancer therapy (E2100 study).[64] A statistically significant improvement in PFS (11.8 months vs 5.9 months; HR=0.60; 95%CI 0.51-0.70; p<0.001) and objective responses (36.9% vs 21.2%; p>0.001) was observed with the addition of bevacizumab. The OS was superior with the combination therapy, but did not show a statistically significant difference. Among the side effects, the addition of bevacizumab to paclitaxel resulted in a higher incidence of arterial hypertension, bleeding, grade 3/4 proteinuria and neuropathy.

In another phase III study, bevacizumab (at two different doses: 7.5 and 15 mg/kg) in combination with docetaxel was compared with docetaxel alone.[65.66] A significant advantage was observed in PFS (about two months) and in the rate of objective responses with the combination therapy and particularly with the higher dose of bevacizumab. The final data failed to show an OS advantage.

The results of the RIBBON-1 study were recently presented, where bevacizumab added to different chemotherapy regimens (one cohort received capecitabine and the other anthracyclines or taxanes) significantly improved PFS and response rate, but not OS.[67]

The RIBBON-2 study is a randomized phase III trial conducted in patients with HER2 negative breast cancer pretreated for metastatic disease.[68] The therapeutic options included taxanes, gemcitabine, capecitabine, vinorelbine versus the same treatment associated with bevacizumab. The study showed an advantage in PFS

(about two months) and in the rate of objective responses. The interim OS analysis did not show any differences between the two treatments.

The statistically significant improvement in PFS achieved with bevacizumab and first-line chemotherapy was confirmed by a meta-analysis of the three studies, accompanied by a non-statistically significant improvement in OS.[69]

Based on these data, in Italy bevacizumab is indicated in combination with paclitaxel in the first-line treatment of HER2 negative metastatic breast cancer, and is not indicated in combination with any other chemotherapy or monotherapy.

Duration of treatment with bevacizumab in responding patients: In the E2100 study, which led to the registration of bevacizumab in association with paclitaxel, the combined treatment was administered until disease progression or unacceptable toxicity. In addition, in patients where paclitaxel was interrupted in the absence of disease progression, only therapy with bevacizumab could be continued until disease progression or intolerance.

PARP-inhibitors

The results of the phase III study Olympiad, conducted in patients with HER2 negative metastatic breast cancer with germline mutation of the BRCA gene, pretreated in up to two previous lines of chemotherapy for metastatic disease, were published in 2017.[70] In this trial patients were randomized to receive olaparib (205) or chemotherapy (97) with one of the following drugs: capecitabine, eribulin or vinorelbine, at the investigator's discretion. About 70% of patients had received at least one line of chemotherapy for metastatic disease. The results showed a higher median PFS in patients treated with olaparib than in control arm patients and a 42% reduction in the risk of progression or death in favor of olaparib (7 months vs 4.2 months; HR for progression or death 0.58; 95% CI 0.43-0.80; p<0.001). Treatment with olaparib was superior in terms of objective responses (59.9% vs. 28.8%). The incidence of adverse events of grade 3 or higher was 36.6% in the group treated with olaparib and 50.5% in the control group.

The EMBRACA Phase III study evaluated the efficacy and safety of talazoparib versus a standard therapy selected by the investigator (capecitabine, eribulin, gemcitabine or vinorelbine) in patients with metastatic breast cancer and BRCA1/2 germline mutation. Median PFS was 8.6 months for patients treated with talazoparib and 5.6 months for patients in the control arm (HR = 0.542, P < .0001). The probability of progression was 45.8% lower for patients treated with talazoparib. In terms of 24-week ORR and CBR, a statistically significant advantage in favor of talazoparib was also observed. Specifically, the ORR was 62.6% vs 27.2% (HR = 4.99, P < .0001) for patients in the experimental arm compared to those in the control arm; 24-week CBR was 68.6% for patients treated with talazoparib compared to 36.1% for patients treated with a standard therapy chosen by the investigator. OS data were not yet mature, but a trend in favor of talazoparib was observed, with a death risk reduction of 24%. In addition, the time to clinical deterioration was 24.3 months for patients treated with talazoparib and 6.3 months for patients treated with chemotherapy.

9.5 Pharmacological treatment of bone metastases

Bone metastases are the first metastatic site in 20-30% of breast cancer patients, and more than 80% of patients who die from metastatic breast cancer have bone lesions.

PHOSPHONATES

Therapeutic indications:

- Prevention of events related to the skeletal system (pathological fractures, vertebral compression, bone radiotherapy or surgery, neoplastic hypercalcemia) in adult patients with advanced malignant tumors affecting the bone.

- Treatment of adult patients with neoplastic hypercalcemia.

Drugs and doses:

- Pamidronate 90 mg ev infusion over 1-2 hours every 4 weeks

- Zoledronate 4 mg ev infusion over 15 minutes every 3-4 weeks[71]

- Ibandronate:[72,73]

  - 6 mg ev infusion over about 1 hour every 3-4 weeks

  - 50 mg oral per day. The tablets should be taken following overnight fast (at least six hours) and before the first food and drink of the day (at least 30 minutes).

Duration:

An optimal duration has not been established. The recommended duration of treatment with bisphosphonates is two years; treatment beyond two years can only be continued in selected cases and with the awareness that only anecdotal information on long-term efficacy and toxicity is available.

Toxicity:

Further information on the side effects of bisphosphonates, in particular zoledronate, has recently been made available. The most important toxicity is the risk of renal damage with administration of this drug;[74] accordingly, all patients must undergo regular renal function evaluations and dose adjustments are necessary for patients with impaired renal function. However, it appears that a simple measurement of serum creatinine may not be sufficient to identify mild renal failure.[75]

A second toxicity worthy of note, although less frequent, is osteonecrosis of the jaws. The first cases were reported in dental surgery journals already in 2001, and recently other papers have been published that report an incidence of osteonecrosis of the jaws of 2.9% in patients with breast cancer treated with both zoledronic acid and pamidronate.[76,77] The duration of treatment seems to be the most important risk factor, but the type of diphosphonate (zoledronic acid > pamidronate), the simultaneous administration of chemotherapy or corticosteroids, poor oral hygiene with dental abscesses and periodontopathies and dental procedures carried out during treatment appear to have a role. Guidelines for the prevention, diagnosis and treatment of this complication have also been drawn up.[78] In general, it is recommended that patients who are candidates for bisphosphonate therapy perform a routine dental examination before starting treatment (see AIOM's Guidelines for the treatment of bone metastases).

Long bone fractures not associated with the presence of metastatic lesions in patients treated with bisphosphonates have also been described, although the incidence is quite low.[79]

In addition, an increased risk of atrial fibrillation has been reported in patients who received zoledronate as a treatment for osteoporosis.[80] The same data emerged for patients treated with alendronate, another bisphosphonate, also for osteoporosis.[81] At present, this toxicity has not been reported in women treated with bisphosphonates for breast cancer.

Supplementation:

Patients with bone metastases should be prescribed calcium citrate (1000-1500 mg/day) and vitamin D3 (400-800 IU/day) in combination with bisphosphonates.

DENOSUMAB

Denosumab is a human monoclonal antibody that binds to the RANK protein (RANKL), blocking it. This suppresses the function of osteoclasts and inhibits bone resorption. The drug was shown to be effective in patients resistant to bisphosphonates, and in a comparison study with zoledronic acid in patients with breast cancer with bone metastases it significantly prolonged the time to the first and subsequent skeletal events, with a reduction in the risk of developing multiple skeletal events of 23%. Denosumab also reduced the average skeletal softness rate by 22%. Treatment with denosumab also resulted in increased suppression of bone turnover markers. OS and PFS were similar in both arms, as was the incidence of side effects and serious side effects. Osteonecrosis of the mandible occurred in a low percentage of patients, without significant differences between the two drugs; hypocalcemia and odontalgia were more frequent with denosumab, while renal failure, fever, bone pain, arthralgia and acute reactions were observed more frequently with zoledronic acid.[82]

Denosumab is registered in Italy for "the prevention of events related to the skeletal system (pathological fractures, bone radiotherapy, spinal cord compression or bone surgery) in adults with advanced malignancies involving the bone." The recommended dose is 120 mg given as a single subcutaneous injection once every four weeks. All patients treated with denosumab should receive a supplement of at least 500 mg calcium and 400 IU vitamin D, except in the case of hypercalcemia.

It should be emphasized that the benefit of bisphosphonates and denosumab consists in the reduction of skeletal events, i.e. control of bone pain, reduction of the risk of pathological fractures, reduction of the use of radiotherapy for analgesic purposes on symptomatic bone lesions and finally reduction of the need for local interventions, such as spinal decompression. Not all bone sites are symptomatic and not all are at risk of an adverse skeletal event.

For this reason, **treatment with bisphosphonates and denosumab should be considered if there is evidence of lytic or mixed bone metastases that require treatment in order to reduce the risk of adverse skeletal events or in case of hypercalcemia (see AIOM's Guidelines for the treatment of bone metastases).**

9.6 Surgery

Surgery is indicated in specific situations in metastatic breast cancer.

About 5-7% of breast cancers present with synchronous metastases at diagnosis, with a recent increase in incidence probably linked to the use of more sensitive preoperative staging methods (*stage-shift*). While breast cancer surgery is a priority in non-metastatic disease, its role in improving the patient's prognosis in the presence of synchronous metastases is not known.[83] Retrospective analyses have shown that patients undergoing primary tumor surgery had a better prognosis than those treated with systemic therapy alone.[84-86] In favor of a possible role of local treatment in the prognosis of de novo metastatic disease, there are also data suggesting that a local approach aimed at improved local-regional control (surgery + radiotherapy, axillary dissection) was superior to breast lesion surgery/mastectomy alone.[84] The methodological strength of these studies, however, is weakened by potential selection bias; for example, patients with a more limited metastatic disease and/or responding to medical treatment were more likely to undergo primary tumor surgery than patients with more advanced disease and/or no response to medical treatment. Only two randomized studies are available in the literature, one published in full and the other available as conference abstracts, which have evaluated the efficacy of stage IV breast cancer surgery at the onset:

1) Tata Memorial Hospital:[87] 350 women were enrolled in this study, of which 173 were assigned to primary tumor surgery + medical therapy and 177 to medical therapy alone. Note that women considered "ineligible" for hormone therapy (366/350) received systemic chemotherapy and were randomized after documentation of objective response to medical treatment. This study did not show differences in OS between women assigned to surgery + medical therapy and those assigned to medical therapy alone. Surgical therapy was found to be associated with better local-regional PFS, but also with worse DPFS.

2) MF07-0188: this study enrolled 274 women, of which 138 were assigned to primary tumor surgery (+/- axillary dissection) + chemotherapy (+ trastuzumab if HER2+) and 136 to chemotherapy alone (+ trastuzumab if HER2+). Patients with HR+ tumors could receive hormone therapy. The protocol included an upfront randomization (before the start of medical therapy) and the option of primary tumor surgery upon local progression in the group assigned to medical therapy only. This study showed a significant increase in median survival in patients assigned to upfront primary tumor surgery (46 vs 37 months, HR 0.66, p < 0.005). An unscheduled analysis of subgroups showed that survival was higher for local-regional treatment in women with luminal tumors, aged <55 years, and with solitary bone metastases.

3) Finally, a recent prospective cohort study shows that in patients responsive to line I treatment, primary tumor surgery does not affect either PFS or OS, since the prognostic role of responsiveness to medical treatment, histopathologic characteristics and disease burden is predominant.[89]

Four other randomized studies are currently underway, two of which have completed enrollment, and may provide additional evidence for this question.

In a patient with *de novo* metastatic breast cancer, primary tumor surgery is mainly palliative in nature (e.g. ulcerated lesions or lesions at risk of ulceration). In the absence of conclusive data on survival improvement, this procedure must/should not be performed outside of clinical studies. If it is considered – in selected cases and after discussion with the patient – it is necessary to explain to the patient that the effectiveness of such an approach is currently uncertain.

Surgery may also find indication in the case of:

- Vertebral metastases with spinal compression;
- Single visceral metastasis (liver, lung, brain);
- Pathological fractures;
- Pleural or pericardial effusions.

9.7 Radiation therapy

In metastatic disease, radiation therapy plays an important role in palliative care and in the treatment of oncological emergencies such as spinal cord compression, with the aim of improving the symptoms and quality of life of the patient, frequently used in association with systemic therapies.

Radiation therapy may therefore be indicated, as a palliative measure, in patients with:

- Symptomatic inoperable primary tumor;
- Painful or lytic bone metastases at risk of fracture;
- Cerebral metastases, symptomatic or asymptomatic;
- Metastatic spinal cord compression;
- Stabilization after spinal decompression surgery;
- Stabilization after fixation of pathologic fractures;
- Mediastinal syndrome.

In selected cases, for example in oligometastatic cancer patients, radiotherapy may be performed with a radical intent. This integrated approach requires a multidisciplinary discussion.

9.8 Radiometabolic therapy

A possible role in pain palliation of diffuse bone lesions with Strontium-89 ([89Sr])[90] has been reported. A recent review of the role of radioisotopes in controlling pain from bone metastases has shown that they can reduce pain in the short to medium term (1-6 months), but with frequent severe side effects (leukopenia and thrombocytopenia).[91]

10. Breast cancer in elderly women

According to AIRTUM data, in Italy 22% of new cases of breast cancer and 15% of deaths caused by breast cancer are expected to occur in women aged ≥70 years.[1]

This chapter will only deal with topics for which elderly specific literature is available. For topics not covered in this section, reference should be made to the relevant chapters for the general population.

10.1. Competing causes of death other than breast cancer

Many older patients with breast cancer die from non-cancer-related causes. The American study SEER (Surveillance Epidemiology and End Results), which included women with breast cancer, showed that, at a follow-up of 28 years, 80% of women over 70 dying for non-tumor-related causes had negative lymph nodes and 60% had positive lymph nodes.[2] However, it should be noted that breast cancer is the cause of death in a substantial number of elderly women. In women ≥80 years of age at diagnosis, about 40% die from cancer.[3] A correct evaluation of the patient's health status is therefore essential, because, while unnecessarily aggressive treatments must be avoided, it is well established that undertreatment represents a risk factor for disease recurrence and death.[4]

10.2. Multidimensional geriatric assessment

The estimation of expected survival and treatment tolerability can be improved by conducting a multidimensional geriatric assessment of the patient.
There are no specific recommendations on the application of multidimensional geriatric assessment to breast cancer patients. A literature review focused on the implementation of a pre- or postoperative geriatric evaluation in breast cancer patients led a Task Force of the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) to recommend co-operation with a geriatrician in order to optimize standards of care in oncology and consider a screening tool as a reasonable first step to identify patients who are candidates for a more extensive geriatric assessment.[5]
For patients in good health, a geriatric assessment adds little to the evaluation of a patient diagnosed with cancer, but it becomes important in vulnerable patients, where it can provide indications for interventions aimed at maintaining functional status and improving quality of life.[6]

Screening tests are available, which identify those patients who could benefit from a more detailed geriatric evaluation.[7,8]

10.3. Local-regional treatments

SURGERY versus PRIMARY HORMONE THERAPY

CLINICAL QUESTION No. 19 (Figure 2)

In fit elderly women with ER-positive tumors, can primary hormone therapy alone be an alternative to surgery?

Several clinical studies have evaluated exclusive hormone therapy with tamoxifen vs surgery with or without tamoxifen in women aged 70 years or older with operable tumors and who were considered fit for surgery.

The joint analysis of these studies within the Cochrane review[9] reported the following results:

1. No difference in survival (data include a total of 1,081 deaths recorded in 1,571 patients); HR for overall survival for surgery vs primary therapy: 0.98 (95% CI 0.81 - 1.20, P = 0.85; 3 studies, 495 participants); HR for surgery + adjuvant hormone therapy vs primary therapy 0.86 (95% CI 0.73 - 1.00, P = 0.06; 3 studies, 1,076 participants)

2. Statistically significant advantage in terms of progression-free survival in favor of surgery with or without hormone therapy. HR for progression-free survival for surgery vs primary therapy: 0.55 (95% CI 0.39-0.77, P = 0.0006); HR for surgery + adjuvant hormone therapy vs primary therapy 0.65 (95% CI 0.53 - 0.81, P = 0.0001)

The risk of postoperative complications increases with age, but these complications are generally moderate and are not associated with an increased risk of mortality. In addition, inadequate local control can have a negative impact on the quality of life and functional status of the patient. Surgical treatment remains the standard of care, and alternative therapies should be reserved for patients with severe comorbidities that represent a high risk of death from competing causes other than cancer.

Primary hormone therapy may include both tamoxifen and aromatase inhibitors.

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
A	In fit elderly women with ER-positive tumors, primary hormone therapy alone may be an alternative to surgery[18]	**Strong Negative**

AXILLARY LYMPHADENECTOMY

Two randomized clinical studies compared complete axillary dissection with no axillary exploration in elderly women with breast cancer and clinically negative axillar.[10-11] The majority of patients had ER-positive tumors and all received tamoxifen for 5 years. Omission of axillary dissection did not have a negative effect on survival, and a low incidence of axillary recurrences was reported.

Both studies were initiated in the 1990s and did not include selective sentinel lymph node biopsy, which is now the standard of care in elderly patients.

The omission of sentinel lymph node examination can be considered in fragile or very old patients.

RADIATION THERAPY AFTER CONSERVATIVE SURGERY (see Clinical question No. 20).

Recently, two meta-analyses have confirmed that the addition of radiotherapy in patients treated with conservative surgery and adjuvant hormone therapy increases local control, but has no impact on overall survival.[12,13]

Omission of adjuvant radiation therapy can be considered in patients aged 70 years or older presenting with breast cancer with a favorable prognosis (T <2 cm, cN0, ER and PGR positive, endocrine therapy in progress, Ki-67 <20%), after explaining potential risks (increased risk of recurrence) to the patient.

CLINICAL QUESTION No. 20 (Figure 2)

In patients aged ≥70 years undergoing conservative surgery for invasive breast cancer, with cN0, ≤2 cm, ER-positive tumor, receiving adjuvant endocrine therapy, is the omission of radiotherapy recommended?

Regarding the addition of radiotherapy to conservative surgery in women aged 70 years and older, data from the EBCTCG 2005 meta-analysis[14] indicate that the absolute benefit in terms of local recurrence in patients with negative axillary lymph nodes is about 11% at 5 years (19% over the entire population regardless of age). In this population, there is no effect on the reduction of mortality at 15 years (cancer-related mortality: HR 0.98; p=0.19; overall mortality: HR 1.07; p=0.17) **(SIGN Level of evidence 1+).**[54]

In the group of patients aged 70 years and over, with ≤2 cm, cN0, ER-positive tumor, a randomized phase III study was conducted involving treatment with tamoxifen associated or not with residual breast tissue radiotherapy after conservative surgery.[15] The primary endpoints of the study were time to local or regional recurrence, frequency of mastectomy for disease recurrence, breast cancer-specific survival, time to distant metastases and overall survival. This study enrolled 636 women, and at a follow-up of 12.6 years there were no differences in terms of overall survival, distant metastasis-free survival, second primary tumor, mastectomy rate (including when performed after a recurrence) between the two treatment groups; a significant difference was observed only in the rate of local-regional recurrences (at 10 years: 2% vs 10%, 6 vs 32 cases, in favor of radiotherapy) (**SIGN Level of evidence 1**+).[16] It should be noted that the study does not have the power to investigate non-inferiority between the two arms in terms of absolute or specific cause survival. Only 3% of all randomized patients in the study died of breast cancer. Even if with the statistical limitations already underlined, this study prospectively confirms what had already been hypothesized based on the results of the EBCTCG 2005 meta-analysis,[14] and it also highlights that, in this group of patients with limited oncological risk, the main causes of death are attributable to diseases other than cancer, as was to be expected based on their age.

No data is available yet to identify a subgroup of patients where RT could definitely be omitted.[17is]The multicenter study PRIME II[18] enrolled 1,326 patients aged 65 years or older with early-stage breast cancer and a "prognostically favorable" phenotype (e.g. hormone-receptor positive, pN0, pT1 and pT2 up to 3 cm, negative resection margins). All patients received adjuvant hormone therapy and were randomized to receive or not receive complementary breast radiation therapy. After a median 5-year follow-up, ipsilateral mammary recurrences (primary endpoint) were **1.3%** (95% CI 0.2-2.3; n=5) after RT and **4.1%** (2.4-5.7; n=26) without RT (p=0.0002) with HR of 5.19 (95% CI 1.99-13.52).

The number of patients to treat to avoid one local event is estimated at 31.8 (95% CI 27.4-55.0), which translates into an absolute risk reduction of 3.1%. No differences were observed between the arms in terms of regional recurrences, distant metastases, contralateral tumors and overall survival.

Therefore, in the subgroup of patients aged 65 years and over with low-risk disease, complementary radiotherapy seems to significantly reduce the risk of local recurrence, even if the absolute risk of local recurrence is modest, and the median follow-up of the study is still short. A careful multifactorial and

multidisciplinary evaluation is therefore necessary to identify the optimal therapeutic strategy, assessing the oncological situation and the factors that may influence the risk of recurrence and considering the psychological and physical conditions of each individual elderly patient.

A recent observational study conducted by Eaton et al.[19] showed a significant reduction in breast cancer-specific death at 5 years for elderly patients (≥ 70 years) with T1-2N0 (ER)-negative breast cancer who received adjuvant RT (10.8% and 24.1%, p <0.001). In addition, the recent analysis conducted by Herskovic et al. showed that adjuvant radiotherapy improved OS in elderly patients with early-stage ER-positive breast cancer who received hormone therapy.

The overall 5-year survival rate was 93.0% (95% confidence interval 92.7-93.3) in the adjuvant RT group and 83.6% (95% confidence interval 82.5-84.7) in the non-adjuvant RT group (P <0.0001). Although these results have not yet been confirmed by Phase III studies, the hypothesis generated by these evaluations should be taken into account in the choice of treatment.[20]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
B	In patients aged ≥70 years undergoing conservative surgery for invasive breast cancer with cN0, ≤2 cm, ER-positive tumor, receiving adjuvant endocrine therapy, omission of radiotherapy could be a feasible option.[14,15]	**Conditional Positive**

10.4. Adjuvant systemic therapy

The decision whether or not to administer an adjuvant treatment to an elderly patient should be based on the assessment of life expectancy and risk of cancer recurrence.

A careful evaluation of comorbidities is essential because, besides having an impact on survival (see competing causes of death), they can also affect the tolerability of the treatments selected.

Unless otherwise specified, the considerations included in this chapter refer to fit patients.

Adjuvant hormone therapy (see also section 5.2.2)

In a woman with operated ER-positive and/or PgR positive breast cancer, the benefit of adjuvant hormone therapy with both tamoxifen and an aromatase inhibitor is independent of age.[21-22]

Therefore, in elderly patients who are considered candidates for adjuvant hormone treatment, it is appropriate to follow the same approach applied to younger menopausal patients. In the absence of absolute contraindications, an aromatase inhibitor should be included in the adjuvant hormone treatment using a sequential or upfront approach. **CLINICAL QUESTION 7 can therefore be extended to elderly patients (see section 5.2.2).**

In elderly patients in good overall condition, who have completed 5 years of treatment with tamoxifen, the use of anti-aromatase agents with an extended strategy may be considered.

In the MA.17 study, the advantage in DFS (hazard ratio=0.46; *P*=.0004) associated with the extension of letrozole therapy after 5 years of tamoxifen was significant only in women under 60 years of age.[23] However, due to the lack of interaction between age and treatment in the analysis of disease-free time or overall survival, extended hormone therapy may be considered in fit elderly patients.

There are no analyses available on extended strategy in elderly patients pretreated with aromatase inhibitors.

A Danish population study showed that patients ≥60 years of age with ER-positive pT1a-bN0 breast cancer who were not treated with adjuvant hormone therapy did not have a higher risk of mortality than women of the same age group without cancer.[24] Currently, omission of adjuvant hormone treatment may be an option in elderly women with extremely low risk of cancer recurrence, e.g. pT1a G1 tumors, or in women with severe comorbidities.[14,25]

Treatment tolerability is an important factor, because it affects treatment compliance. There is increasing evidence that reduced compliance/adherence to hormone therapy is associated with reduced survival.[26,27] Age has been identified as a risk factor for early discontinuation of adjuvant hormone therapy due to side effects.[7] Side effects of tamoxifen are age-related; the risk of death from pulmonary embolism and uterine cancer increases with age.[28] Therefore, aromatase inhibitors would be preferable to tamoxifen in the elderly patient.[14,25]

However, the negative impact of aromatase inhibitors on bone density is particularly problematic in the elderly, where bone demineralization and osteoporosis are prevalent. In the EBCTCG meta-analysis, in patients treated with an aromatase inhibitor for 5 years, the absolute additional risk of having a bone fracture within 5 years of treatment compared to the tamoxifen group for 5 years was 1% in women <50 years of age, 2% in the 55-69 age group, and 4% in women ≥70 years of age.[2]

Adjuvant chemotherapy

CLINICAL QUESTION No. 21 (Figure 4, Figure 7)

Is polychemotherapy recommended for fit elderly patients with operated breast cancer who are candidates for adjuvant chemotherapy?

The EBCTCG meta-analysis showed decreasing benefit from adjuvant chemotherapy with increasing age (Evidence level SIGN 1++). The benefit observed in women aged >70 years was in the same range as that observed in women aged 50-70, but was not significant due to the limited sample size.[1]

Important data on the role of adjuvant chemotherapy in elderly patients comes from the CALGB 49907 study, where 633 patients aged ≥65 years were randomized to receive standard chemotherapy (AC or CMF) or capecitabine.[29] At 3 years, recurrence-free survival and overall survival were statistically and clinically lower in the group of women treated with capecitabine (recurrence-free survival 68% vs 85%, overall survival 86% vs 91%) (SIGN Level of evidence 1++). The benefit of standard treatment was observed mainly in women with ER-negative tumors.

A survival benefit from adjuvant chemotherapy in elderly patients with endocrine non-responsive breast tumors has also been highlighted by data from SEER registries, with particular evidence of benefit in patients with axillary lymph node involvement (SIGN Level of evidence 3).[30,31]

The role of chemotherapy in elderly patients with ER-positive tumors is more limited. In a French study, which randomized 338 women aged >65 years with positive lymph nodes to receive tamoxifen for 3 years or low weekly doses of epirubicin (6 cycles) associated with tamoxifen (3 years), at a median follow-up of 6 years an improvement in disease-free survival with the use of anthracycline and tamoxifen was demonstrated, related to a low rate of local-regional recurrence.[32]

It is suggested to consider the addition of chemotherapy to adjuvant hormone therapy, according to the same criteria applied to younger patients, in women with a life expectancy of more than 10 years, to evaluate the addition of chemotherapy if an absolute benefit >3% in terms of OS at 10 years is expected in women with a life expectancy of 5-10 years, and to omit chemotherapy in women with a life expectancy <5 years.[33]

As regards the choice of the CMF chemotherapy regimen, AC and T-Cyclo are regimens whose feasibility has been demonstrated in elderly women.[29,34,35] Four AC cycles are preferred to 6 cycles of poorly tolerated CMF

in elderly patients.[14,25,36,37] Cardiotoxicity linked to the use of anthracyclines can be a factor to consider in elderly patients. In fact, the use of anthracycline-containing regimens in women between 66 and 70 years of age has been associated with an incidence of heart failure at 10 years of 47% versus 33% observed in women treated with CMF and 28% in women not treated with chemotherapy.[38] Taxane-based chemotherapy can be used as an alternative to anthracycline therapy to reduce the risk of cardiotoxicity.[14,25] The cyclophosphamide-docetaxel combination (T-Cyclo) was more active than 4 cycles of AC in terms of disease-free survival and overall survival also in a subgroup of women aged ≥65 years (16% of the study population).[34] A retrospective study involving 110 patients treated with adjuvant chemotherapy according to the T-Cyclo regimen showed that administration of this regimen is also feasible in patients >70 years of age.[35]

The use of sequential regimens (e.g. anthracyclines followed by taxanes) in elderly patients is not validated by clinical studies. Therefore, these regimens should be reserved for fit patients with biologically aggressive tumors.[14,25] A retrospective analysis of data from 3 randomized CALGB trials (CALGB 8541: comparison of 3 different doses of chemotherapy according to the CAF regimen; CALGB 9344: AC vs AC followed by paclitaxel; CALGB 9741: AC followed by paclitaxel every 3 or 2 weeks) showed that the incidence of treatment-related deaths increased linearly with increasing patient age.[39]

The EORTC guidelines recommend the use of primary prophylaxis with G-CSF when using chemotherapy regimens associated with a risk of febrile neutropenia >20%. In the case of regimens carrying an intermediate risk of febrile neutropenia (10-20%), the assessment of patient-related risk factors that may be associated with an increased risk of this adverse event is recommended, and since age ≥65 years is considered a risk factor, growth factors should be used.[40]

Based on data from the CALGB 49907 study, polychemotherapy is the standard of care in elderly patients. In elderly patients with biologically aggressive and/or advanced breast cancer who are not eligible due to their general condition/high risk of toxicity from polychemotherapy, a specially tailored treatment can be considered. Although paclitaxel monochemotherapy failed to demonstrate non-inferiority versus the AC combination, the favorable toxicity profile and an absolute difference of only 1% in OS makes paclitaxel a reasonable option for unfit patients who "need" chemotherapy.[41]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
A	In fit elderly patients with operated breast cancer who are candidates for adjuvant chemotherapy, polychemotherapy should be considered in the first instance.[41]	**Strong Positive**

Adjuvant trastuzumab

CLINICAL QUESTION No. 22 (Figure 5, Figure 6)

In fit elderly patients with operated HER2-positive breast cancer with a diameter greater than 1 cm or N+, is the use of trastuzumab recommended?

The addition of trastuzumab to adjuvant chemotherapy in HER2-positive tumors increases disease-free survival and overall survival, but trials conducted to date included only a small percentage of patients aged ≥65 years.

A STEP analysis conducted within the HERA study showed that the efficacy of trastuzumab in the adjuvant setting, expressed in terms of disease-free survival at 3 years, is homogeneous across different age groups from 40 years of age.[42]

Data from a German observational study involving 3,940 patients, 507 of whom aged 65 to 69 years and 507 aged ≥70 years, showed that the long-term benefit of adjuvant treatment including trastuzumab is comparable across age classes.[43]

Age >50 years represents a risk factor for cardiac toxicity (symptomatic heart failure) in patients treated with anthracyclines and trastuzumab.[44] Retrospective population-based studies have shown that the incidence of heart failure/cardiomyopathy associated with the use of trastuzumab plus anthracyclines increases with age also beyond the age of 50, and that the incidence of cardiac events in elderly patients treated with regimens containing trastuzumab is generally higher than the incidence observed in clinical studies that enrolled younger patients more accurately selected according to comorbidities.[45-48]

In particular, in a study of about 10,000 women aged >65 with stage I-III breast cancer treated with chemotherapy, 2,203 of which had received trastuzumab, a higher incidence of heart failure was found in patients treated with trastuzumab (29.4%) than in patients not treated with the anti-HER2 agent (18.9%), p<0.001[47] (SIGN Level of evidence 2+). Advanced age (>80 years; HR 1.24), the presence of coronary artery disease (HR 1.82) and hypertension (HR 1.24) and the weekly administration of trastuzumab emerged as risk factors for cardiac events. [47] A higher incidence of cardiac events in patients treated with trastuzumab in "real practice" compared to clinical studies was also observed in the general population.[49-52]

Adjuvant treatment with trastuzumab in combination with chemotherapy should be offered to "fit" elderly patients with HER2-positive breast cancer.[14,25] A careful cost-benefit analysis of the adjuvant treatment is required in elderly patients with HER2-positive low-risk tumors, i.e. T<1 cm. The increased risk of age-dependent cardiac events observed with both anthracyclines and trastuzumab and the "anthracycline-free" arm efficacy data from the BCIRG 006 study should be considered when choosing the chemotherapy regimen to associate with trastuzumab in elderly patients.

The association of paclitaxel + trastuzumab[53] can be considered not only in low-risk patients, as in the case of younger patients, but also in elderly patients with breast cancer at high risk of recurrence who are considered at high risk of toxicity from the polychemotherapy-anti HER2 agent combination.

In selected cases, in the presence of a high risk of toxicity from chemotherapy due to comorbidities, the administration of trastuzumab as monotherapy or in combination with hormone therapy may be a reasonable option that counterbalances the high-risk profile associated with HER2 positive tumors.[54]

As regards the association of trastuzumab-pertuzumab in the Aphinity study, 13% (n=315) of patients randomized in the "double block" arm were ≥65 years of age. A subgroup analysis showed no differences in terms of age-dependent disease-free survival.[55]

SIGN Quality of evidence	Clinical recommendation	Strength of clinical recommendation
B	In fit elderly patients with operated HER2-positive breast cancer with a diameter greater than 1 cm or N+, trastuzumab should be considered in the first instance.[14,44,46]	**Strong Positive**

10.5. Systemic therapy of metastatic disease

Hormone therapy

Hormone therapy should be the treatment of choice for elderly patients with ER-positive and HER2 negative metastatic breast cancer in the absence of rapidly evolving disease. The choice of treatment follows the same criteria applying to the treatment of younger menopausal patients.

The following data are available on the combination of hormone therapy with target agents in the elderly.

Everolimus

In the BOLERO 2 study, where menopausal patients with advanced ER-positive and HER2 negative breast cancer were randomized to receive exemestane +/- everolimus, the addition of everolimus to hormone therapy led to an age-independent increase in progression-free survival hazard ratio (HR), i.e. 0.59 [≥ 65 years] and 0.45 [≥ 70 years][56] (SIGN Level of evidence 1+ for detection bias (unscheduled analysis of a non-stratified subgroup).

Elderly patients treated with everolimus had a higher death rate due to side effects. Overall, considering the two treatment arms (EE/E), the incidence of deaths due to adverse events was the same in patients aged <70 years (1.3% per arm) and 7.7%/0% in patients over 70. Treatment with everolimus was discontinued due to adverse events in 17.4% of patients ≥70 years versus 6.3% in younger patients.

A subgroup analysis was also conducted in the Ballet study, an expanded-access study, which therefore enrolled less-selected patients than BOLERO 2. Five hundred and sixty-three patients ≥70 years of age were enrolled in Ballet. The study confirmed that treatment is generally less tolerated in elderly patients, with a higher incidence of treatment interruption due to adverse events (23.8% vs 13.0%) and dose reductions (37.7% vs 26.7%). [57]

In elderly patients, careful monitoring of toxicities and proactive treatment of side effects are therefore useful.

Pharmacokinetic studies have shown that an adjustment of the initial dose of everolimus in elderly patients is not necessary.

Cyclin-dependent kinase inhibitors

A joint analysis of three clinical studies (PALOMA 1, PALOMA 2 and PALOMA 3) involving 872 patients (221 of whom (25%) ≥65-74 years old and 83 (10%) ≥75 years old) treated with palbociclib plus letrozole or fulvestrant showed that the addition of palbociclib to hormone therapy increases PFS independently of age.[58] From the point of view of tolerability, a higher incidence of myelosuppression was observed in patients aged ≥75 years, but with a similar distribution of grade ≥3 events in the different age groups. With regard to the comparison of hormone therapy versus hormone therapy plus palbociclib, an increase in infections, asthenia, nausea, stomatitis, diarrhea and appetite loss was observed, mainly of grade 1-2, in patients treated with cyclin inhibitors. It should be noted, however, that a grade 2 toxicity may have a major impact on the function and quality of life of an elderly patient, so that it would be desirable in this population to conduct a separate analysis for grade 2 toxicities. Treatment has been discontinued for toxicity in 9% of patients treated with palbociclib, with a discontinuation rate of 13% in patients aged ≥ 65-74 years and 19% in patients ≥75 years.

A subgroup analysis of the Monaleesa-2 study showed that patients aged ≥65 years (n=295 treated with letrozole+ribociclib) had efficacy and tolerability outcomes comparable to the general population of the study.[59]

Pharmacokinetic studies showed that an adjustment of the initial dose of palbociclib and ribociclib in elderly patients is not necessary.[58-59]

A subgroup analysis of the MONARCH 3 and MONARCH 2 studies, evaluating abemaciclib in combination with a non-steroidal aromatase inhibitor and fulvestrant, respectively, demonstrated an age-independent PFS advantage from the addition of the cyclin inhibitor to hormone therapy.[60,61]

Chemotherapy

Chemotherapy is indicated in patients with ER-negative, hormone-resistant or rapidly evolving breast cancer.

Patients aged >70 years who are treated with chemotherapy benefit from the treatment as much as younger patients. The Piedmont Oncology Association compared the efficacy and tolerability of different chemotherapy regimens administered to patients of different age groups in five clinical trials. In particular, 70 patients ≥70 years were compared with 60 patients aged 60-69 years and 40 patients <50 years. All patients were outpatients or capable of self-management and had adequate hematological, hepatic and renal function. The objective response rates in the three age groups (from the youngest to the oldest) were 40%, 31%, and 29% respectively (P = .53). No differences were observed in terms of time to progression or overall survival (SIGN Level of evidence 3).[62]

Monochemotherapy is generally preferable to polychemotherapy, which is associated with multiple side effects.[5] A preference should be given to chemotherapy agents with a good toxicity profile, such as weekly taxanes, liposomal doxorubicin, capecitabine, and vinorelbine, which have been studied in the elderly population (Evidence level SIGN 2).[14,63-67]

These SIOG and Eusoma recommendations were published before data became available on the efficacy/safety of eribulin and nab-paclitaxel in the elderly patient.[68-70]

There is little data on polychemotherapy in elderly patients with advanced breast cancer. A combination of oral cytotoxics (vinorelbine and capecitabine) has been evaluated in a population of patients aged ≥ 70 years with advanced cancer, including many patients with breast cancer, and was shown to be active and well tolerated (SIGN Level of evidence 3).[71]

Thanks to its good tolerability and evidence of a reasonable efficacy, metronomic chemotherapy could represent a therapeutic option of interest in elderly patients who are not candidates for or refuse classic chemotherapy.[72]

With regard to the association of paclitaxel with bevacizumab, an analysis conducted within the E2100 study, comparing paclitaxel with paclitaxel in combination with an anti-angiogenic drug, showed that the combination provides an age-independent advantage in terms of progression-free survival, although this benefit seems to be less significant in elderly patients. From the point of view of tolerability, in the ATHENA study a higher incidence of grade 3-4 adverse events was reported in elderly patients (≥ 70 years) treated with bevacizumab and chemotherapy than in young patients, in particular hypertension, but no increase in thrombo-embolic events was observed.[74] Age should not be a criterion for excluding a patient who would otherwise be eligible for first-line treatment containing bevacizumab.

Anti-HER2 therapy

Data on treatment with anti-HER2 agents in the elderly are limited.

The regisHER observational study analyzed the efficacy and tolerability of first-line treatment with trastuzumab in patients with HER2 positive metastatic breast cancer by age group (<65 years, 65-74, ≥75 years).[75] Overall, elderly patients had a higher incidence of cardiovascular disease, and those treated with trastuzumab received the drug less frequently in combination with chemotherapy than younger patients (ER distribution was similar across different age groups). At the multivariate analysis, first-line treatment with

trastuzumab was associated with an age-independent advantage in progression-free survival (SIGN Level of evidence 3). A survival advantage was observed in all age groups but was statistically significant only in patients <65 years. The incidence of heart failure was higher in patients ≥75 years (3.2% versus 1.9% and 1.5%, respectively, in the <65 and 65-74 age groups).[75]

Even more limited is data concerning lapatinib. Only 12% (n=37) of patients enrolled in the lapatinib registration study in combination with capecitabine were ≥65 years of age, making it impossible to carry out an analysis of age subgroups. In a combined analysis of nine studies (Phase I-II-III) that included different types of tumor, and where lapatinib was administered as a single agent (=929) or in combination with capecitabine (=198) or taxanes (=687), 13% of patients treated with lapatinib were ≥70 years old.[76] Diarrhea was reported in 7% of elderly patients, with severity, onset and resolution similar to patients <70 years. However, the subgroup of elderly breast cancer patients had a higher grade 3 toxicity rate than patients <70 years (33% vs 19%).[76]

In a retrospective analysis aimed to assess the incidence of rash, diarrhea and liver toxicity secondary to lapatinib administration and their association with age in the NeoALTTO neoadjuvant therapy study, it was observed that the incidence and clinical significance of skin rash was age dependent.[77]

Recently, data from a preplanned retrospective analysis has been published, which assessed the efficacy and tolerability of the docetaxel, trastuzumab and pertuzumab combination in the CLEOPATRA study by age group (<65 vs ≥65 years).[78] Of the 808 total patients enrolled in the study, 127 were aged ≥65 years (placebo arm n=67; pertuzumab arm n=60). In both age groups, the addition of pertuzumab to standard treatment was associated with an advantage in terms of progression-free survival (<65 years: HR 0.65, 95% CI 0.53-0.80; ≥65 years: HR 0.25, 95% CI 0.31-0.86). (SIGN 1+ level of evidence for detection bias (unscheduled analysis of a subgroup not subject to stratification)

Diarrhea, asthenia, fatigue, reduced appetite, vomiting and dysgeusia have been reported more frequently in older women than in young patients. There is a higher incidence of grade 3 peripheral neurotoxicity (n=5 vs 1) and grade 3 diarrhea (n or % not reported) in elderly patients treated with pertuzumab compared to elderly patients who received placebo. The incidence of neutropenia and febrile neutropenia has been reported more frequently in young women than in patients over 65; a higher frequency of docetaxel dose reductions and a lower median number of docetaxel cycles administered in elderly patients may explain this unexpected distribution of hematological toxicity. The combination of dual blockade with paclitaxel is an interesting alternative for elderly patients who are considered not eligible for treatment with docetaxel.

A subgroup analysis of the EMILIA study and the TH3RESA study, which compared T-DM1 with capecitabine-lapatinib and therapy selected by the doctor, respectively, showed that the activity of the drug is age independent. An integrated analysis of the toxicity profile of 884 patients treated with TDM-1 in the context of clinical studies suggested a higher incidence of ≥3 grade side effects in patients aged ≥65 years (n=122).[79] This data has recently been confirmed by Barios et al, who evaluated the safety of TDM-1 in a larger number of patients (n=373) treated in the Kamilla study.[80] In comparison to patients <65 years of age, in the elderly population there was a higher incidence of grade ≥3 toxicity (43% vs 33%) and treatment discontinuation due to toxicity (14% vs 9.5%).

Fit elderly patients with HER2-positive metastatic breast cancer should receive targeted anti-HER2 treatment according to the same criteria applying to therapy younger patient.[5]

In fragile elderly patients with hormone-receptor negative, HER2 positive metastatic breast cancer who are not eligible for chemotherapy, first-line treatment with trastuzumab alone may be indicated (with a clinical benefit of 40%) (SIGN Level of evidence 2+).[81]

In elderly patients with hormone-receptor positive, HER2 positive metastatic breast cancer with contraindications to chemotherapy, the association of an anti-HER2 agent with an anti-aromatase agent (trastuzumab + anastrozole or lapatinib + letrozole) may be indicated.

11. Special clinical situations

11.1. Bilateral breast cancer

The incidence of bilateral breast cancer is about 3% of all breast cancers: specifically, synchronous cancers (concomitant bilateral cancer) account for 0.6%, while metachronous cancers account for 2.2%. For both bilateral synchronous and contralateral metachronous tumors, treatment should be planned considering the two tumors separately, in consideration of the esthetic outcome.

11.2. Male breast cancer

Male breast cancer accounts for approximately 0.5-1% of all breast cancers.[1,2] The main risk factors include testicular diseases, benign breast conditions, age, familiarity and Klinefelter syndrome. BRCA2 mutations predispose to the development of breast cancer in man, and are implicated in 4 to 14% of all cases. A recently published review indicates that 81% of male tumors are ER-positive, 74% are PgR-positive and 30% overexpress HER2. In addition, male tumors generally appear at a more advanced stage (with a median diameter and an incidence of lymph node metastases a third higher), less frequently Grade I or of lobular histology.[3]

Until recently, male patients were not included in controlled clinical trials, and therefore management has traditionally followed the recommendations for female breast cancer.

Prognostic factors are comparable to those of women, and survival is similar to that of women of the same age and stage.

About 85% of male patients undergo mastectomy.[4] After surgery, the indications for radiotherapy do not differ from those for female breast cancer.

The choice of adjuvant therapy follows the same guidelines as for female breast cancer: tamoxifen is the standard adjuvant hormone therapy; in metastatic disease the therapy of choice is hormone therapy, and chemotherapy should be reserved for patients who no longer respond to hormone therapy.

Experience with aromatase inhibitors in male breast cancer is more limited than with tamoxifen. Some retrospective cases show levels of estrogen suppression and antitumor activity comparable to those observed in postmenopausal women with hormone-related metastatic tumors.[5,6] One potential problem is the increase in FSH and testosterone levels due to a feedback mechanism linked to the reduction of circulating estrogen during treatment. An increase in testosterone levels would make more substrate available for the aromatase enzyme, resulting in a potential attenuation of the antineoplastic effect. For this reason, with the Determination of December 9, 2008, AIFA approved the use of aromatase inhibitors in association with LHRH-analogues in the treatment of hormone-positive male breast cancer.

11.3. Breast cancer during pregnancy

Breast cancer is the most frequently type of cancer diagnosed during pregnancy (PABC: pregnancy-associated breast cancer): about 1 pregnancy every 3,000 is complicated by a diagnosis of breast cancer.[7]

Several studies showed that there is no difference in the prognosis of patients with PABC compared to women with non-pregnancy-associated breast cancer if size of the tumor, lymph node status and other prognostic markers are comparable.[8-15] On the contrary, breast cancer diagnosed during breastfeeding seems to increase the risk of death from cancer. Breast cancer during pregnancy is often diagnosed at a more advanced stage due to diagnostic delay.[12] Histologically, breast cancer during pregnancy is more often undifferentiated, does not express hormone receptors and in 30% of cases is HER2 positive.[13,14,16,17]

During pregnancy, in the presence of suspicious breast lump, the first step is a **specialist examination** and an **ultrasound scan**,[18] which represents the first-choice examination in this set of patients. **Mammography** can

be performed in pregnant women using appropriate abdominal shielding to minimize fetal exposure to ionizing radiation.[12,19-22]

For the histopathologic diagnosis, **biopsy** is the most appropriate technique in this setting, because of the widespread hyperproliferative cellular changes related to pregnancy that can lead to an increased rate of false positives with cytological sampling. The use of Magnetic Resonance Imaging **(MRI)** to diagnose breast cancer in pregnancy has not been adequately studied and is still controversial. Most patients are diagnosed with ductal carcinoma, often associated with aggressive biological characteristics (high incidence of high-grade tumors, lympho-vascular invasion, hormone receptor negativity).[10]

Staging examinations are generally limited to **chest X-ray,** performed with abdomen shielding, and **abdominopelvic ultrasound**. **Bone scan** and **CT scan** should be avoided during pregnancy, especially in the first trimester, since radiation can cause congenital malformations; **MRI without contrast agent** can be performed if there is a strong suspicion of liver, bone and brain metastases.[23]

The protocol for the treatment of breast cancer in pregnant women should be as similar as possible to that offered to non-pregnant women; it should be individualized, considering the biology of the tumor, the stage of the disease, the gestational age and the patient's preferences.

There is no clinical evidence that termination of pregnancy improves prognosis.[24] Pregnancy termination should be discussed with the patient and should be advised when the planned treatment is likely to harm the fetus or when continuation of pregnancy requires a delay in the start of cancer treatments that could harm the mother: this situation occurs especially when cancer is diagnosed during the first trimester.[25]

Breast surgery is the primary treatment of operable PABC, and can be performed throughout the pregnancy without negative consequences for the fetus related to anesthesia Only Observational studies reported: 1-2% risk of abortion during the first trimester and the risk of premature birth (relative risk 1.5-2.0) in the second and third trimesters..[26]

Pregnancy does not change indications of the type of surgery, radical or conservative.

Some evidences suggest that if the tumor/gland volume ratio is favorable, conservative surgery may be performed at the end of the second and third trimester,[27-29] with radiotherapy after childbirth, without significant impact on recurrence rate and survival compared to women treated with radical surgery. During the first trimester, conservative surgery may result in an excessive delay in the initiation of postoperative radiation therapy, and therefore radical surgery may be preferable.

Multiple studies have shown that SLN biopsy can be carried out during pregnancy, and that the dose absorbed by the fetus is lower than the risk dose of 0.1-0.2 Gy, even in the most adverse conditions.[30-36]

Radiotherapy should only be given at the end of gestation, as pregnancy is an absolute contraindication to radiation.[37-40]

Indications for chemotherapy during pregnancy should not differ from those in non-pregnant women.[12]

The use of chemotherapy during the first trimester increases the risk of miscarriage, fetal death and severe malformations: the latter can have an incidence ranging from 10 to 20%.[41-44] Because of these risks to the fetus, if it is decided to continue the pregnancy, the onset of chemotherapy should be delayed after completion of the 14th-16th week of gestation.[45] In the second and third trimester, chemotherapy does not appear to be associated with fetal abnormalities, although cases of intrauterine growth retardation, intrauterine and neonatal deaths, prematurity and spinal cord aplasia have been reported.[26,46] In this scenario, the data from short-term follow-up of children exposed to prenatal chemotherapy for breast cancer, including the incidence of congenital malformations, are reassuring.[47-54] The results of a recent observational study of 70 children exposed to chemotherapy *in utero* are comforting: the general health of these children, their growth, and heart, auditory, and central nervous system function do not differ from those of the healthy population.[62]

However, a greater number of preterm births was observed, with alterations in cognitive development: hence the indication to avoid premature iatrogenic delivery whenever possible.[62]

Various chemotherapy regimens have been used for the treatment of breast cancer in pregnancy: these regimens should, as far as possible, be similar to those used in non-pregnant women; moreover, during pregnancy, dose should not differ from those used outside gestation. The use of anthracycline-based regimens after the first trimester is feasible and does not increase risks for the pregnancy and/or the fetus.[63] One of the most widely used regimens is FAC.[27] Data on taxanes are more limited, however safety data from published studies do not seem to correlate the use of taxanes during pregnancy with a higher risk of miscarriage and intrauterine death. Therefore, the use of paclitaxel or docetaxel during pregnancy should be considered.[64]

Methotrexate should not be used during pregnancy, as it is associated with an increased risk of severe malformations.[65]

For patients with HER2 positive tumor, the toxicity profile of trastuzumab during pregnancy is not sufficiently understood. The clinical data available about the use of trastuzumab during pregnancy are based on only 15 published cases: in more than 50% of these, there has been a reduction in amniotic fluid that is known to increase the risk of premature birth and fetal morbidity and mortality. This effect, probably due to the action of trastuzumab on the fetal kidney, where HER2 is highly expressed, appears to be related to the duration of exposure rather than the gestation period when the drug was administered.[66,67] Trastuzumab should be postponed until after childbirth.

During pregnancy, the use of any hormonal therapy is contraindicated.

As far as supportive therapies are concerned, little data is available on the safety of the use of both G-CSF (granulocyte colony-stimulating factor) and erythropoietin in pregnant women. Some evidences suggest that they are safe, but ,few data are available, so their use should be limited when they are really needed.[68]

With regard to antiemetic therapy, the use of steroids and ondansetron in second and third trimester does not seem to be related to malformations in humans. Among 5-HT3 antagonists, ondansetron is the the most extensively studied during pregnancy,[69,70] and therefore should be preferred to other agents of the same class. About steroids, methylprednisolone and hydrocortisone, being massively metabolized by the placenta, are the preferred.[62]

When planning delivery time in pregnant breast cancer patients, several factors should be taken into account, while fetal monitoring should be performed at least every 3-4 weeks with umbilical artery ultrasound. Preterm delivery should only be performed if indicated for obstetrical reasons; to minimize the risk of maternal and fetal neutropenia and subsequent infections, delivery should be avoided during maternal nadir, usually 2-3 weeks after three-weekly chemotherapy; chemotherapy should not be administered after 34-35 weeks of gestation, because spontaneous delivery may occur before bone marrow recovery. A 3-week delay in delivery induction after chemotherapy also allows fetal excretion of medications through the placenta.

For the health of the fetus, maximum effort should be made to delay delivery to the 35th-37th week of gestation: indeed, neonatal complications are usually effect of preterm delivery including feeding problems and subarachnoid hemorrhages.[50,71,72]

,Postponement of chemotherapy initiation is less likely with vaginal delivery, as it is associated with less morbidity than caesarean section.[10]

Although placental metastases from breast cancer are rare, the placenta should be histopathologically examined.[10]

Breastfeeding during chemotherapy and hormone therapy is contraindicated, as most of the drugs used may be excreted in breast milk.[10]

The main points in the practical clinical management of breast cancer in pregnancy are summarized below.[73]

Practical clinical management of breast cancer in pregnancy

- There is no evidence that termination of pregnancy improves the prognosis of breast cancer diagnosed during pregnancy. Therefore, VTP should only be proposed to patients if gestation delays the treatment with possible impact on prognosis. This situation usually occurs when the tumor is diagnosed in the first trimester and requires the timely initiation of (neo) adjuvant chemotherapy.

- Breast surgery in pregnant women is safe and is not a risk for the fetus, therefore surgical treatment of breast cancer in pregnancy should follow as closely as possible the guidelines used in the treatment of breast cancer in non-pregnant women.

- Radiotherapy cannot be performed during pregnancy and should be postponed until after delivery.

- Chemotherapy should not be given before 14-16 weeks of pregnancy. Administration of chemotherapy agents in the first trimester is associated with an increased incidence of miscarriage and fetal malformations (10-20%).

- After the 14th week of pregnancy, chemotherapy does not pose a risk to the fetus. Anthracycline and taxane-based regimens should be used (FAC/FEC→taxane, AC/EC→taxane).

- Close fetal monitoring is required during chemotherapy.

- Chemotherapy should not be given after 34-35 weeks of gestation, since delivery should not coincide with maternal nadir, which would expose the mother and fetus to an increased risk of infection. For the same reason, delivery should be avoided in the first three weeks after the last chemotherapy cycle.

- There is no evidence in favor of inducing premature birth. On the contrary, iatrogenic premature delivery should be avoided, as it is associated with increased fetal mortality and morbidity. Maximum effort should be made to postpone delivery until at least 35-37 weeks of gestation.

12. Genetic counseling

About 18% of all breast cancers are due to familiarity alone, while 13% depend on a hereditary predisposition related to high[1,2] and moderate penetrance genes.[3]

The two main genes involved in the hereditary predisposition to these tumors are *BRCA1,[1]* located on chromosome 17, and *BRCA2,[2]* located on chromosome 13. Mutations in these genes confer an increased risk of developing breast and/or ovarian cancer. Genetic mutations in the *BRCA2* gene also confer an increased risk of male breast cancer. Other genes considered responsible for a 1.5 to 7.5-time increase in the risk of developing breast cancer compared to the general population are *CHEK2, BRIP1, MSH6, BARD1, ATM, RAD51D* and *PALB23.*

The risk estimates reported are heterogeneous. A prospective cohort study[4] conducted in a population of nearly 10,000 *BRCA1/2* carriers estimated the average cumulative risk of breast and ovarian cancer at age 80, as reported in Table 12.1.

Table 12.1 - Average cumulative risk of breast and ovarian cancer at 80 years of age in women with BRCA 1-2 mutation (*Modified from Kuchenbaecker KB, JAMA 2017[4]*).

	BRCA1 mutation	BRCA2 mutation
Risk of breast cancer	72% (95% CI, 65% - 79%)	69% (95% CI, 61% - 77%)
Risk of ovarian cancer	44% (95% CI, 36% - 53%)	17% (95% CI, 11% - 25%)

The same work also estimated the risk of contralateral breast cancer in BRCA1/2 carriers after the first diagnosis, as reported in Table 12.2.

Table 12.2. Age-specific risk of contralateral breast cancer after first diagnosis (*Modified from Kuchenbaecker KB, JAMA 20174*)

Years after first diagnosis	Risk of contralateral breast cancer	
	BRCA1 (SD)	BRCA2 (SD)
< 5	0,13 (0,06)	0,08 (0,06)

>5-10	0,23 (0,07)	0,16 (0,09)
>10-15	0,32 (0,08)	0,21 (0,09)
>15-20	0,40 (0,10)	0,26 (0,13)
>20-45	0,53 (0,18)	0,65 (0,73)

DS = Standard Deviation

The possibility of identifying carriers of predisposing mutations or individuals belonging to families with multiple cases of tumor had important consequences on the clinical care plan, and laid the foundations for the development of Oncogenetic Counseling.

In accordance with current US[5] (www.nccn.org) and UK[6] (www.nice.org.uk/guidelines) guidelines, genetic testing should only be offered after adequate oncogenetic counseling, during which individuals or family members can fully understand the meaning of what is being proposed to them and what hereditary determinants are, be informed of available clinical management options, and independently choose the most appropriate course of action.

The counseling process should encourage and promote an informed, independent, and fully aware choice both of the genetic test (when indicated) and the surveillance and/or prevention options (intensive surveillance, chemoprevention, prophylactic surgery).

During this process, four levels of risk for breast and/or ovarian cancer can be defined:
1. Low or similar to that of the general population;
2. Moderately increased compared to the general population;
3. High without confirmed genetic mutation;
4. High with confirmed genetic mutation.

Criteria for referral to oncogenetic counseling

It is considered appropriate to refer to oncogenetic counseling a person who meets at least one of the following criteria:[7]
Personal or family history* of:
1. Known mutation in a predisposing gene (*BRCA1, BRCA2, P53, PTEN*, etc.);
2. Male with breast cancer;
3. Woman with breast and ovarian cancer;
4. Woman with breast cancer <36 years;
5. Woman with triple negative breast cancer <60 years;
6. Woman with high-grade serous ovarian cancer at any age;
7. Woman with bilateral breast cancer <50 years;
8. Woman with breast cancer <50 years and at least 1 first-degree relative with:
    - Breast cancer <50 years;
    - Non-mucinous or borderline ovarian carcinoma at any age;
    - Bilateral breast cancer;
    - Male breast cancer;
9. Woman with >50 years of breast cancer and family history of breast or ovarian cancer in 2 or more relatives who have a first-degree* relation with each other (including 1 who has a first-degree relation with her*).

10. Woman with ovarian cancer and at least 1 first-degree relative* with:

  - Breast cancer <50 years;
  - Ovarian carcinoma at any age;
  - Bilateral breast cancer;
  - Male breast cancer.

Presence of a first-degree relative (parent, sibling, child) with the specified disease characteristics. For the paternal side of the family, also consider second-degree family members (grandmother, aunts).

Genetic testing must first be carried out on a family member who has already developed the disease (index case). The genetic test allows to obtain:

- *An informative result* (the predisposing mutation has been identified),

 or

- *A non-informative result* (the predisposing mutation has not been identified, but its presence cannot be ruled out; a mutation of uncertain meaning has been identified to which no risk level can be attributed).

The classification of mutations is based on the 5-class division proposed by the ENIGMA group:[8]

- Class 1: non-pathogenic
- Class 2: likely non-pathogenic
- Class 3: of uncertain significance
- Class 4: likely pathogenic
- Class 5: pathogenic

The genetic test is therefore truly negative only when a mutation previously identified in a family member is not identified in the individual under examination.

Only if the result is informative, the genetic test can be extended to other family members who wish to perform it, from the age of 18.

Testing minors is not indicated, as increased risk of cancer emerges in adulthood.

In the case of mutations of uncertain significance, the extension of the test to the family members of the index case should not be proposed, except in the context of research projects, and the proposed surveillance program should be based on family history or other established risk factors.

A- INCREASED-RISK MANAGEMENT IN HEALTHY WOMEN WITH BRCA1/2 MUTATION

When the test result is informative, the increased risk of developing breast or ovarian cancer in carriers of BRCA1/2 mutation can be managed, regardless of whether they are healthy or affected, through three different approaches ranging from intensive surveillance to chemoprevention studies to prophylactic surgery.

Since the scientific information gathered on hereditary susceptibility to breast cancer are very recent, there is currently no conclusive evidence on the proper management of carriers of pathogenic mutations in the *BRCA1-2* genes.

A probabilistic model developed by Kurian et al. shows that without any intervention (i.e. no screening and no prophylactic mastectomy), the probability of survival at 70 years is 53% for BRCA-1 carriers and 71% for BRCA-2 carriers compared to 84% survival in the general US female population, while the combination of prophylactic mastectomy at 25 years and prophylactic oophorectomy at 40 years increases the overall survival at 70 years of age of BRCA-1 carriers up to 79% and of BRCA-2 carriers up to 83%, similar to that of the general female population (84%).[9]

An online platform that can be used by patients and their doctors has also been developed for this purpose (http://brcatool.stanford.edu).[10]

A recently published meta-analysis on the efficacy of prophylactic mastectomy in *BRCA1/2* women considers 5 retrospective studies, two of which show a significant reduction in the risk of death from breast cancer, ranging from 99.5% to 80.9%, a third one shows a reduction of 78% but in association with bilateral salpingo-ooforectomy and two show a non-significant reduction[11]

BILATERAL PROPHYLACTIC MASTECTOMY

The only approach that has proven effective in significantly reducing the risk of developing breast cancer is prophylactic surgery: it is estimated that bilateral prophylactic mastectomy, i.e. removal of the mammary glands, can reduce the risk of developing breast cancer by 90-100%.[12-15]

The type of prophylactic mastectomy may range from total mastectomy to skin sparing or nipple skin-sparing mastectomy, which provide superior cosmetic results and, although data are limited, do not appear to be associated with an increased risk of local recurrence even if there is a small percentage of residual risk in the axilla and retroareolar region.[16,17]

A recent study conducted in 9 institutions in the United States did not report any recurrences at 3 years (compared to 22 recurrences predicted by some risk models) in 346 BRCA-mutated women (median age 41 years) treated with prophylactic nipple sparing mastectomy.

The different surgical options should be discussed with the patient along with the risks and benefits of immediate reconstruction. Any breast reconstruction should precede the salpingo-oophorectomy in order to avoid complications.[19]

According to literature data, sentinel lymph node biopsy is not recommended in patients who had prophylactic mastectomy.[20]

PROPHYLACTIC SALPINGO-OOPHORECTOMY

Although the risk of developing ovarian cancer in a woman with a BRCA mutation is lower than the risk of developing breast cancer, the lack of reliable methods for early diagnosis and the poor prognosis of ovarian cancer diagnosed at an advanced stage lead to consider bilateral prophylactic adnexectomy. A meta-analysis of 10 studies conducted in BRCA-mutated patients showed a reduction in ovarian cancer risk of about 80% after bilateral salpingo-oophorectomy.[21] Similarly, in a large prospective study of 1,079 BRCA-mutated women, bilateral salpingo-oophorectomy leads to an 85% reduction in the risk of gynecological tumors (ovarian, fallopian tube, peritoneal cancers) compared to the control group at a median follow-up of 3 years.[22]

In a retrospective study, prophylactic oophorectomy was associated with an 80% reduction in the risk of ovarian, fallopian tube or primary peritoneal cancer in BRCA1 or BRCA2-mutated women, and a 77% reduction in death from all causes.[23]

After salpingectomy and residual prophylactic oophorectomy, however, there is a 5% risk of developing primary peritoneal cancer.[24]

Bilateral salpingo-oophorectomy in BRCA-mutated women is also correlated with a reduction in breast cancer risk of approximately 50% thanks to the decreased hormonal exposure following surgical removal of the ovaries.[25,26] The greatest reduction in breast cancer risk was observed in women with *BRCA1* mutation who had a salpingo-oophorectomy by 40 years of age.[27-30]

Prophylactic salpingo-oophorectomy should be offered as a risk reduction option to all carriers of BRCA1 and BRCA2 mutations from the age of 35-40 years, and however after fulfilling their wish to have children. Surgical removal should include the ovaries and tubes up to their uterine insertion. In order to identify occult fallopian tube carcinomas, a specific pathology dissection protocol of the fallopian tubes should be followed.[31] Subsequently, in consideration of the residual risk, even if low, of developing a primary peritoneal tumor

(linked to the possible presence of clusters of ovarian tissue in the peritoneum that could evolve into cancer), the dosage of CA125 should continue to be carried out also after surgery.

The removal of the uterus is generally not indicated, although in BRCA1-mutated women a statistically significant increase in serous endometrial tumors was observed, and this information should be provided within the oncogenetic counseling to this class of women.[32] A cost-benefit analysis of hystero-adnexectomy conducted in *BRCA1*-mutated women at the age of 40 shows a 4.9-month survival gain, which is considered cost-effective.[33]

To avoid early menopause induced by prophylactic salpingo-oophorectomy and improve quality of life, some studies are evaluating the possibility of performing a salpingectomy at a young age followed by delayed oophorectomy as an alternative procedure in women with *BRCA1/2* mutation.[34-36]

CLINICAL & IMAGING SURVEILLANCE PROGRAM

With regard to recommended surveillance strategies in women with *BRCA* mutations who have not undergone prophylactic surgery, guidelines have recently been published by the US Preventive Task Force which define some recommendations on the basis of a systematic review[30] that does not show an advantage with intensive screening of women at genetic risk. Annual MRI may give rise to a higher rate of false positives, but in combination with mammography its sensitivity is close to 100% (Table 12.3).[37-48]

However, the impact of breast MRI on breast cancer mortality in the surveillance strategy is still to be demonstrated.[49-50]

Table 12.3. High-risk women including those with BRCA-mutation: comparison between mammography and MRI.

Author	MRI		Mammography		Combined MRI and Mammography	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Cortesi L et al, 2006[37]	100%	NR	50%	NR	NR	NR
Leach MO et al, 2005[45]	77%	81%	40%	93%	94%	77%
Le-Petross HT et al, 2011[46]	92%	87%	NR	82%	NR	NR
Kriege M et al, 2004[39]	79%	90%	33%	95%	NR	NR
Rijnsburger AJ et al, 2010[47]	77%*	89.7%	35.5%*	94.6%	NR	NR
Sim LS et al, 2004[38]	93%	63.6%	54%	86%	NR	NR
Warner E et al, 2004[41]	77%	95.4%	36%	99.8%	86%	94%

Lehman CD et al, 2007[42]	100%	NR	33%	NR	NR	NR
Weinstein SP et al, 2009[43]	71%	79%	33%	94%	NR	NR
Sardanelli F et al, 2011[44]	91%	97%	50%	99%	93%	96%
Cho N et al, 2017[48]	88%	90%	53%	96%	100%	87%

*Only invasive cancer

The addition of mammary ultrasound to mammography compared to mammography alone was evaluated in a prospective study of 2,809 women at risk, with an increase of detection rate of 1.1 per 1,000 people per year, although this produced a concomitant increase of false positives.[51]

In Italy, some regions have approved guidelines for the surveillance of subjects with genetic mutations, and Table 12.4 shows the procedures recommended by the Emilia-Romagna Region.[7]

Table 12.4. Recommended procedures for surveillance of *BRCA1/2* mutation carriers

Method
Six-monthly mammary ultrasound from the time of mutation detection.
Annual mammography from 35 to 69 years, then biennial.
Annual breast magnetic resonance imaging (MRI) from the age of 25.
Transvaginal ultrasound and CA-125 test every 6 months from the age of 30.

CHEMOPREVENTION

ASCO[52] confirmed the role of tamoxifen (20 mg/day for 5 years) as a chemopreventive agent for women at risk of breast cancer (index ≥2) against estrogen-dependent forms, but data on carriers of *BRCA1/2* mutations are very limited. All prospective studies conducted to date in this population have failed to demonstrate a statistically significant effect in reducing the risk of breast cancer for the small number of women evaluated.[53,54]

As reported by a recent meta-analysis,[55] tamoxifen has shown a significant reduction in the risk of contralateral breast cancer in patients with *BRCA* mutation,[56-58] and specifically 53% in *BRCA1* carriers and 61% in *BRCA2* carriers, but further studies are currently needed to evaluate the pros and cons of tamoxifen in these patients.

In Italy, with the Determination of 11.29.2017, AIFA has included tamoxifen in the list of medicines that can be fully reimbursed by the National Health Service, established pursuant to Law no. 648 of December 23, 1996, for the preventive treatment of breast cancer in women at high risk (women with a risk of developing breast cancer in the next 5 years ≥1.66% according to the Gail model or with a risk >8% at 10 years in the 40-50 years decade or >30% over their lifetime according to the Tyrer-Cuzick model).

In addition, with the same Determination of 11.29.2017, AIFA has included raloxifen in the list of medicines that can be fully reimbursed by the National Health Service for the preventive treatment of breast cancer in high-risk postmenopausal women (risk of developing breast cancer in the next 5 years ≥1.66% according to

the Gail model or with a risk >8% at 10 years in the 40-50 years decade or >30% over their lifetime according to the Tyrer-Cuzick model).

To date, the indication for the use of aromatase inhibitors in the chemoprevention of breast cancer is not registered in any country, and their use is therefore off-label.

However, the guidelines of the National Institute of Health Care Excellence (NICE) recommend offering tamoxifen and anastrozole to women at high/moderate risk, pre- and postmenopausal, respectively. High-risk women include women with known germline mutation of BRCA1, BRCA2, or TP53 genes and with rare conditions that increase the risk of breast cancer, such as Peutz-Jeghers syndrome (STK11), Cowden syndrome (PTEN) and hereditary diffuse gastric cancer (E-cadherine).[6]

- LIFESTYLE MODIFICATION (diet and physical activity)

With regard to women with BRCA mutations in particular, the possible impact of lifestyle and diet on breast cancer risk has been assessed in some studies. Total caloric intake and being overweight in adulthood are indeed related to an increased risk of breast cancer.[59]

An inverse correlation between healthy diet and breast cancer risk has been demonstrated, and physical activity during adolescence seems to be associated with a reduction in breast cancer risk.[61]

A case-control study in families with mammary and ovarian tumors[62] showed that high serum levels of IGF-1 are associated with increased penetration of BRCA genes. Therefore, a randomized controlled study in *BRCA*-mutated women was started to evaluate the effect of diet and physical activity on the reduction of IGF-1 levels.[63]

HORMONAL FACTORS AND RISK OF BREAST CANCER IN *BRCA1/2*-MUTATED WOMEN

Regarding the use of the contraceptive pill, a meta-analysis did not show a significant increase in the risk of developing breast cancer in both *BRCA1* and *BRCA2* carriers, compared to a significant reduction in the risk of ovarian cancer.[64] The data were also confirmed in a retrospective study conducted on 2,547 women with a confirmed mutation or a high-risk profile, in whom the use of the pill did not increase the risk of breast cancer regardless of the duration of treatment.[65]

There are no conclusive studies on the impact of pregnancy as a risk factor in *BRCA1/2* carriers. In a study of 1,601 affected and healthy women, there were no significant differences between nulliparous and multiparous participants, and pregnancies at an older age (40 years) would even seem to reduce the risk of breast cancer.[66]

More recently, a retrospective study of 2,522 women with a genetic or family risk of breast cancer has shown that pregnancy and breastfeeding reduce the risk of breast cancer in BRCA-mutated women by 73% and 76%, respectively.[67] Better designed studies are still necessary to establish the impact of pregnancy in this specific population.

Finally, with regard to assisted reproduction techniques, a case-control study does not seem to demonstrate an increased risk of breast cancer in *BRCA1/2* carriers who use in vitro fertilization,[68] even if the numbers are too small to draw a conclusion.

B- TREATMENT OF BRCA-MUTATED PATIENTS WITH *BRCA1/2* MUTATIONS AND BREAST CANCER DIAGNOSIS

SURGERY AND RADIOTHERAPY

Still debated is the surgical option to be reserved for patients with *BRCA1/2* mutation and diagnosis of breast cancer: conservative surgery and radiotherapy or radical surgery.

A meta-analysis compared 526 BRCA-mutated patients with 2,320 controls, showing that the risk of ipsilateral recurrence at 10 years is 17%, similar to that observed in non-mutated patients (11%). By extending the follow-up period beyond 7 years, a risk of developing a second ipsilateral breast event at 15 years of around 24% is observed, but in most cases this is a second primary tumor, and not a recurrence.[69] A recent meta-analysis[70] did not show significant increases in the risk of developing second ipsilateral tumors following radiotherapy, although comparing BRCA1/2-mutated patients undergoing conservative surgery with the same type of patients undergoing mastectomy, the risk of ipsilateral recurrence at 15 years after quadrantectomy and radiotherapy was significantly increased (23.5% vs. 5.5%, p<0.0001).[71] Based on some studies on the use of diagnostic mammography, which seems to increase the risk of first tumors in young women, it is considered appropriate to offer radical surgery without RT to affected women under 30 years of age.[72-73] Although with different results across studies, radiotherapy, chemotherapy, oophorectomy and tamoxifen are associated with a decreased risk of ipsilateral events, as is the case in sporadic breast cancer. The risk of contralateral breast cancer does not seem to vary for women undergoing conservative surgery compared to unilateral mastectomy.[74] Finally, no difference in 15-year OS was observed between BRCA1/BRCA2 -mutated patients who choose to undergo mastectomy compared to conservative surgery.[75]

As for the risk of developing a contralateral tumor, we have seen how it can reach up to 53% and 65% in BRCA1 and BRCA2 carriers, respectively, after 25 or more years from the first diagnosis.[4] This risk is higher also in BRCA-mutated women who have had an adnexectomy[74] and depends on their age at the time of initial diagnosis.[76] Due to an increased risk of developing a second primary tumor, many mutated patients choose to have a bilateral mastectomy at the time of breast cancer diagnosis. The choice of bilateral prophylactic mastectomy at the time of surgery for the first tumor suggests the need for a rapid genetic test (within 4 weeks). Moreover, it has now been demonstrated that the option of a bilateral mastectomy at the onset of the first tumor is more accepted by women than delayed contralateral surgery (41.7% vs. 4.7%).[77]

Finally, some data suggest that this procedure may improve disease-free and overall survival.[78-83]

Recently, a multicenter study has generated evidence that contralateral prophylactic mastectomy in women with unilateral cancer and documented BRCA1 or BRCA2 mutation leads to a decrease in breast cancer mortality (HR =0.52). The reduction appears to be more substantial in the second decade after surgery (HR=0.20).[84]

SYSTEMIC THERAPIES

As with all hereditary tumors, BRCA-related breast cancer also occurs more frequently in young women than sporadic forms.[85-86] Compared to BRCA2-related and sporadic forms, BRCA1-mutated breast cancer is often associated with histopathologic features indicative of an unfavorable prognosis (high grade, high proliferation, triple-negative tumors).[87-90] However, current evidence suggests that the prognosis is comparable to that of tumors that have occurred sporadically.[91-96] A first meta-analysis of 66 retrospective studies concluded that current evidence does not confirm a worse prognosis for *BRCA1/2* carriers in the adjuvant setting,[97] while a subsequent meta-analysis of *BRCA1* and *BRCA2* subtype studies showed a significant increase in the risk of death for BRCA1-mutated patients.[98] There are even some retrospective studies that seem to show better survival;[99] moreover, the prospective POSH cohort study has recently been published, which compared *BRCA*-related tumors with a control population, demonstrating that BRCA-mutated patients had significantly better survival in the first two years after diagnosis.[100]

Further studies are still needed.

As regards oncological treatment, there is evidence of increased chemosensitivity to platinum derivatives in patients with *BRCA*-related breast cancer.[101-104] For *BRCA*-mutated triple-negative forms, the use of neoadjuvant chemotherapy with regimens containing platinum-based agents produced complete pathologic complete response rates ranging from 58% to 77%.[103, 105]

With regard to clinical trials with PARP-inhibitors, the phase III randomized study OlympiAd, comparing olaparib and chemotherapy chosen by the physician (vinorelbine, capecitabine, eribulin, gemcitabine), conducted in 310 BRCA1/2-mutated patients with metastatic breast cancer who had received up to two lines

of chemotherapy for metastatic disease, reported a median PFS of 7 months with olaparib vs 4.2 months with chemotherapy, with an overall reduction in the risk of progression or death of 48% (HR 0.58; 95% CI 0.43-0.80; p<0.001). In the subgroup analysis, the reduction in the risk of progression or death was 57% for triple-negative tumors.[106] Similar results were recently presented at ASCO 2018 for the randomized phase III trial Embraca, comparing talazoparib with a physician-selected chemotherapy (vinorelbine, capecitabine, eribulin, gemcitabine) in 431 first/second-line metastatic patients and showing a PFS of 8.6 months with talazoparib versus 5.6 months with chemotherapy in both triple-negative and hormone-responsive patients. The OS curves show a non-significant trend in favor of talazoparib.[106]

An international study is currently underway with olaparib in the adjuvant breast cancer treatment setting.

This information implies the need for wider access to genetic counseling and testing in appropriate cases, with low costs, short response times and free coverage by the NHS.

13. Palliative care

The following question on the integration of early palliative care was formulated by AIOM's Early Palliative Care Workgroup.

CLINICAL QUESTION No. 20 (refer to GRADE Question No. 6)

In patients with advanced/metastatic cancer, is the integration of early palliative care with cancer treatment recommended compared to the "solo practice model"?

GRADE Global quality of evidence	Clinical recommendation	Strength of clinical recommendation
Very low	In patients with advanced/metastatic cancer, is the integration of early palliative care with cancer treatment recommended compared to the "solo practice model"?	**Strong Positive** (where a palliative care team is available) **Conditional Positive** (where a palliative care team is not available)

Recommendations according to GRADE methodology

Refer to Annex 1 for the rationale, the summary of evidence and the details of the recommendation.

14. Recommendations formulated with GRADE

GRADE QUESTION No. 1: In premenopausal women with operated hormone-receptor positive, HER2 negative, low-risk breast cancer, is the addition of ovarian suppression to tamoxifen recommended?

RECOMMENDATION: In premenopausal women with operated hormone-receptor positive, HER2 negative, low-risk breast cancer, the addition of ovarian suppression to tamoxifen should not be considered.

Strength of recommendation: Conditional NEGATIVE

Quality of evidence: outcome of benefit: Moderate; outcome of harm: Low

Comments to Benefit and Harm

To answer this question, randomized studies comparing the association of ovarian suppression + tamoxifen with tamoxifen alone were selected, including any updated analyses (1,2,3) and the combined analysis of patient-reported outcomes (4). The analysis was carried out considering only patients not pretreated with chemotherapy, since the characteristics of these patients are similar to those of low-risk patients. The following factors must be considered in the definition of high-risk patients: age <35 years, N ≥4 lymph nodes, G3, high ki67 level. The prognostic weight of each factor, assessed individually and in combination, should be established on a case-by-case basis, applying the conclusions of the TEXT and SOFT studies (4,5).

The study by Francis et al., (2) showed no statistically significant differences in terms of DFS (HR 0.76, 95% CI 0.52-1.12) or of risk of death (HR 1.96, 95% CI 0.67-5.73) between the two treatment arms at a median follow-up of 7.4 years. It is important to note how the short follow-up period (also underlined by the authors in the discussion of the published work) and the small number of events make the study too immature to highlight differences in global survival.

The study by Teevarwerk et al (2) showed no significant differences either in terms of DFS (HR 1.16, 95% CI 0.64 to 2.08) or OS (HR 1.19, 95% CI 0.52 to 2.7) between the study arms at a median follow-up of 9.9 years.

As regards the side effects of ovarian suppression, when data have been reported, the addition of the analogue has been associated with an increased risk of hot flashes, mood disorders, osteoporosis and fractures. The differences reported between critical outcomes, i.e. fractures and mood disorders, were not clinically relevant.

In view of the unclear benefit of adding the LHRH-analogue to tamoxifen in the subgroup of patients not pretreated with chemotherapy, and based on toxicity profile, all panel members voted for an uncertain benefit/harm ratio, with a majority in favor of a weak negative recommendation.

Benefit and harm voting			
Favorable	**Uncertain (favorable)**	**Uncertain (unfavorable)**	**Unfavorable**
		9	
Strength of recommendation voting			
Strong Positive	**Conditional Positive**	**Conditional Negative**	**Strong Negative**
		9	
Implications for future research: a longer follow-up of the studies under examination is necessary in order to highlight a difference in survival.			

April 2016 - updated July 2018

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GRADE QUESTION No. 2: In premenopausal women with operated hormone-receptor positive, HER2 negative, high-risk breast cancer, is the addition of ovarian suppression to tamoxifen recommended?

RECOMMENDATION: In premenopausal women with operated hormone-receptor positive, HER2 negative, high-risk breast cancer, the addition of ovarian suppression to tamoxifen should be considered in the first instance.

Strength of recommendation: STRONG POSITIVE

Comments to Benefit and Harm

To answer this question, a randomized study comparing the association of LHRH-analogue + tamoxifen with tamoxifen alone (1) and the combined analysis of patient-reported outcomes (2) were selected. The analysis was carried out considering only patients pretreated with chemotherapy, since the characteristics of these patients are similar to those of high-risk patients. The following factors must be considered in the definition of high-risk patients: age <35 years, N ≥4 lymph nodes, G3, high ki67 level. The prognostic weight of each factor, assessed individually and in combination, should be established on a case-by-case basis, applying the conclusions of the TEXT and SOFT studies (3,4).

The study by Francis et al., (1) showed no statistically significant differences in terms of DFS (HR 0,82, 95% CI 0,64 to 1,07) or of risk of death (HR 0,64, 95% CI 0,42 to 0,96) in favor of the combination arm with tamoxifen plus ovarian suppression.

In view of the significant improvement in survival with the combination treatment and the toxicity profile highlighted in Francis' study, all panel members voted for a favorable benefit/harm ratio, and eight panel members were in favor of a strong positive recommendation.

Strenght of Recommendation voting				Benefit and Harm		
Strong Positive	**Conditional Positive**	**Conditional Negative**	**Strong Negative**	**Favorable**	**Uncertain**	**Unfavorable**
8	1	0	0	9	0	0

Implications for future research: The study by Francis et al. is still immature to highlight differences in survival and requires a longer follow-up period. Further studies are needed to confirm which subgroup of patients may benefit from the addition of LHRH-a to tamoxifen.

Quality of Evidence
The quality of evidence was judged as **MODERATE** for the following reasons:
Some estimates are imprecise and have wide confidence intervals.
It should also be noted that in some studies it was not possible to assess the risk of bias due to lack of information.

Global quality of evidence: MODERATE

April 2016

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GRADE QUESTION No. 3: In premenopausal women with operated hormone-receptor positive, HER2 negative, high-risk breast cancer who are candidates for ovarian suppression, is treatment with an aromatase inhibitor recommended rather than treatment with tamoxifen?

RECOMMENDATION: In premenopausal women with operated hormone-receptor positive, HER2 negative, high-risk breast cancer who are candidates for ovarian suppression, treatment with an aromatase inhibitor may be considered.

Recommendation strength: Conditional POSITIVE

Comments to Benefit and Harm

The joint analysis of the SOFT and TEXT studies (1,2) was selected to answer this question. For the critical DFS and distant recurrence outcomes, data from the subgroup treated with chemotherapy, evaluated separately in each study, were used. This separate analysis is not available for the OS outcome, for which data from the joint analysis in the subgroup treated with chemotherapy were considered. Only patients treated with chemotherapy were considered, as they had characteristics similar to those of high-risk patients.

The ABCSG-12 study (4) was not included because it enrolled low-risk patients and the treatment was administered for three years.

The combined analysis of the TEXT and SOFT studies (1,2), conducted in patients with operated hormone-receptor positive breast cancer, shows a significant advantage in DFS and time free from distant recurrence in favor of treatment with exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression at a follow-up of 68 months. Specifically, the combination with exemestane is associated with a significant reduction in the risk of recurrence of 28% (HR 0.72, 95% CI 0.6 to 0.85) and of distant recurrence of 22% (HR 0.78, 95% CI 0.62 to 0.97). No significant differences were observed between the two arms in terms of overall survival (HR 1.14, 95% CI 0.86 to 1.51), a result which was considered still immature in the light of the short follow-up period.

With regard to the toxicity profile (1-3), as expected, treatment with an inhibitor was associated with a reduction in the risk of thromboembolism and an increase in the risk of fractures. As far as critical harm outcomes are concerned, the data on increased risk of myocardial ischemia and reduced risk of hemorrhagic and ischemic stroke were deemed inconclusive: the high quality of these outcomes indicates that it can confidently be concluded that the two interventions are unlikely to differ in terms of incidence of such adverse events, in spite of the fact that these are rare events.

In view of the relevance of the results of the combined analysis of the TEXT and SOFT studies, which were assigned a moderate quality, panel members unanimously considered the benefit/harm ratio as in favor of the combination of AI and ovarian suppression. The lack of survival data led 8 panel members to vote in favor of a weak positive recommendation.

Strenght of Recommendation voting				Benefit and Harm		
Conditional Negative	Strong Negative	Conditional Negative	Strong Negative	Favorable	Uncertain	Unfavorable

1	8	0	0	9	0	0
Implications for future research: The overall survival data from the combined analysis of the TEXT and SOFT studies and additional prospective studies may further clarify the role of AIs in premenopausal women.						
Quality of Evidence The quality of evidence was judged as MODERATE due to indirectness of results, since the OS outcome was evaluated in all patients, including low- and high-risk patients,.Some estimates were found to be imprecise (in addition to including non-effect, confidence intervals werevery wide).						
Overall quality of evidence: MODERATE						

April 2016

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GRADE QUESTION No. 4: In women with operated HER2 negative breast cancer and positive lymph nodes who are candidates for chemotherapy, are dose-dense regimens containing anthracyclines and taxanes recommended rather than conventional treatments?

RECOMMENDATION:

In women with operated HER2 negative breast cancer and positive lymph nodes who are candidates for chemotherapy, dose-dense regimens containing anthracyclines and taxanes should be considered as a treatment option in the first instance.

Strength of Recommendation: STRONG POSITIVE

Comments to Benefit and Harm:

To answer this question, randomized studies comparing dose-dense chemotherapy regimens containing anthracyclines and taxanes to traditional regimens were selected. On the basis of this criterion, 5 randomized studies were identified, published between 2003 and 2015, conducted on patients with operated breast cancer and positive lymph nodes; only 1 study also included high-risk patients with negative lymph nodes.

In the study by Swain et al.(1), 4,894 women with operated breast cancer and positive lymph nodes were randomized to receive:

- Traditional chemotherapy with TAC (docetaxel, doxorubicin, cyclophosphamide) for 6 cycles;
- Dose-dense chemotherapy (dose-dense (q14) doxorubicin and cyclophosphamide + pegfilgrastim followed by 4 cycles of dose-dense (q14) paclitaxel (175 mg/mq) + pegfilgrastim);
- Dose-dense chemotherapy (dose-dense (q14) doxorubicin and cyclophosphamide + pegfilgrastim followed by 4 cycles of paclitaxel (175 mg/mq) in combination with dose-dense (q14) gemcitabine (2000 mg/mq) + pegfilgrastim).

By limiting the comparison to the two arms not containing gemcitabine, no significant differences were observed in terms of reduction of the risk of death (HR 0.86, 95% CI 0.7 to 1.07) or recurrence (HR 0.93, 95% CI 0.8 to 1.09) at a median follow-up of 64 months.

In the Citron et al (2) study, 2,005 patients with operated breast cancer were randomized to receive one of the following regimens:

- Traditional chemotherapy regimen: doxorubicin (A) x 4 cycles → paclitaxel (T) x 4 → cyclophosphamide (C) x 4 every 3 weeks;
- Dose-dense chemotherapy with doxorubicin x 4 cycles → paclitaxel x 4 → cyclophosphamide x 4 every 2 weeks with filgrastim;
- Traditional chemotherapy regimen: AC x 4 → T x 4 every 3 weeks;
- Dose-dense chemotherapy with AC x 4 → T x 4 every 2 weeks with filgrastim support.

By limiting the analysis to the last two arms, the dose-dense regimen resulted in a relative 50% reduction in the risk of recurrence at a median follow-up of 36 months (HR 0.50, 95% CI 0.3 to 0.83), with no difference in terms of death risk reduction (HR 0.81, 95% CI 0.66 to 1).

In the study by Moebus et al (3), 1,284 patients with operated breast cancer and ≥4 positive axillary lymph nodes were randomized to receive:

- A sequence of epirubicin, paclitaxel, and cyclophosphamide each for 3 cycles every 2 weeks with filgrastim support;
- The combination of epirubicin/cyclophosphamide for 4 cycles followed by paclitaxel for 4 cycles every 3 weeks.

At a 62-month median follow-up, the dose-dense schedule produced a relative reduction in the risk of death of 24% (HR 0.76, 95% CI 0.59 to 0.97) and a relative reduction in the risk of recurrence of 28% (HR 0.72, 95% CI 0.59 to 0.87), both statistically significant.

In the Burnell et al (4) study, 2,104 high-risk patients with operated breast cancer, age ≤60 years and positive or negative axillary lymph nodes were randomized to receive:

- CEF every 28 days for 6 cycles;
- EC every 14 days for 5 cycles followed by paclitaxel every 21 days for 4 cycles;
- AC every 21 days for 4 followed by paclitaxel every 21 for 4 cycles.

Analyzing the sequential arms at a median follow-up of 30.4 months, the dose-dense schedule resulted in a relative reduction in the risk of recurrence of 41% (HR 0.59, 95% CI 0.44 to 0.8); survival data were not reported due to immaturity.

In the 2x2 factorial study by Del Mastro et al. (5), 2,091 patients with operated breast cancer and positive lymph nodes were randomized to receive:

- Traditional chemotherapy regimen: FEC x 4 cycles followed by paclitaxel x 4 cycles;
- Traditional chemotherapy regimen: EC x 4 cycles followed by paclitaxel x 4 cycles q21;
- Dose-dense chemotherapy c–n - FEC x 4 (q14) followed by paclitaxel (q14) x 4 with pegfilgrastim support;
- Dose-dense chemotherapy with EC x 4 (q14) followed by paclitaxel (q14) with pegfilgrastim support.

When evaluating arms not containing fluorouracil, the dose-dense schedule resulted in a reduction in the risk of death by 35% (HR 0.65 CI 95% 0.51 to 0.84) and of recurrence by 23% (HR 0.77, 95% CI 0.65 to 0.92).

The toxicity spectrum showed no clinically significant differences between the two regimens, with a lower incidence of neutropenia (g3/4) and febrile neutropenia in patients treated with the dose-dense schedule including GCSF, alongside an increased risk of anemization (g3/4) and neuropathy (g3/4).

Overall, 2 studies showed a significant reduction in death risk ranging from 24% to 35%, and 4 studies showed a significant reduction in recurrence risk ranging from 23% to 50% in favor of the dose-dense schedule.

In light of the DFS advantage and the (less evident) OS advantage (which was also considered a critical outcome, but less clinically significant than DFS in the adjuvant setting) against an acceptable toxicity

profile, panel members unanimously judged the risk/benefit ratio resulting from the administration of the dose-dense schedule as favorable.

Strenght of Recommendation voting				Benefit and Harm		
Condition al Negative	Strong Negative	Conditiona l Negative	Strong Negative	Favorable	Uncertain	Unfavorable
6	1	0	0	7	0	0

Quality of Evidence

The quality of evidence was judged as **MODERATE** due to imprecision, because the confidence interval of some estimates, in addition to including non-effect, was very wide. In addition, in the study by Burbnell et al (4), the directness of results was problematic, as patients with negative lymph nodes were also enrolled (28% of cases).

It should also be noted that for some studies it was impossible to assessment of the risk of bias risk due to lack of information.

Overall quality of evidence: MODERATE

March 2015

Three reviewers (G.C;F.B; S.C) do not agree with this recommendation. The reviewers are not part of the multidisciplinary group of authors that formulated this question, evaluated the scientific evidence and rated the recommendation according to the GRADE methodology.

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GRADE QUESTION No. 5: In women with TRIPLE-NEGATIVE breast cancer (hormone-receptor negative and HER2 negative) who are candidates for primary/neoadjuvant chemotherapy, is the addition of platinum to a standard regimen with anthracyclines and taxanes recommended rather than anthracyclines and taxanes alone?

RECOMMENDATION: In women with triple-negative breast cancer (hormone-receptor negative and HER2 negative) who are candidates for primary/neoadjuvant chemotherapy, the addition of platinum to a standard regimen with anthracyclines and taxanes may be considered.

Strength of Recommendation : Conditional POSITIVE

Quality of evidence: Outcome of benefit: Very low; Outcome of harm: Low

Comments to Benefit and Harm:

Benefit outcome. The Panel judged the following benefit outcomes as critical: overall survival (OS), disease/event-free survival (DFS/EFS), invasive disease-free survival (iDFS), and pCR rates. Only 5 randomized studies (RCTs) where platinum was added to the same standard regimen of anthracyclines and taxanes (1-7) were considered for this question. None of the included studies reported invasive-DFS. Three RCTs reported OS and DFS/EFS and five reported pCR rates. No significant differences were found in favor of the addition of platinum either in DFS/EFS (HR 0.72, 95% CI 0.49-1.06) or OS (HR 0.86, 95% CI 0.46-1.63). In RCTs that reported pCR rates from the addition of platinum to the same chemotherapy regimen with anthracyclines and taxanes (only in the BrighTness study was platinum administered in association with veliparib), the risk was 550 pCRs every 1,000 patients in the platinum arm and 372 every 1,000 patients in the control arm (RR 1.48, 95% CI 1.20-1.83). The quality of evidence supporting the pCR outcome was low due to the presence of possible detection bias (no evaluator masking) and heterogeneity (I-squared=55%). Despite the lack of evidence showing a difference in survival (due to the low number of events and the short follow-up of the selected studies), in the light of the difference in pCR rates, the Panel judged as MODERATE the significance of the desirable effect of adding platinum to an anthracycline/taxane regimen.

Harm outcome. The Panel identified the following harm outcomes: febrile neutropenia, anemia (grade 3-4), thrombocytopenia, serious adverse events (SAEs). Only febrile neutropenia and SAEs were considered critical outcomes. The addition of platinum to a standard regimen of anthracyclines and taxanes was associated with an increased risk of grade 3-4 anemia (RR 27.05, 95% CI 8.57 to 85.30), SAEs (RR 2.25, 95% CI 1.21 to 4.19) and grade 3-4 thrombocytopenia (RR 9.29, 95% CI 3.49 to 24.71). No significant differences were noted in the risk of febrile neutropenia (RR 1.40, 95% CI 0.97 to 2.01). The Panel, also in the light of the heterogeneity of the chemotherapy regimens used in different studies, which influenced the incidence of adverse events, considered as SMALL the significance of undesirable predictable effects.

Although the impact on survival of adding platinum to standard neoadjuvant chemotherapy remains undefined, the Panel judged the benefit/harm ratio as uncertain in favor of the intervention based on the increase in pCRs obtained at an acceptable cost in terms of toxicity profile.

	Benefit and harm voting		
Favorable	**Uncertain (favorable)**	**Uncertain (unfavorable)**	**Unfavorable**
	10	1	
	Strength Recommendation voting		
Strong Positive	**Weak Positive**	**Weak Negative**	**Strong Negative**
	10	1	

Implications for future research: a longer follow-up of the studies considered is necessary in order to highlight a difference in survival.

June 2018

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5.   Treatment of operable infiltrating cancer

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10. Breast cancer in elderly women

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Annex 1: GRADE evidence profiles & EtD framework

GRADE QUESTION NO. 1

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + tamoxifen	tamoxifen	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment							**№ of patients**		**Effect**			
OS - Francis 2018 (follow up: median 7.4 years)												
1	randomised trials	not serious a	not serious	not serious	serious b,c	none	10/473 (2.1%)	5/476 (1.1%)	HR 1.96 (0.67 to 5.73)	1 more per 100 (from 0 fewer to 5 more)	⊕⊕⊕◯ MODERATE	CRITICAL
OS - Tevaarwerk 2014 (follow up: median 9.9 years)												
1	randomised trials	not serious	not serious	not serious	serious d	none	11/170 (6.5%)	13/167 (7.8%)	HR 1.19 (0.52 to 2.70)	1 more per 100 (from 4 fewer to 12 more)	⊕⊕⊕◯ MODERATE	CRITICAL
DFS - Francis 2018 (follow up: median 7.4 years; assessed with: recurrence of invasive breast cancer, invasive controlateral breast cancer, second (nonbreast) invasive cancer, or death)												
1	randomised trials	not serious a	not serious	not serious	serious d	none	47/473 (9.9%)	60/476 (12.6%)	HR 0.76 (0.52 to 1.12)	3 fewer per 100 (from 1 more to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
DFS - Tevaarwerk 2014 (follow up: median 9.9 years; assessed with: recurrence of breast cancer, new primary breast cancer or death)												
1	randomised trials	not serious	not serious	not serious	serious d	none	21/170 (12.4%)	24/167 (14.4%)	HR 1.16 (0.64 to 2.08)	2 more per 100 (from 5 fewer to 13 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. random-stratified subgroup
b. We decided to not downgrade quality of evidence for imprecision due to the low event rate in both arms.
c. Clinical data still immature (see Discussion, p 135)
d. 95% confidence interval includes no effect and the lower and upper confidence limit crosses the minimal important difference (MID)

Author(s): MC IC GLP
Date:
Question: Ovarian function suppression (OFS) + tamoxifen compared to tamoxifen in pre-menopausal hormone-receptor-positive low risk breast cancer patients
Setting:
Bibliography: Francis PA, NEJM 2015; 372:436-46 Francis PA, NEJM 2018; 379:122-137 Tevaarwerk AJ, J Clin Oncol 2014; 32:3948-3958 Ribi K, J Clin Oncol. 2016 May 10;34(14):1601-10

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + tamoxifen	tamoxifen	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment							№ of patients		Effect			
Flushing (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [b]	serious [c]	none	861	861	-	MD 4 lower (9 lower to 0)	⊕⊕⊕◯ LOW	IMPORTANT
Flushing (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	133/1005 (13.2%)	76/1006 (7.6%)	RR 1.75 (1.34 to 2.29)	6 more per 100 (from 3 more to 10 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Flushing (grade 3/4) - Tevaarwerk 2014 (follow up: median 9.9 years)												
1	randomised trials	not serious	not serious	not serious	not serious	none	28/174 (16.1%)	8/171 (4.7%)	RR 3.43 (1.60 to 7.29)	11 more per 100 (from 3 more to 29 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mood disorders (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: AIBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	861	861	-	MD 2 higher (1 lower to 5 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Mood disorders (grade 3/4) - Francis 2015 (follow up: median 67 months; assessed with: Depression)												
1	randomised trials	not serious	not serious	not serious	not serious	none	44/1005 (4.4%)	38/1006 (3.8%)	RR 1.16 (0.76 to 1.77)	1 more per 100 (from 1 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mood disorders (grade 3/4) - Tevaarwerk 2014 (follow up: median 9.9 years; assessed with: includes anxiety and depression)												
1	randomised trials	not serious	not serious	not serious	not serious [a]	none	4/174 (2.3%)	4/171 (2.3%)	RR 0.98 (0.25 to 3.87)	0 fewer per 100 (from 2 fewer to 7 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Osteoporosis (any grade) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	201/1005 (20.0%)	124/1006 (12.3%)	RR 1.63 (1.33 to 2.00)	8 more per 100 (from 4 more to 12 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Osteoporosis (any grade) - Tevaarwerk 2014 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. We decided to not downgrade quality of evidence for imprecision due to the low event rate in both arms.
b. data provided for the whole population (low and high risk)
c. 95% CI crosses the MID (+- 8 points)

Author(s): MC IC GLP
Date:
Question: Ovarian function suppression (OFS) + tamoxifen compared to tamoxifen in pre-menopausal hormone-receptor-positive low risk breast cancer patients
Setting:
Bibliography: Francis PA, NEJM 2015; 372:436-46 Francis PA, NEJM 2018; 379:122-137 Tevaarwerk AJ, J Clin Oncol 2014; 32:3948-3958 Ribi K, J Clin Oncol. 2016 May 10;34(14):1601-10

Nₒ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + tamoxifen	tamoxifen	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment							**Nₒ of patients**		**Effect**			
Fractures (any grade) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	54/1005 (5.4%)	49/1006 (4.9%)	RR 1.10 (1.74 to 2.11)	0 fewer per 100 (from 4 more to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Fractures (any grade) - Tevaarwerk 2014 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Vaginal dryness (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious b	serious c	none	861	861	-	MD 6 lower (10 lower to 2 lower)	⊕⊕○○ LOW	IMPORTANT
Vaginal dryness (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/1005 (0.0%)	0/1006 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT
Vaginal dryness (grade 3/4) - Tevaarwerk 2014 (follow up: median 9.9 years)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1/174 (0.6%)	0/171 (0.0%)	RR 1.97 (0.07 to 58.26)	0 fewer per 100 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Changes in libido (pts sel reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious b	not serious	none	861	861	-	MD 3 lower (7 lower to 1 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Changes in libido (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/1005 (0.0%)	0/1006 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT
Changes in libido (grade 3/4) - Tevaarwerk 2014 (follow up: median 9.9 years)												
1	randomised trials	not serious	not serious	not serious	not serious a	none	1/174 (0.6%)	0/171 (0.0%)	RR 1.97 (0.07 to 58.21)	0 fewer per 100 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **HR**: Hazard Ratio; **MD**: Mean difference; **RR**: Risk ratio

Explanations

a. We decided to not downgrade quality of evidence for imprecision due to the low event rate in both arms.
b. data provided for the whole population (low and high risk)
c. 95% CI crosses the MID (+- 8 points)

GRADE QUESTION NO. 2

Author(s): MC IM
Date:
Question: Ovarian function suppression (OFS) + tamoxifen compared to tamoxifen in pre-menopausal hormone-receptor-positive high-risk breast cancer patients
Setting:
Bibliography: Francis PA, NEJM 2015; 372:436-46

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + tamoxifen	tamoxifen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Quality assessment							№ of patients		Effect			
OS - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious [1]	not serious	not serious	not serious	none	39/542 (7.2%)	57/542 (10.5%)	HR 0.64 (0.42 to 0.96)	**4 fewer per 100** (from 0 fewer to 6 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DFS - Francis 2015 (follow up: median 67 months; assessed with: recurrence of invasive breast cancer, invasive controlateral breast cancer, second (nonbreast) invasive cancer, or death)												
1	randomised trials	not serious [1]	not serious	not serious	serious [2]	none	107/542 (19.7%)	122/542 (22.5%)	HR 0.82 (0.64 to 1.07)	**4 fewer per 100** (from 1 more to 7 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Flushes - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [3]	serious [4]	none	861	861	-	MD **4 lower** (9 lower to 0)	⊕⊕◯◯ LOW	IMPORTANT
Flushing (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	113/1005 (11.2%)	76/1006 (7.6%)	RR 1.75 (1.34 to 2.29)	**6 more per 100** (from 3 more to 10 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mood (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [3]	not serious	none	861	861	-	MD **2 higher** (1 lower to 5 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + tamoxifen	tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Mood disorders (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	44/1005 (4.4%)	38/1006 (3.8%)	**RR 1.16** (0.76 to 1.77)	**1 more per 100** (from 1 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Osteoporosis (any grade) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	201/1005 (20.0%)	124/1006 (12.3%)	**RR 1.63** (1.33 to 2.00)	**8 more per 100** (from 4 more to 12 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Fractures (any grade) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	serious [5]	none	54/1005 (5.4%)	49/1006 (4.9%)	**RR 1.10** (0.76 to 1.61)	**0 fewer per 100** (from 1 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Vaginal dryness (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [3]	serious [4]	none	861	861	-	MD **6 lower** (10 lower to 2 lower)	⊕⊕◯◯ LOW	IMPORTANT
Vaginal dryness (grade 3/4) - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/1005 (0.0%)	0/1006 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT
Changes in libido - Francis 2015 (follow up: median 67 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/1005 (0.0%)	0/1006 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT
Changes in libido (pts self reported) - Ribi 2016 (follow up: median 67 months; assessed with: IBCSG QoL core Form at 60 months (higher value indicates better status); Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	serious [3]	not serious	none	861	861	-	MD **3 lower** (7 lower to 1 higher)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **HR:** Hazard Ratio; **MD:** Mean difference; **RR:** Risk ratio

1. Random-stratified subgroup

200

2. 95% confidence interval includes no effect and the lower confidence limit crosses the minimal important difference (MID)
3. Data provided fo the whole population (high and low risk)
4. 95% CI crosses the MID (+- 8 points)
5. 95% confidence interval includes no effect and the upper confidence limit crosses the minimal important difference (MID)

GRADE QUESTION NO. 3

Author(s): MC IM
Date:
Question: Ovarian function suppression (OFS) + aromatase inhibitors compared to OFS + tamoxifen administered for 5 years in pre-menopausal hormone-receptor-positive breast cancer patients
Setting: inpatient
Bibliography: Bernhard J. Lancet oncol 2015;16:848-58 Pagani O, NEJM 2014; 371:107-18 Regan MM, The Breast 2013, 22:1094-1100

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + aromatase inhibitors	OFS + tamoxifen administered for 5 years	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Quality assessment							**No of patients**		**Effect**			
OS - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	serious [3]	none	102/2346 (4.3%)	92/2344 (3.9%)	HR 1.14 (0.86 to 1.51)	1 more per 100 (from 1 fewer to 2 more)	⊕⊕⊕◯ MODERATE	CRITICAL
DFS - Pagani 2014 (follow up: median 68 months; assessed with: recurrence of invasive breast cancer, second invasive (non-breast) cancer or death)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	216/2346 (9.2%)	298/2344 (12.7%)	HR 0.72 (0.60 to 0.85)	34 fewer per 1.000 (from 18 fewer to 49 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Distant recurrence - Pagani 2014 (follow up: median 68 months; assessed with: not reported)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	142/2346 (6.1%)	183/2344 (7.8%)	HR 0.78 (0.62 to 0.97)	2 fewer per 100 (from 0 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Thromboembolism (any grade) - Pagani 2014 (follow up: median 68 months)												
1	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	24/2318 (1.0%)	50/2325 (2.2%)	RR 0.48 (0.30 to 0.78)	1 fewer per 100 (from 0 fewer to 2 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Osteoporosis (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	894/2318 (38.6%)	586/2325 (25.2%)	RR 1.53 (1.40 to 1.67)	13 more per 100 (from 10 more to 17 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Fracture (any grade) - Pagani 2014 (follow up: median 68 months)												

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + aromatase inhibitors	OFS + tamoxifen administered for 5 years	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
		Quality assessment					№ of patients		Effect			
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	158/2318 (6.8%)	120/2325 (5.2%)	**RR 1.32** (1.05 to 1.66)	**2 more per 100** (from 0 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Vaginal dryness (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	1214/2318 (52.4%)	1101/2325 (47.4%)	**RR 1.11** (1.04 to 1.17)	**5 more per 100** (from 2 more to 8 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Vaginal dryness (any grade) - Bernhard 2015 - (follow up: median 5.7 years; assessed with: IBCSG's QoL core form 60 months (Higher scores mean better status); Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	2045	2051	-	MD **7 lower** (10 lower to 5 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Musculoskeletal symptoms (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	2057/2318 (88.7%)	1766/2325 (76.0%)	**RR 1.17** (1.14 to 1.20)	**13 more per 100** (from 11 more to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Musculoskeletal (Bone or joint pain) - Bernhard 2015 (follow up: median 5.7 years; assessed with: IBCSG's QoL core form 60 months (Higher scores mean better status); Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	2045	2051	-	MD **5 lower** (7 lower to 3 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Hypertension (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	527/2318 (22.7%)	509/2325 (21.9%)	**RR 1.04** (0.93 to 1.16)	**9 more per 1.000** (from 15 fewer to 35 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Myocardial ischemia (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious [4]	none	16/2318 (0.7%)	7/2325 (0.3%)	**RR 2.29** (0.94 to 5.56)	**0 fewer per 100** (from 0 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke (hemorrhage) (any grade) - Pagani 2014 (follow up: median 68 months)												

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ovarian function suppression (OFS) + aromatase inhibitors	OFS + tamoxifen administered for 5 years	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
		Quality assessment					№ of patients		Effect			
2	randomised trials	not serious	not serious	not serious [1,2]	not serious [4]	none	15/2318 (0.6%)	21/2325 (0.9%)	RR 0.72 (0.37 to 1.36)	0 fewer per 100 (from 0 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke (ischemia) (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious [4]	none	5/2318 (0.2%)	11/2325 (0.5%)	RR 0.45 (0.16 to 1.31)	0 fewer per 100 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Hot flushes (grade 3-4) Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	232/2318 (10.0%)	279/2325 (12.0%)	RR 0.83 (0.71 to 0.98)	20 fewer per 1.000 (from 2 fewer to 35 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Hot flushes pts self reported -Bernhard 2015 (follow up: median 5.7 years; assessed with: IBCSG's QoL core form 6 months (Higher scores mean better status) ; Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	2045	2051	-	MD **8 higher** (6 higher to 10 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mood - Bernhard 2015 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Libido (any grade) - Pagani 2014 (follow up: median 68 months)												
2	randomised trials	not serious	not serious	not serious [1,2]	not serious	none	1042/2318 (45.0%)	950/2325 (40.9%)	RR 1.10 (1.03 to 1.18)	41 more per 1.000 (from 12 more to 74 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio; **MD:** Mean difference
1. In the SOFT trial the ovarian function suppression via LHRH chosen in 91% patients
2. Tha majority of patients received chemotherapy before randomization
3. 95% confidence interval includes no effect and the upper confidence limit crosses the minimal important difference (MID)

GRADE QUESTION NO. 4

Author(s): MC IC
Date: 2015-03-25
Question: Should dose-dense antraciclines/taxanes based chemotherapy vs conventional chemotherapy be used in N-positive breast cancer patients?
Settings:
Bibliography: Citron M, JCO 2003; 21:1431-1439 Burnell M, JCO 2010; 28:77-82 Moebus V, JCO 2010; 28:2874-2880 Swain SM, JCO 2013; 31:3197-3204 Del Mastro L, TheLancet 2015; published online 2nd march

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dose-dense antraciclines/taxanes based chemotherapy	Conventional chemotherapy	Relative (95% CI)	Absolute		
OS - Citron 2003 (follow-up median 36 months)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	75/988 (7.6%)	107/985 (10.9%)	HR 0.81 (0.66 to 1)	2 fewer per 100 (from 4 fewer to 0 more)	⊕⊕⊕◯ MODERATE	CRITICAL
OS - Burnell 2010 - not reported												
												CRITICAL
OS - Moebus 2010 (follow-up median 62 months)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/641 (17.8%)	139/611 (22.7%)	HR 0.76 (0.59 to 0.97)	5 fewer per 100 (from 1 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
OS - Swain 2013 (follow-up median 64 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	167/1618 (10.3%)	185/1617 (11.4%)	HR 0.86 (0.7 to 1.07)	2 fewer per 100 (from 3 fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL

OS - Del Mastro 2015 (follow-up median 7 years)

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/1002 (10.3%)	149/1001 (14.9%)	HR 0.65 (0.51 to 0.84)	5 fewer per 100 (from 2 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

DFS - Citron 2003 (follow-up median 36 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136/988 (13.8%)	179/985 (18.2%)	HR 0.50 (0.3 to 0.83)	9 fewer per 100 (from 3 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

DFS - Burnell 2010 (follow-up median 30.4 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[3]	no serious imprecision	none	74/701 (10.6%)	105/702 (15%)	HR 0.59 (0.44 to 0.8)	6 fewer per 100 (from 3 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

DFS - Moebus 2010 (follow-up median 62 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/641 (28.4%)	226/611 (37%)	HR 0.72 (0.59 to 0.87)	9 fewer per 100 (from 4 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

DFS - Swain 2013 (follow-up median 62 months)

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	320/1613 (19.8%)	327/1610 (20.3%)	HR 0.93 (0.8 to 1.09)	1 fewer per 100 (from 4 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL

DFS - Del Matro 2015 (follow-up median 7 years)

206

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	224/1002 (22.4%)	270/1001 (27%)	HR 0.77 (0.65 to 0.92)	5 fewer per 100 (from 2 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Anemia (grade 3/4) - Citron 2003 (follow-up median 36 months; assessed with: Hemoglobin)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	2/983 (0.2%)	1/979 (0.1%)	RR 0.99 (0.14 to 7.06)	0 fewer per 100 (from 0 fewer to 1 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Anemia (grade 3/4) - Burnell 2010 (follow-up median 30.4 months; assessed with: Hemoglobin)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[3]	no serious imprecision	none	199/687 (29%)	7/674 (1%)	RR 27.89 (58.82 to 13.22)	28 more per 100 (from 13 more to 60 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Anemia (grade 3/4) - Moebus 2010 (follow-up median 62 months)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/623 (8.5%)	6/587 (1%)	RR 8.32 (3.61 to 19.22)	7 more per 100 (from 3 more to 19 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Anemia (grade 3/4) - Swain 2013 (follow-up median 64 months; assessed with: not reported)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	25/1612 (1.6%)	3/1607 (0.19%)	RR 2.31 (2.51 to 27.46)	0 more per 100 (from 0 more to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Anemia (grade 3/4) - Del Mastro 2015 (follow-up median 7 years; assessed with: not reported)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/988 (1.4%)	2/984 (0.2%)	RR 6.97 (1.59 to 30.6)	1 more per 100 (from 0 more to 6 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Neutropenia (grade 3/4) - Citron 2003 - not reported												

												IMPORTANT
												IMPORTANT

Neutropenia (grade 3/4) - Burnell 2010 - not reported

												IMPORTANT

Neutropenia (grade 3/4) - Moebus 2010 (follow-up median 62 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	288/580 (49.7%)	309/541 (57.1%)	RR 0.87 (0.78 to 0.97)	7 fewer per 100 (from 2 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Neutropenia (grade 3/4) - Swain 2013 - not reported

												IMPORTANT

Neutropenia (grade 3/4) - Del Mastro 2015 (follow-up median 7 years)

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/988 (14.9%)	433/984 (44%)	RR 0.34 (0.29 to 0.4)	29 fewer per 100 (from 26 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Febrile neutropenia (grade 3/4) - Citron 2003 - not reported

												IMPORTANT

Febrile neutropenia (grade 3/4) - Burnell 2010 (follow-up median 30.4 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[3]	no serious imprecision	none	111/701 (15.8%)	32/702 (4.6%)	RR 3.47 (2.37 to 5.07)	11 more per 100 (from 6 more to 19 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Febrile neutropenia (grade 3/4) - Moebus 2010 (follow-up median 62 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/623 (7.1%)	12/587 (2%)	RR 3.45 (1.84 to 6.48)	5 more per 100 (from 2 more to 11 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Febrile neutropenia (grade 3/4) - Swain 2013 (follow-up median 64 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/1612 (3.2%)	144/1607 (9%)	RR 0.35 (0.26 to 0.48)	6 fewer per 100 (from 5 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Febrile neutropenia (grade 3/4) - Del Mastro 2015 - not reported												
												IMPORTANT
Thrombocytopenia (grade 3/4) - Citron 2003 - not reported												
												IMPORTANT
Thrombocytopenia (grade 3/4) - Burnell 2010 - not reported												
												IMPORTANT
Thrombocytopenia (grade 3/4) - Moebus 2010 (follow-up median 62 months)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/623 (9.3%)	6/587 (1%)	RR 9.11 (3.96 to 20.95)	8 more per 100 (from 3 more to 20 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Thrombocytopenia (grade 3/4) - Swain 2013 - not reported												
												IMPORTANT

Thrombocytopenia (grade 3/4) - Del Mastro 2015 (follow-up median 7 years)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision[4] | none | 6/988 (0.61%) | 4/984 (0.41%) | RR 1.49 (0.42 to 5.28) | 0 more per 100 (from 0 fewer to 2 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Mucositis (grade 3/4) - Citron 2003 (follow-up median 36 months; assessed with: Stomatitis)

| 1 | randomised trials | no serious risk of bias[2] | no serious inconsistency | no serious indirectness | no serious imprecision[4] | none | 13/983 (1.3%) | 19/979 (1.9%) | RR 0.68 (0.34 to 1.37) | 1 fewer per 100 (from 1 fewer to 1 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Mucositis grade 3/4 - Burnell 2010 (follow-up median 30.4 months; assessed with: Stomatitis)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[3] | no serious imprecision | none | 68/701 (9.7%) | 5/702 (0.71%) | RR 13.62 (5.52 to 33.57) | 9 more per 100 (from 3 more to 23 more) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

Mucositis (grade 3/4) - Moebus 2010 - not reported

| | | | | | | | | | | | | IMPORTANT |

Mucositis (grade 3/4) - Swain 2013 (follow-up median 64 months)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision[4] | none | 18/1612 (1.1%) | 15/1607 (0.93%) | RR 1.20 (0.61 to 2.37) | 0 more per 100 (from 0 fewer to 1 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Mucositis (grade 3/4) - Del Mastro 2015 (follow-up median 7 years; assessed with: Stomatitis)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision[4] | none | 9/988 (0.91%) | 3/984 (0.3%) | RR 2.99 (0.81 to 11.00) | 1 more per 100 (from 0 fewer to 3 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Neurological toxicity (grade 3/4) - Citron 2003 - not reported

											IMPORTANT

Neurological toxicity (grade 3/4) - Burnell 2010 (follow-up median 30.4 months; assessed with: sensory neuropathy)

| 1 | randomised trials | no serious risk of bias[1] | no serious inconsistency | serious[3] | serious[5] | none | 41/701 (5.8%) | 37/702 (5.3%) | RR 1.11 (0.72 to 1.71) | 1 more per 100 (from 1 fewer to 4 more) | ⊕⊕◯◯ LOW | IMPORTANT |

Neurological toxicity (grade 3/4) - Moebus 2010 - not reported

| | | | | | | | | | | | IMPORTANT |

Neurological toxicity (grade 3/4) - Swain 2013 (follow-up median 64 months; assessed with: sensory neuropathy)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 99/1612 (6.1%) | 16/1607 (1%) | RR 6.17 (3.65 to 10.41) | 5 more per 100 (from 3 more to 9 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Neurological toxicity (grade 3/4) - Del Mastro 2015 (follow-up median 7 years)

| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[6] | none | 35/988 (3.5%) | 25/984 (2.5%) | RR 1.39 (0.84 to 2.31) | 1 more per 100 (from 0 fewer to 3 more) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

Acute leucosis/myelodysplasia (grade 3/4) - Citron 2003 - not reported

| 1 | - | - | - | - | - | none | 527/2318 (22.7%) | 509/2325 (21.9%) | - | - | ⊕⊕⊕◯ MODERATE | IMPORTANT |

Acute leucosis/myelodysplasia (grade 3/4) - Burnell 2010 (follow-up median 30.4 months)

1	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[3]	no serious imprecision[4]	none	4/701 (0.57%)	0/702 (0%)	RR 8.01 (0.42 to 151.26)	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Acute leucosis/myelodysplasia (grade 3/4) - Moebus 2010 (follow-up median 62 months)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	4/623 (0.64%)	0/587 (0%)	RR 7.54 (0.40 to 142.27)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Acute leucosis/myelodysplasia (grade 3/4) - Swain 2013 (follow-up median 64 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	11/1612 (0.68%)	5/1607 (0.31%)	RR 2.19 (0.76 to 6.30)	0 more per 100 (from 0 fewer to 2 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Acute leucosis/myelodysplasia (grade 3/4) - Del Mastro 2015 (follow-up median 7 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	2/988 (0.2%)	0/984 (0%)	RR 3.98 (0.18 to 88.24)	-	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] It was not possible to judge the the whole risk of bias of the study because of lack of information. We considered an UNCLEAR risk for all bias
[2] 95% confidence interval includes no effect and the lower confidence limit crosses the minimal important difference (MID)
[3] 28% of patients in both arms were node negative
[4] We decided to not downgrade quality of evidence for imprecision due to the low number of events in both arms
[5] 95% confidence interval includes no effect and the lower and upper confidence limit crosses the minimal important difference (MID)
[6] 95% confidence interval includes no effect and the upper confidence limit crosses the minimal important difference (MID)

GRADE QUESTION NO. 5

Author(s): MC
Date:
Question: Should a platinum-based regimen be added to a taxane- and anthracycline-based neoadjuvant chemotherapy compared to taxane- and anthracycline-based neoadjuvant chemotherapy only for triple-negative breast cancer patients
Setting: inpatients
Bibliography: Poggio F. Annals of incology In press

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a platinum-based regimen be add to a taxane- and anthracycline-based neoadjuvant chemotherapy	taxane- and anthracycline-based neoadjuvant chemotherapy only	Relative (95% CI)	Absolute (95% CI)		
Overall survival (follow up: range 39 months to 47.3 months)												
3 [a]	randomised trials	not serious	serious [b]	not serious	serious [c]	publication bias strongly suspected [d]	18/408 (4.4%)	20/401 (5.0%)	HR 0.86 (0.46 to 1.63)	1 fewer per 100 (from 3 fewer to 3 more)	⊕○○○ VERY LOW	CRITICAL

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a platinum-based regimen be add to a taxane- and anthracycline-based neoadjuvant chemotherapy	taxane- and anthracycline-based neoadjuvant chemotherapy only	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
			Certainty assessment				№ of patients		Effect			
DFS/EFS												
3 [e]	randomised trials	serious [f]	serious [g]	not serious	serious [h]	publication bias strongly suspected [i]	43/408 (10.5%)	60/401 (15.0%)	HR 0.72 (0.49 to 1.06)	4 fewer per 100 (from 1 more to 7 fewer)	⊕○○○ VERY LOW	CRITICAL
Invasive-free survival - not reported												
												CRITICAL
Pathological complete response rate (studies with same schedule in both arms) (assessed with: no residual invasive tumour in both the breast and the axilla: i.e. ypT0/is pN0)												
5 [j]	randomised trials	serious [k]	serious [l]	not serious	not serious	none	338/623 (54.3%)	227/611 (37.2%)	RR 1.48 (1.20 to 1.83)	178 more per 1.000 (from 74 more to 308 more)	⊕⊕○○ LOW	CRITICAL
Febrile neutropenia grade 3/4/5												
5 [j]	randomised trials	not serious	not serious	not serious [m,n]	serious [h]	none	63/699 (9.0%)	44/693 (6.3%)	RR 1.40 (0.97 to 2.01)	3 more per 100 (from 0 fewer to 6 more)	⊕⊕⊕○ MODERATE	CRITICAL
Anemia												
4 [o]	randomised trials	not serious	not serious	not serious [m,n]	serious [h]	none	94/586 (16.0%)	2/585 (0.3%)	RR 27.05 (8.57 to 85.30)	9 more per 100 (from 3 more to 29 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Seriuos adverse events												
2 [p]	randomised trials	serious [q]	not serious [r]	not serious [m]	serious [h]	none	44/271 (16.2%)	19/265 (7.2%)	RR 2.25 (1.21 to 4.19)	9 more per 100 (from 2 more to 23 more)	⊕⊕○○ LOW	CRITICAL
Thrombocytopenia												
5 [j]	randomised trials	not serious	not serious [s]	not serious [m,n]	serious [h]	none	102/854 (11.9%)	15/694 (2.2%)	RR 9.29 (3.49 to 24.71)	18 more per 100 (from 5 more to 51 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and BrighTness 2018
b. I-squared=63.9%
c. Downgraded for imprecision due to small number of events
d. Only 2 reported survival analysis. Authors of BrighTness study stated they analysed OS but they did not report data
e. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and UMIN000003355 2017
f. Possible detection bias due to lack of masking in GeparSixto
g. I-squared=33%
h. Downgraded for imprecision due to small number of events
i. UMIN000003355 study stated as secondary outcome DFS but it did not report data
j. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355
k. Possible detection bias due to lask of blinded outcome assessor
l. I-squared=55%
m. BrighTness study added veliparib to platinum treatment arm
n. UMIN000003355 and GeparSixto studies reported data not only for TNBC
o. GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355
p. CALGB 40603 Alliance 2014 and BrighTness 2018
q. Possible detection bias due to lack of masking in CALGB 40603 study
r. I-squared=26%
s.I-squared=16%

GRADE QUESTION NO. 6

QUESTION

Should a platinum-based regimen be added to a taxane- and anthracycline-based neoadjuvant chemotherapy vs. taxane- and anthracycline-based neoadjuvant chemotherapy only be used for triple-negative breast cancer patients?
POPULATION: triple-negative breast cancer patients

INTERVENTION:	a platinum-based regimen added to a taxane- and anthracycline-based neoadjuvant chemotherapy
COMPARISON:	taxane- and anthracycline-based neoadjuvant chemotherapy only
MAIN OUTCOMES:	Overall survival; DFS/EFS; Invasive-free survival; Pathological complete response rate (studies with same chemotherapy schedule in both arms); Febrile neutropenia grade 3/4/5; Anemia grade 3/4; Serious adverse events; Thrombocytopenia grade 3/4;
SETTING:	inpatients
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Approximately 30%–40% of triple negative breast cancer (TNBC) patients achieve a pathological complete response (pCR) after standard anthracycline-taxane based neoadjuvant chemotherapy. The achievement of pCR in TNBC patients has a strong prognostic value, larger than in other breast cancer subtypes. Although studies have suggested a possible benefit for platinum-based neoadjuvant chemotherapy in TNBC patients, the current breast cancer guidelines do not include any specific recommendation about the addition of a platinum agent to standard neoadjuvant chemotherapy in unselected TNBC patients.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Four outcomes of benefit were considered as critical by the Panel: overall survival, DFS/EFS, invasive free survival and pCR rate. Only the RCTs in which the same standard anthracycline and taxane-based chemotherapy backbone was used in both groups were considered for analysis. No study reported the invasive free survival outcome. Three RCTs reported the other survival outcomes and five RCTs reported the pCR rates. No significant differences in DFS/EFS (HR 0.72, 95% CI 0.49–1.06) nor in OS (HR 0.86, 95% CI 0.46–1.63) were observed. The short follow-up and the low number of events did not allow highlighting differences in OS. In the five RCTs reporting pCR with the same chemotherapy backbone with or without platinum agent (only BrighTness study added veliparib to platinum treatment arm), the risk was 550 pCR in every 1000 patients in the platinum-based chemotherapy group and 372 in the control group (RR 1.48, 95% CI 1.20-1.83). The quality of evidence for the pCR outcome was low due to possible detection bias (lack of blinded outcome assessor) and heterogeneity (I-squared=55%). The panel considered the absence of evidence for a difference in the survival. However, the difference in the pCR endpoint observed in favor of the addition of a platinum agent was considered sufficient to judge as "moderate" the substantiality of the desirable anticipated effects. The panel considered in this evaluation the challenging clinical population of TNBC.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with taxane- and anthracycline-based neoadjuvant chemotherapy only	Risk with a platinum-based regimen be add to a taxane- and anthracycline-based neoadjuvant chemotherapy				
Overall survival (OS) follow up: range 39 months to 47.3 months	Study population		HR 0.86 (0.46 to 1.63)	809 (3 RCTs)[a]	⊕◯◯◯ VERY LOW[b,c,d]	
	5 per 100	4 per 100 (2 to 8)				
DFS/EFS	Study population		HR 0.72 (0.49 to 1.06)	809 (3 RCTs)[e]	⊕◯◯◯ VERY LOW[f,g,h,i]	
	15 per 100	11 per 100 (8 to 16)				
Invasive-free survival - not reported	-	-	-	-	-	
Pathological complete response rate (studies with	Study population		RR 1.48 (1.20 to 1.83)	1234 (5 RCTs)[j]	⊕⊕◯◯ LOW[k,l]	
	372 per 1.000	550 per 1.000 (446 to 680)				

same schedule in both arms) (pCR) assessed with: no residual invasive tumour in both the breast and the axilla: i.e. ypT0/is pN0					
Febrile neutropenia grade 3/4/5	Study population		**RR 1.40** (0.97 to 2.01)	1392 (5 RCTs)[j]	⊕⊕⊕◯ MODERATE[h,m,n]
	6 per 100	**9 per 100** (6 to 13)			
Anemia	Study population		**RR 27.05** (8.57 to 85.30)	1171 (4 RCTs)[o]	⊕⊕⊕◯ MODERATE[h,m,n]
	0 per 100	**9 per 100** (3 to 29)			
Seriuos adverse events (SAE)	Study population		**RR 2.25** (1.21 to 4.19)	536 (2 RCTs)[p]	⊕⊕◯◯ LOW[h,m,q,r]
	7 per 100	**16 per 100** (9 to 30)			
Thrombocytopenia	Study population		**RR 9.29** (3.49 to 24.71)	1548 (5 RCTs)[j]	⊕⊕⊕◯ MODERATE[h,m,n,s]
	2 per 100	**20 per 100** (8 to 53)			

a. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and BrighTness 2018
b. I-squared=63.9%
c. Downgraded for imprecision due to small number of events
d. Only 2 reported survival analysis. Authors of BrighTness study stated they analysed OS but they did not report data
e. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and UMIN000003355 2017
f. I-squared=33%
g. UMIN000003355 study stated as secondary outcome DFS but it did not report data
h. Downgraded for imprecision due to small number of events
i. Possible detection bias due to lack of masking in GeparSixto
j. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355
k. Possible detection bias due to lask of blinded outcome assessor
l. I-squared=55%
m. BrighTness study added veliparib to platinum treatment arm
n. UMIN000003355 and GeparSixto studies reported data not only for TNBC

o.   GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355
p.   CALGB 40603 Alliance 2014 and BrighTness 2018
q.   I-squared=26%
r.   Possible detection bias due to lack of masking in CALGB 40603 study
s.   I-squared=16%

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The Panel identified the following outcomes of harms: febrile neutropenia, anemia (grade 3-4), serious adverse event (SAE), thrombocitopenia (grade 3-4). Only febrile neutropenia and SAE were considered "critical outcomes". The addition of platinum to a standard anthracycline and taxane-based chemotherapy was associated with an increased risk of grade 3-4 anemia (RR 27.05, 95% CI 8.57 to 85.30), of SAE (RR 2.25, 95% CI 1.21 to 4.19) and of grade 3-4 thrombocitopenia (RR 9.29, 95% CI 3.49 to 24.71). No significant differences were found in the risk of febrile neutropenia (RR 1.40, 95% CI 0.97 to 2.01). The judgement of the panel about the substantiality of the undesirable anticipated effects is small. The panel considered in this discussion the heterogeneity of treatment schedules applied in the different studies, that may have influenced the rate of undesirable effects.	

Outcomes	Anticipated absolute effects[*] (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with taxane- and anthracycline-based neoadjuvant chemotherapy only	Risk with a platinum-based regimen be add to a taxane- and anthracycline-based neoadjuvant chemotherapy				
Overall survival (OS) follow up: range 39 months to 47.3 months	Study population		**HR 0.86** (0.46 to 1.63)	809 (3 RCTs)[a]	⊕◯◯◯ VERY LOW[b,c,d]	
	5 per 100	**4 per 100** (2 to 8)				

DFS/EFS	Study population		**HR 0.72** (0.49 to 1.06)	809 (3 RCTs)[e]	⊕○○○ VERY LOW[f,g,h,i]	
	15 per 100	**11 per 100** (8 to 16)				
Invasive-free survival - not reported	-	-	-	-	-	
Pathological complete response rate (studies with same schedule in both arms) (pCR) assessed with: no residual invasive tumour in both the breast and the axilla: i.e. ypT0/is pN0	Study population		**RR 1.48** (1.20 to 1.83)	1234 (5 RCTs)[j]	⊕⊕○○ LOW[k,l]	
	372 per 1.000	**550 per 1.000** (446 to 680)				
Febrile neutropenia grade 3/4/5	Study population		**RR 1.40** (0.97 to 2.01)	1392 (5 RCTs)[j]	⊕⊕⊕○ MODERATE[h,m,n]	
	6 per 100	**9 per 100** (6 to 13)				
Anemia	Study population		**RR 27.05** (8.57 to 85.30)	1171 (4 RCTs)[o]	⊕⊕⊕○ MODERATE[h,m,n]	
	0 per 100	**9 per 100** (3 to 29)				
Seriuos adverse events (SAE)	Study population		**RR 2.25** (1.21 to 4.19)	536 (2 RCTs)[p]	⊕⊕○○ LOW[h,m,q,r]	
	7 per 100	**16 per 100** (9 to 30)				
Thrombocytopenia	Study population		**RR 9.29** (3.49 to 24.71)	1548 (5 RCTs)[j]	⊕⊕⊕○ MODERATE[h,m,n,s]	
	2 per 100	**20 per 100** (8 to 53)				

    a.   CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and BrighTness 2018
    b.   I-squared=63.9%
    c.   Downgraded for imprecision due to small number of events

d. Only 2 reported survival analysis. Authors of BrighTness study stated they analysed OS but they did not report data e. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014 and UMIN000003355 2017 f. I-squared=33% g. UMIN000003355 study stated as secondary outcome DFS but it did not report data h. Downgraded for imprecision due to small number of events i. Possible detection bias due to lack of masking in GeparSixto j. CALGB 40603 Alliance 2014, GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355 k. Possible detection bias due to lask of blinded outcome assessor l. I-squared=55% m. BrighTness study added veliparib to platinum treatment arm n. UMIN000003355 and GeparSixto studies reported data not only for TNBC o. GeparSixto GBG66 2014, BrighTness 2018, GEICAM/2006-03 2012 and UMIN000003355 p. CALGB 40603 Alliance 2014 and BrighTness 2018 q. I-squared=26% r. Possible detection bias due to lack of masking in CALGB 40603 study s. I-squared=16%	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Reasons for downgrade evidence: Most outcomes were affected by inconsistency of results, imprecision of effect estimates due to small number of events, detection and publication bias.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	According to the Panel there is important uncertainty about or variability in how much people value the achievement of pCR after neoadjuvant chemotherapy and the worse side effects profile due to addition of carboplatin.	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Although it remains unclear whether the addition of platinum to a standard anthracycline-taxane regimen improves survival, the balance between desirable and undesirable effects probably favors the intervention due to the higher pCR rates and to the acceptable toxicity profile with the addition of carboplatin.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	For the Panel the addition of platinum to standard anthraclicline-taxane based chemotherapy and the management of additional toxicity may lead to a moderate increase in overall costs. The cost related to the drug is neglibile, but the costs related to the clinical patient management 8including adverse events) may be moderate. No trial addressed this issue and the judgment was based on Panel opinion.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

| ○ Very low
● Low
○ Moderate
○ High
○ No included studies | The certainty of the evidence of resource requirements is low. No trial addressed this issue and the judgment was based on Panel opinion. | |

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Considering the significant improvement in pCR rates and the toxicity profile, the panel judged the cost-effectiveness of the intervention as probably favorable for the intervention. Uncertainty is due to lack of significant difference in DFS/EFS and OS and to the additional toxicities with the addition of carboplatin.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	The intervention is widely accessible and probably has no impact on health equity. No trial addressed this issue and the judgment was based on Panel opinion.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention probably is acceptable to key stakeholders. No trial addressed this issue and the judgment was based on Panel opinion.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	For the Panel the intervention is feasible to implement.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT					
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

225

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

The panel expressed the opinion that the benefit/harm ratio PROBABLY FAVORS the intervention (10/11). The two patient representatives and 2 clinicians were absent from the vote.

Benefit/harm ratio: 10/11 UNCERTAIN FAVORABLE.

The recommendation was rated as WEAK POSITIVE (10/11).

GRADE QUESTION NO. 6

Should the integration of early palliative care with oncology treatment VS. the "solo practice model" be recommended for patients with advanced/metastatic cancer?	
POPULATION:	Patients with advanced/metastatic cancer
INTERVENTION:	Early palliative care integrated with oncology treatment.
	For years the integrated model of care of cancer patients with advanced stage / metastatic disease has received great attention from the scientific community, with the aim of ensuring the patient the best quality of life in all phases of the disease. In particular, the aim of early palliative care is to control pain and other symptoms, assess nutritional needs, manage psychological distress, provide realistic information on the prognosis and expectations of cancer therapies, avoid drop-out in the advanced stages of disease and define, through a shared continuity of care, the most appropriate care setting.
	Since 2003, ESMO has been implementing an accreditation program for oncology centers, which ensures the early provision of palliative care to all symptomatic patients receiving active cancer treatment. In the last decade, the results published in the literature and the opinion of experts have confirmed the benefit of this approach on quality of life and symptom control parameters, so much so that the main guidelines (ESMO; ASCO, NCCN; WHO, EAPC), recommend the early inclusion of palliative care in the course of active oncological treatment for all patients with advanced / metastatic

	disease. Despite these recommendations, the integration of active cancer treatment and palliative care does not currently follow a homogeneous model, neither in Europe nor in the United States, where this objective is expected to be achieved in 2020. In Italy in 2017, 42 oncology centers were accredited by ESMO for the integrated model. Although it is not excluded that other oncology centers may be able to offer early palliative care in combination with cancer treatment, the Italian palliative care network, which is mainly territorial and does not have the same level of development throughout the national territory, does not currently guarantee the shared systematic care of patients by oncologists and palliative care teams (palliative doctors and other professionals required to cover the needs of the patient). The early identification of healthcare professionals whose objective is the patient's quality of life aims to ensure a better planning and improved coordination even at the advanced-terminal stage. Ensuring continuity of care has become a priority for all Healthcare Systems, since discontinuity leads to increased costs, errors in care planning and frequent re-hospitalizations, and also ensures greater patient safety. Since 2009 AIOM, through a dedicated workgroup, promotes educational actions and support to oncology centers to help them obtain ESMO accreditation, has fostered a dialogue with the SICP (Italian Society of Palliative Care) to share an integration model (see AIOM-SICP document) and has promoted training events so that, where a palliative care team is not available, the relief and control of symptoms is guaranteed to all patients by oncologists. It is necessary to spread an organizational model that can concretely implement integrated care by oncologists and palliative care teams, to the benefit of quality of life and continuity of care for all cancer patients in the advanced/metastatic stage of disease.
COMPARISON:	solo practice model
MAIN OUTCOMES:	quality of life; symptom intensity; overall survival; chemotherapy in the last week of life; location of death; caregiver quality of life;
SETTING:	outpatients/inpatients
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem		
Is the problem a priority?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	IT IS A PRIORITY TO SPREAD THROUGHOUT THE COUNTRY AN INTEGRATED APPROACH BETWEEN ANTI-CANCER TREATMENTS AND EARLY PALLIATIVE CARE, IN ORDER TO IMPROVE SYMPTOMS, ENSURE PAIN CONTROL, ASSESS NUTRITIONAL NEEDS, MANAGE PSYCHO-SOCIAL DISTRESS, AND ENSURE THE BEST QUALITY OF LIFE TO ALL PATIENTS.	

Desirable Effects		
How substantial are the desirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with solo model	Risk with early palliative care integrated with oncology				
Quality of life	The mean quality of life was **0** SD	SMD **0.22 SD higher** (0.1 higher to 0.33 higher)[a]	-a	1190 (6 RCTs)[b]	⊕◯◯◯◯VERY LOWc,d,e,f,g	
Symptom intensity[h]	The mean symptom intensity was **0** SD	SMD **0.23 SD higher** (0.06 higher to 0.4 higher)[a]	-a	562 (4 RCTs)[i]	⊕◯◯◯◯VERY LOWc,g,h	
Overall Survival (OS)	Study population		**HR 1.01** (0.77 to 1.31)	271 (2 RCTs)[j]	⊕◯◯◯◯VERY LOWd,g,k,l	
	35 per 100	**35 per 100** (28 to 43)				
Chemotherapy in the last week - not reported	-	-	-	-	-	
Appropriate location of death - not reported	-	-	-	-	-	

Quality of life - caregiver - not reported	-	-	-	-	-	

The authors of the meta-analysis combined different scales measuring this outcome of interest across studies by applying SMDs. By conventional criteria, an SMD of 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988).

Tattersall 2014, Temel 2010, Temel 2017, Zimmermann 2014, Maltoni 2016, Groenvold 2017

In Zimmermann 2014 et al. trials, participants were blinded, all other studies were not blinded. Regarding the blinding of outcome assessment, 5 of the 6 studies were considered at unclear risk of bias. In Zimmermann et al. investigators were not blinded. For these reasons we decide to downgrade the quality of the evidence.

Allocation concealment was considered at high risk of bias for 2 studies (Temel 2010 and Zimmermann 2014). Tattersal et al. was considered at high risk of attrition bias and in Groenvold et al. study there were no information in order to exclude this bias. For these reasons we decided to downgrade the quality of the evidence.

I2=67%

Higher score indicates better HRQOL. Each researcher used a different scale: FACI-Pal, TOI, of FACT-Help, TOI of FACT-L, FACT-G, Mc Gill Quality of life, FACIT-Sp., for this reason we decided to downgrade the quality of evidence for indirectness.

Notes: two studies (Maltoni 2016 and Temel 2010) included only patients with advanced pancreatic cancer and lung cancer. In Temel 2017 et al. patients included had a metastatic lung or noncolorectal GI cancer

Included studies used 6 different scales to measure symptoms intensity: Edmonton Symptom assessment system, ESAS, quality of life et End of life, QUAL-E Symptom impact subscale, hepatobiliary cancer subscale, HCS, of the functional assessment of cancer therapy-hepatobiliary, FACT-Hep, symptom distress scale, SDS, Rotterdam symptom checklist- Physical symptoms, RCS, and lung-cancer subscale, LCS, of functional assessment of cancer therapy lung, FACT-L

Tattersall 2010, Maltoni 2016, Temel 2010, Zimmermann 2014

Tattersall 2014 and Temel 2010

I2=92%

	According to the GRADE Handbook, we decided to downgrade the quality of evidence for imprecision, as the optimal information size (OIS) criterion was met, but the 95% confidence interval around the difference in effect between intervention and control included 1. The 95% CI fails to exclude harm	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**ANY** UNDESIRABLE EFFECTS OF THE APPLICATION OF THE INTEGRATED MODEL HAVE NOT BEEN INVESTIGATED YET IN THE STUDIES INCLUDED IN THE LITERATURE AND THEREFORE CANNOT BE ASSESSED, BUT SHOULD BE MONITORED BASED ON PERSONAL EXPERIENCE, THE GROUP BELIEVES THAT SYMPTOM CONTROL IS A KEY ELEMENT IN IMPROVING THE QUALITY OF LIFE OF PATIENTS AND SHOULD THEREFORE BE PURSUED. THIS MODEL HAS RECEIVED POSITIVE FEEDBACK FROM PATIENTS.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence was considered VERY LOW for these reasons: In Zimmermann 2014 et al. trials, participants were blinded, while in all other studies partecipants were not blinded. Regarding the blinding of outcome assessment, 5 of the 6 studies were considered at unclear risk of bias. In Zimmermann et al. investigators were not blinded. For these reasons we decide to downgrade the quality of the evidence. Allocation concealment was considered at high risk of bias for 2 studies (Temel 2010 and Zimmermann 2014). Tattersal et al. was considered at high risk of attrition bias and in Groenvold et al. study there were no information in order to exclude this bias. For these reasons we decided to downgrade the quality of the evidence. I2=67% for the quality of life outcome Higher score indicates better HRQOL. Each study used a different quality of life scale: FACI-Pal, TOI, of FACT-Help, TOI of FACT-L, FACT-G, Mc Gill Quality of life, FACIT-Sp. For this reason, we decided to downgrade the quality of evidence for indirectness. Notes: two studies (Maltoni 2016 and Temel 2010) included only patients with advanced pancreatic cancer and lung cancer. In Temel 2017 et al. patients included had a metastatic lung or noncolorectal GI cancer Included studies used 6 different scales to measure symptoms intensity: Edmonton Symptom assessment system, ESAS, quality of life et End of life, QUAL-E Symptom impact subscale, hepatobiliary cancer subscale, HCS, of the functional assessment of cancer therapy-hepatobiliary, FACT-Hep, symptom distress scale, SDS, Rotterdam symptom checklist- Physical symptoms, RCS, and lung-cancer subscale, LCS, of functional assessment of cancer therapy lung, FACT-L I2=92% for the overall survival outcome According to the GRADE Handbook, we decided to downgrade the quality of evidence for imprecision, as the optimal information size (OIS) criterion was met, but the 95% confidence interval around the difference in effect between intervention and control included 1. The 95% CI fails to exclude harm	
Values		
Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	MAINTAINING THE BEST QUALITY OF LIFE IS THE MAIN GOAL IN THE ADVANCED-STAGE PATIENT: THE PANEL THEREFORE CONSIDERS THAT THE CRITICAL OUTCOMES VOTED BY THE GROUP ARE PERFECTLY IN LINE WITH THE MAIN OBJECTIVE OF PATIENTS:

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	CURRENTLY, AVAILABLE EVIDENCE SUPPORTS EARLY INTEGRATION OF PALLIATIVE CARE WITH CANCER THERAPIES IN PATIENTS WITH NON-THALASSAEMIC LUNG CANCER AND GASTROINTESTINAL CANCER. THE LACK OF EVIDENCE ON THE ADVANTAGE OF THE INTEGRATED MODEL IN SOME RANDOMIZED STUDIES THAT HAVE INCLUDED OTHER TYPES OF CANCER MAY BE DUE TO: 1. METHODOLOGICAL LIMITS OF THE STUDIES THEMSELVES; 2. TIMING OF EVALUATION OF DIFFERENCE IN QoL IN THE TWO ARMS (TOO EARLY); 3. STATISTICAL DESIGN; 4. USE OF DIFFERENT SCALES FOR ASSESSING QOL AND SYMPTOM INTENSITY; 5. DISHOMOGENEITY OF THE POPULATION STUDIED, WITH DIFFERENT TYPES OF TUMORS, AVAILABILITY OF ACTIVE TREATMENTS, AND HIGHLY VARIABLE NATURAL HISTORY 6. EXPERTISE OF ONCOLOGISTS IN SYMPTOM CONTROL (GOOD SYMPTOM CONTROL OBTAINED IN THE "SOLO PRACTICE MODEL" CONTROL ARMS).	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate long-term savings ○ Large savings ○ Varies ○ Don't know	COST DATA NOT CURRENTLY AVAILABLE. IT CAN BE ASSUMED THAT, IN THE SHORT TERM, INVESTMENTS ARE NEEDED TO MAKE PALLIATIVE CARE SERVICES LOCALLY AVAILABLE AND ENSURE INTEGRATION WITH ONCOLOGY AND RADIOTHERAPY DEPARTMENT, TRAINING OF STAFF, REVIEW OF ORGANIZATIONAL & CARE PATHWAYS, AND ACTIVATION OF DEDICATED CLINICS. IN THE MEDIUM AND LONG-TERM, IT CAN BE EXPECTED THAT THE SYSTEMATIC ACTIVATION OF EARLY AND SIMULTANEOUS PALLIATIVE CARE WILL BE ABLE TO REDUCE THE NUMBER OF ER VISITS, THE NUMBER AND DURATION OF HOSPITAL ADMISSIONS, AND CANCER TREATMENTS AT THE END OF LIFE, EXTENDING EARLY ACCESS TO PALLIATIVE CARE AT HOME AND HOSPICE, AND CONSEQUENTLY REDUCING THE COSTS OF BOTH CARE AND PHARMACEUTICAL EXPENDITURE. IN SMALL HOSPITALS, THE IMPLEMENTATION OF THE INTEGRATED MODEL IS LIKELY TO BE MORE DIFFICULT FOR THE ALLOCATION OF RESOURCES AND SPACES TO THE INTERDISCIPLINARY PALLIATIVE CARE TEAM	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	THERE ARE CURRENTLY NO STUDIES THAT HAVE EVALUATED THIS SPECIFIC ASPECT. ON THE BASIS OF CONSOLIDATED EXPERIENCE OF PALLIATIVE CARE IN THE TERMINAL PHASE OF DISEASE, IT IS KNOWN THAT THE COSTS OF PALLIATIVE CARE ARE LOWER THAN PATIENT HOSPITALIZATION, AND THAT THE INTEGRATED MODEL GUARANTEES CONTINUITY OF CARE FOR	

	CANCER PATIENTS. THIS MODEL SHOULD THEREFORE REDUCE THE COST OF CARE FOR PATIENTS IN THE ADVANCED-METASTATIC STAGE. ONCE THE INTEGRATED MODEL ACCREDITED BY ESMO IS ACTIVATED, IT SHOULD BE COST-EFFECTIVE ALSO FROM AN ORGANIZATIONAL POINT OF VIEW.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	THE COST-EFFECTIVENESS EVALUATION OF THE PROPOSED MODEL REQUIRES HOC STUDIES (in progress). THE LONG-TERM BENEFITS FOR PATIENTS AND THE ORGANIZATION OUTWEIGH THE INITIAL DIRECT COSTS REQUIRED TO ACTIVATE THE INTEGRATION MODEL.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	NO SCIENTIFIC EVIDENCE IS AVAILABLE ON THIS ISSUE. THE ACTIVATION OF DEDICATED OUTPATIENT CLINICS (WHERE THE INTEGRATION BETWEEN EARLY PALLIATIVE CARE AND CANCER THERAPIES IS CARRIED OUT) THROUGHOUT THE COUNTRY WILL	

● Increased ○ Varies ○ Don't know	MAKE A SERVICE THAT IS CURRENTLY AVAILABLE ONLY IN SOME CENTERS HOMOGENEOUS AND ACCESSIBLE TO ALL. TODAY THERE IS INDEED A DISPARITY IN DIFFERENT ITALIAN REGIONS. ALTHOUGH ITALY HAS THE LARGEST NUMBER OF ESMO-ACCREDITED CENTERS (42), MOST OF THESE ARE LOCATED IN THE NORTH AND CENTER. EQUITY IN THE PROVISION OF EARLY AND SIMULTANEOUS PALLIATIVE CARE WILL BE ACHIEVED WHEN THE INTEGRATED MODEL IS IMPLEMENTED THROUGHOUT THE COUNTRY.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	NO LITERATURE DATA ARE AVAILABLE. INDIVIDUAL EXPERIENCES SHOW A GOOD ACCEPTANCE OF THIS TYPE OF SERVICE BY PATIENTS AND THEIR FAMILIES. THE INTEGRATED OUTPATIENT CLINIC ALLOWS TO SUPPORT AND HELP THE PATIENT IN CHOSING THERAPEUTIC OPTIONS AND PLANNING THE TREATMENT COURSE, TO ENSURE AND STRENGTHEN DISEASE AWARENESS, AND TO HELP THE PATIENT AND THEIR FAMILY TO ACCEPT ADVANCED-STAGE DISEASE. IT ALSO ALLOWS A FLEXIBLE MANAGEMENT OF THE PATIENT AND THEIR NEEDS, WITH APPROPRIATE OBJECTIVES IN EACH INDIVIDUAL SITUATION THROUGH EVALUATION, PLANNING, COORDINATION, MONITORING, SELECTION OF CARE OPTIONS AND SERVICES. EARLY PALLIATIVE CARE HAS ALSO HAD A POSITIVE IMPACT ON CAREGIVERS, IMPROVING QUALITY OF LIFE, REDUCING DEPRESSIVE SYMPTOMS AND ENABLING THEM TO MAINTAIN THEIR VITALITY AND SOCIAL FUNCTION. THE WILLINGNESS OF ONCOLOGISTS AND RADIOTHERAPISTS TO SHARE THE TREATMENT COURSE WITH THE PALLIATIVE CARE TEAM AND TO PROMOTE THE IMPLEMENTATION OF THE INTEGRATED MODEL IS INDISPENSABLE.	

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	THE IMPLEMENTATION OF AN INTEGRATED OUTPATIENT CLINIC IS ESSENTIAL TO SHARE THE CARE COURSE AND INTEGRATED DECISION-MAKING CHOICES BETWEEN ONCOLOGISTS AND PALLIATIVE CARE TEAM. IN CLINICAL PRACTICE, REFERRAL TO PALLIATIVE CARE IS OFTEN STILL LIMITED TO THE TERMINAL STAGE OF THE DISEASE. IT IS DESIRABLE THAT ALL RESOURCES ARE PUT IN PLACE TO ACTIVATE THE PALLIATIVE CARE TEAM IN THE VICINITY OF ONCOLOGY OR RADIOTHERAPY SERVICES IN ORDER TO ALLOW THE ACTIVATION OF INTEGRATED OUTPATIENT CLINICS. IN THE ABSENCE OF A PALLIATIVE CARE TEAM CLOSE TO THE ONCOLOGY UNIT, IT IS EQUALLY IMPORTANT THAT MEDICAL ONCOLOGISTS, BY THEMSELVES OR THROUGH EXTERNAL CONSULTATIONS, CONTINUE TO GUARANTEE ADEQUATE CONTROL OF SYPTOMS, PAIN AND ALL OTHER FACTORS THAT ALLOW THE PATIENT TO HAVE THE BEST POSSIBLE QoL.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No.	Probably not	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**

JUDGEMENT							
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No.	Probably not	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No.	Probably not	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	●

WHERE A PALLIATIVE CARE TEAM IS AVAILABLE: STRONG POSITIVE RECOMMENDATION.

WHERE NO PALLIATIVE CARE TEAM IS AVAILABLE: WEAK POSITIVE RECOMMENDATION.

CONCLUSIONS

Recommendation

THE INTEGRATED MODEL (EARLY AND SIMULTANEOUS PALLIATIVE CARE CONCOMITANT WITH ACTIVE CANCER THERAPIES) SHOULD ALWAYS BE CONSIDERED AS A FIRST OPTION FOR PATIENTS IN THE METASTATIC OR SYMPTOMATIC PHASE, **WHERE A PALLIATIVE CARE TEAM IS AVAILABLE (STRONG POSITIVE RECOMMENDATION).**

WHERE NO PALLIATIVE CARE TEAM IS AVAILABLE, THE MEDICAL ONCOLOGIST SHOULD ENSURE ADEQUATE SYMPTOM CONTROL FOR ALL METASTATIC PATIENTS UNDER ACTIVE CANCER TREATMENT, AND PROMOTE THE ACTIVATION OF INTEGRATED OUTPATIENT CLINICS TO ENSURE EARLY AND SIMULTANEOUS PALLIATIVE CARE FOR ALL PATIENTS (**WEAK POSITIVE RECOMMENDATION**)

Justification

RANDOMIZED STUDIES HAVE DEMONSTRATED THE ADVANTAGE OF AN EARLY AND SIMULTANEOUS APPROACH TO PALLIATIVE CARE (CONCOMITANT WITH ACTIVE ONCOLOGICAL THERAPIES) ON QUALITY OF LIFE PARAMETERS OF METASTATIC PATIENTS, ESPECIALLY IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER (NSCLC) AND IN PATIENTS WITH GASTROINTESTINAL CANCER.

ON THE BASIS OF THESE STUDIES, INTERNATIONAL GUIDELINES (IN PARTICULAR ASCO, ESMO, NCCN, AND THE AIOM-SICP DOCUMENT) RECOMMEND THE EARLY EVALUATION OF THE METASTATIC PATIENT RECEIVING ACTIVE ONCOLOGICAL TREATMENT BY A TEAM OF PALLIATIVE CARE, ALTHOUGH THE LITERATURE DOES NOT CURRENTLY CONFIRM THE ADVANTAGE FOR ALL TYPES OF CANCER.

Subgroup considerations

IT IS NECESSARY TO PROMOTE THE DIFFUSION OF THE INTEGRATED MODEL AND THE CONSEQUENT SHARED COURSES AND CLINICS, IN ORDER TO GUARANTEE THE BEST POSSIBLE QUALITY OF LIFE TO ALL CANCER PATIENTS IN THE METASTATIC PHASE THROUGHOUT THE NATIONAL TERRITORY.

Implementation considerations

IT IS STILL TO BE ESTABLISHED WHEN TO REFER THE PATIENT TO EARLY PALLIATIVE CARE. ACCORDING TO THE AIOM-SICP DOCUMENT, THE PATIENT REFERRAL SHOULD FIRST OF ALL BE BASED ON LIFE EXPECTANCY (SPECIFICALLY, PHYSICIANS SHOULD ASK THEMSELVES: "WOULD YOU BE SURPRISED IF THE PATIENT DIED WITHIN 12 MONTHS?", IF THE ANSWER IS NO, THIS IS IN ITSELF A VALID REASON TO CONSIDER THE PATIENT A CANDIDATE FOR EARLY AND SIMULTANEOUS PALLIATIVE CARE), PERFORMANCE SCORE, THE PRESENCE AND SEVERITY OF SYMPTOMS, ANY PSYCHOLOGICAL OR SOCIAL ISSUES, TREATMENT PROSPECTS, AGE AND THE PRESENCE OR ABSENCE OF A CAREGIVER (Consensus document of the Italian Association of Medical Oncology and the Italian Society of Palliative Care on early palliative care. Corsi D et al. Tumori 2018, August 29 DOI:101177/0300891618792478).

THE OBJECTIVE OF EARLY PALLIATIVE CARE IS: 1) TO CONTROL SYMPTOMS, PAIN AND NUTRITIONAL PROBLEMS; 2) TO DISCUSS TREATMENT PROSPECTS AND REALISTIC BENEFITS THAT CAN BE ANTICIPATED; 3) TO ADDRESS THE ISSUE OF PROGNOSIS; 4) TO BUILD A RELATIONSHIP WITH THE PATIENT AND THEIR FAMILY IN VIEW OF END-OF-LIFE CARE; 5) TO EVALUATE THE PATIENT'S WISHES AT THE END OF LIFE; 6) TO COORDINATE OTHER POSSIBLE PARTICIPANTS INVOLVED IN THE TREATMENT PROCESS; 7) TO DIRECT THE PATIENT, WHERE NECESSARY, TO OTHER SERVICES (E.G. TERRITORIAL PALLIATIVE CARE CENTER).

Monitoring and evaluation

AIOM IS COMMITTED TO MONITORING THE IMPLEMENTATION AND DIFFUSION OF THE INTEGRATED MODEL BY VERIFYING ACCREDITATION OF ONCOLOGY CENTERS ACCORDING TO THE ESMO PROGRAM AND THE RE-ACCREDITATION OF ALREADY ACCREDITED CENTERS.

THE EFFECTIVENESS OF THE INTEGRATED MODEL, ONCE DISSEMINATED AT A NATIONAL LEVEL, CAN BE ASSESSED THROUGH AD HOC SURVEYS AND QUESTIONNAIRES TO BE DISTRIBUTED TO PATIENTS TO ALSO ASSESS THEIR SATISFACTION AND WHETHER THIS MODEL MEETS THEIR NEEDS.

Research priorities

 IT IS DESIRABLE TO PROMOTE FURTHER PROSPECTIVE STUDIES TO IMPLEMENT SCIENTIFIC EVIDENCE, WHICH IS CURRENTLY VERY SCARCE IN THIS AREA.

Annex 2: Intraductal proliferative lesions and lobular neoplasia

* INTRADUCTAL PROLIFERATIVE LESIONS. They are a group of proliferations, with heterogeneous cytological and structural features, which originate from the terminal ductal lobular unit and are associated with an increased risk, albeit of different magnitude, of developing a subsequent infiltrating carcinoma.

Traditionally, the following categories, difficult to differentiate from a histopathologic point of view, have been recognized:

- Usual ductal hyperplasia (UDH);
- Flat epithelial atypia (FEA);
- Atypical ductal hyperplasia (ADH);
- Ductal carcinoma in situ (DCIS).

Risk levels for the subsequent development of infiltrating breast cancer range from 1.5 times that of the reference population for UDH, to 3-5 times for ADH, to 8-10 times for DCIS. Immunophenotypic and molecular studies have also provided new information indicating that the notion of linear progression from normal epithelium to hyperplasia, atypical hyperplasia, carcinoma in situ and infiltrating carcinoma is too simplistic, and that there are more complex interconnections between these various intraductal proliferative lesions and infiltrating carcinoma.

These data have suggested that:

- In most cases, UDH has little similarity to ADH, DCIS or infiltrating carcinoma;
- ADH has many features in common with low-grade DCIS;
- Low-grade DCIS and high-grade DCIS seem to represent genetically distinct disorders leading to distinct forms of infiltrating carcinoma;
- FEA is a clonal neoplastic lesion with the morphological, immunohistochemical and molecular characteristics of ADH and low-grade DCIS, supporting the notion of continuous transformation and the common definition of "intraepithelial neoplasia".

Therefore, in 2001 Tavassoli et al[4] proposed to replace the traditional terminology of intraductal proliferative lesions with ductal intraepithelial neoplasia (DIN), reserving the term "carcinoma" for infiltrating tumors. In the Tavassoli classification, intraductal carcinoma is therefore classified in the context of ductal intraepithelial neoplasia (DIN) as reported in Table 16.1.

Table 16.1- Classification of intraductal proliferative lesions	
Traditional terminology	DIN terminology (ductal intraepithelial neoplasia) acc. to WHO 20031
Usual ductal hyperplasia (UDH)	Usual ductal hyperplasia (UDH)
Flat epithelial atypia (FEA)	Ductal intraepithelial neoplasia, grade 1 A (DIN 1 A)
Atypical ductal hyperplasia (ADH)	Ductal intraepithelial neoplasia, grade 1 B (DIN 1 B)
Ductal carcinoma in situ, low grade (DCIS grade 1)	Atypical intraepithelial neoplasia, grade 1C (DIN 1 C)
Ductal carcinoma in situ, intermediate grade (DCIS grade 2)	Atypical intraepithelial neoplasia, grade 2 (DIN 2)

Ductal carcinoma in situ, high grade (DCIS grade 3)	Atypical intraepithelial neoplasia, grade 3 (DIN 3)

In the WHO edition of 2012, DIN terminology was not recognized. This may be due to the failure to introduce new diagnostic criteria (useful for reducing inter-observer variability and diagnostic difficulties between ADH and some low-grade DCIS cases), and terminological variation that did not help to reduce inter-observer variability[4] (see section 3.4).

** *LOBULAR NEOPLASIA*. It includes atypical epithelial lesions that originate in the terminal ductal lobular unit and are characterized by a proliferation of small, non-cohesive cells with small, uniform nuclei, with or without pagetoid involvement of terminal ducts.[2]

The distinction between **atypical lobular hyperplasia (ALH)** and **lobular carcinoma in situ (LCIS)** is based on the extent of proliferative lesion:[2] classic lobular carcinoma in situ is diagnosed when more than half of the acini in a lobular unit are distended and distorted by the proliferation of the cells described above.

A variant of LCIS is the pleomorphic form of LCIS,[5] characterized by marked nuclear pleomorphism with or without apocrine features and comedonecrosis (see section 4.1.3).

In the WHO 2003 classification,[1] the term intraepithelial lobular neoplasia (LIN) was proposed to emphasize the non-invasive nature of this lesion; based on morphological criteria and clinical outcome, the WHO 2003 classification[1] proposed the following definition of IHN, with a subdivision into three grades:

- LIN1: atypical lobular hyperplasia
- LIN2: classic lobular carcinoma in situ
- LIN3: lobular carcinoma in situ with central necrosis, or pleomorphic, or signet ring cell carcinoma.

However, the proposed LIN terminology is not widely accepted yet (see section 3.4).

Lobular neoplasia is a risk factor, and not an obligatory precursor, for the subsequent development of infiltrating breast carcinoma (both ductal and lobular), but only in a minority of women and after a long follow-up.

In the eighth edition of the American Joint Committee on Cancer-2017, lobular carcinoma in situ (LCIS) was removed from the staging classification system and is no longer included in the carcinoma in situ (pTis) category.

LCIS is treated as a benign enitity associated with a risk of developing cancer in the future, but not as a malignant entity capable of developing metastases. However, a commentary is made on a small group of LCIS that has a high nuclear grade and may exhibit central necrosis corresponding to pleomorphic LCIS, which may have similar features to ductal carcinoma in situ (DCIS), including the potential to develop calcifications. The panel of experts discussed whether to include this LCIS variant in the pTis category; however, according to the authors, literature data regarding the prognosis and diagnostic reproducibility criteria for this LCIS variant are insufficient. Patients with DCIS and LCIS should be classified as pTis (DCIS).

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Annex 3 - Determination of HER2 status in breast cancer. ASCO/CAP recommendations

In October 2013, the new ASCO/CAP recommendations[1] for the HER2 status determination in breast cancer were published, including some important changes from the previous 2007 guidelines.[2] In particular, the diagnostic algorithm for HER2 was modified taking into account the heterogeneity of the tumor sample and genomic characteristics, bright-field in situ hybridization was added as an accepted method of HER2 evaluation, the most critical scenarios were discussed, and the need for a correlation between test results and clinical and pathological characteristics and for communication between oncologist and pathologist was highlighted. In April 2015, Ian Ellis' Nottingham Group reported some concerns about the ASCO/CAP 2013 guidelines.[3] Some of these requests have been evaluated, and a revision of the guidelines was recently issued including related considerations.[4] In addition to clarifying the immunohistochemical definition of the 2+ positive score and moderating the recommendations for re-testing after a negative biopsy, the new recommendations focus mainly on clarifying some rare in situ hybridization patterns (estimated frequency: about 5%) of difficult interpretation, referring to groups 2, 3, 4 reported in the work by Press and collaborators.[5] The list of changes that have been made is provided in full in Table 1 of 2018 recommendations.[4] The thresholds for positive cut-offs (10% for immunohistochemistry, IHC, and in situ hybridization, ISH, as suggested by 2013 recommendations) have not changed, nor have the ISH thresholds to identify an amplification of the *HER2* gene or an equivocal state, either with single-probe or double-probe staining. For dual-probe staining ISH, the use of the ISH algorithm (*HER2/CEP17* ratio analysis followed by the analysis of the number of copies of the *HER2* gene) introduced with the ASCO/CAP 2013 guidelines, which requires the analysis of *HER2/CEP17* ratio as first step and the analysis of the average number of *HER2* copies as second step, remains unchanged. The introduction of the ISH algorithm stams from the need to overcome the concept of POLISOMY of chromosome 17, which can be deduced indirectly from the number of CEP17 copies when dual-probe testing is used, and which can lower the ratio to <2 even with a number of genes ≥6. The new algorithm allows to reassign all these cases as amplified and makes these patients eligible for treatment *(j, Data Supplement 2: Special Issues - 2B) Polysomy).* This concept is further contextualized in the 2018 update.

The following is a brief summary of critical and innovative points, underlining the need for a careful and complete reading of the recommendations if they are to be applied in clinical practice.

PATIENTS TO TEST: HER2 should be evaluated on the tumor sample of all patients newly diagnosed with breast cancer. For patients who subsequently develop metastases, HER2 should be evaluated on a metastatic site, if tissue is available. The new recommendations recognize that activating mutations of the *HER2* gene in the absence of gene amplification or protein over-expression allow a much less common alternative mechanism of anti-HER2 target therapy that is currently being investigated in clinical trials with tyrosine kinase inhibitors.[6] The data reported in the NRG B-47 trial (ClinicalTrials.gov identifier: NCT01275677) confirmed the absence of benefit from trastuzumab in patients with tumor with 1+/ 2+ score in the absence of gene amplification.[7] Therefore, amplification of the *HER2* gene assessed by ISH or over-expression of the HER2 protein assessed by IHC remain the main predictors of responsiveness to target therapies in breast cancer patients.

TEST SAMPLES: The tissue sample of the primary tumor can be collected by core biopsy or incisional or excisional surgical biopsy. Metastases can be biopsied at the thoracic wall, regional lymph nodes or distant organs, depending on the site of disease. It is essential to ensure that the time from collection to fixation (cold ischemia time) and fixation time (changed from 6-48 hours in 2007 to 6-72 hours in 2013, confirmed in 2018) are recorded and taken into account in the definition of results *(Data Supplement 8: Preanalytic Issues ASCO/CAP 2018).* In summary, if available, the test should be performed on the core biopsy at diagnosis. If the test result is clearly positive or negative, there is no need to repeat the test. If the test is negative and there is a discrepancy with the other histopathologic features of the tumor, or if the sample has not been processed according to the recommendations, the test may be repeated on a tumor section obtained by excisional biopsy.

If the result is positive it is not necessary to proceed with further tests, but if it is negative and the discussion between medical oncologist and pathologist is still inconclusive about the result of the test, it may be appropriate to repeat the test on a different block of tumor tissue: if the result is still negative, no further tests are recommended. Histopathologic features suggestive of a possible discrepancy with the HER2 test result (whether positive or negative) are detailed in Table 2 of the main text of the recommendations.

In the light of additional clinical experience confirming the high concordance between core and excisional biopsy in the HER2 test, the 2018 update[4] of the guidelines eliminated the obligation to re-test grade 3 carcinomas, and the new table 2 of 2018 recommendations states that "if the initial HER2 test in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test *may* be ordered on the excision specimen" in one of the following scenarios: i) grade 3 tumors: ii) small proportion of invasive tumor in biopsy specimen: iii) surgical resection shows a high grade carcinoma that is morphologically distinct from the invasive carcinoma in the core biopsy; iv) the HER2 result on the core biopsy is equivocal after testing by both IHC and ISH; v) there is uncertainty about the handling of the core biopsy specimen (long ischemic time, short time in fixative, different fixative) or the test is suspected by the pathologist to be negative on the basis of testing error.[4]

TYPE OF TESTS: Immunohistochemistry (IHC) and fluorescent *in situ* hybridization (FISH) are the tests of choice; clear-field in situ hybridization methods are also considered a valid alternative to FISH. Both single-probe (for gene *HER2*) and dual-probe (*HER2* and CEP17) ISH methods are approved (Data Supplement 7A of Recommendations 2018). However, there is insufficient evidence to support the use of mRNA tests (e.g. rtPCR) to determine HER2 status in unselected patients (Data Supplement 7A of 2018 Recommendations).

The 2018 update recommends the preferential use of dual-probe testing for the HER2 gene and chromosome 17 centromere, although it does recognize that several single-probe assays have regulatory approval and are widely used.[4] In the equivocal result category defined with single-probe staining, it is recommended, if IHC yields a 2+ score, to re-test with dual-probe staining and follow related recommendations (see next section).

CRITERIA FOR THE EVALUATION OF IMMUNOISTOCHEMISTRY (IHC) AND IN SITU HYBRIDIZATION (ISH) TEST RESULTS

See Figures 1-6 of the main text of ASCO-CAP 2018 Recommendations and the Data supplement entitled "2018-her2-testing-algorithms".[4]

See also Table 1 of the main text of ASCO-CAP 20184 Recommendations.

POSITIVE TEST:

IMMUNOHISTOCHEMISTRY (IHC)

IHC 3+, defined as "complete, intense circumferential staining of a homogeneous and contiguous population of at least 10% of cells". The 30% cut-off of HER2 positive cells recommended in 2007 may cause the exclusion of some patients from treatment. Therefore, it is recommended to use the >10% positive cells cut-off previously established as an eligibility criterion for adjuvant trastuzumab therapy in prospective randomized trials (a, *Data Supplement 1: 2013 Update Rationale and Background Information).* This definition is confirmed by the 2018 recommendations.

IN SITU HYBRIDIZATION (ISH)

Counting at least 20 cells from two separate areas in a homogeneous and contiguous population:

-     <u>With single-probe staining</u>: average number of HER2 copies ≥6

-     <u>With dual-probe staining</u>:
  - *HER2/CEP17* ratio ≥2 and average number of *HER2* copies ≥4 (group 1 according to Press et al.);[5]
  - *HER2/CEP17* ratio ≥2 and average number of *HER2* copies <4 (group 2 according to Press et al.):[5] need for further analysis;
  - *HER2/CEP17* ratio <2 and average number of *HER2* copies ≥*6* (group 3 according to Press et al.):[5] need for further analysis.

=> Further analysis if result is "HER2/CEP17 ratio ≥2 and average number of HER2 copies <*4*": reflex test by IHC if ISH was initally performed, or ISH count by a second operator blinded to previous results with new count of at least <u>20</u> cells. In the case of IHC: if score 3+ is obtained, consider the case as positive; if score 0/1+ is obtained, consider the result as negative with a comment (see*); if score 2+ is obtained: perform second ISH count with operator blinded to previous results with new count of <u>at least</u> 20 cells including the invasion area with IHC score 2+. In the case of ISH: if the pattern of *HER2/CEP17* ratio ≥2 and average number of *HER2* copies <4 is confirmed, then it is advisable to consider the test as negative with a comment (see *); if the result of ISH counts varies by category, experts suggest that the final category be decided according to internal procedures.

This modification by 2018 recommendations for the *HER2/CEP17* ratio ≥2 category aims to address the main criticism of the diagnostic algorithm with dual-probe testing, which includes first the ratio determination and then the evaluation of the number of *HER2* copies, i.e., about to the inclusion among "positive" cases of cases with a low number of *HER2* copies that the single-probe test would have evaluated as "equivocal" or "negative". For example, cases with 1 CEP17 signal (MONOSOMIC and rare) would be assessed as amplified even with only 2 *HER2* copies, because the ratio is ≥2. Bhargava and Dabbs[8] have stressed how it is a "biological nonsense" to consider as amplified cases with a low number of *HER2* signals, since 4 *HER2* genes may be present, for example, in the cell proliferation phase. The same authors contest the bibliographic reference to the HERA trial to justify this choice, because in the outcome definition the 48 cases with these characteristics were not considered separately. Recently, Press and collaborators[5] have also reported outcome data for patients with tumors defined as HER2 positive based on these ISH characteristics, showing no benefit from trastuzumab treatment.

*The comment suggested by expert panel in the case of a negative result following confirmation by the second operator of *HER2/CEP17* ratio ≥2 and average number of HER2 copies <4 is as follows: *"Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with a HER2/CEP17 ratio of ≥ 2.0 and an average HER2 copy number of < 4.0 per cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomly assigned to the trastuzumab arm did not seem to derive an improvement in disease-free or overall survival, but there were too few such cases to draw definitive conclusions. IHC expression for HER2 should be used to complement ISH and define HER2 status. If the IHC result is not 3+ positive, it is recommended that the specimen be considered HER2 negative because of the low HER2 copy number by ISH and the lack of protein overexpression."*

(Type: evidence-based; quality of evidence: intermediate; strength of recommendation: strong recommendation).

Repeating the test on other available tissue samples may be another appropriate approach in such a scenario, and when interpretation is particularly difficult or results are debated, expert consultation may be considered as well as the use of alternative probes or other methods of genetic analysis.

=> Further analysis in case of result "HER2/CEP17 ratio <2 and average number of HER2 copies ≥*6*": IHC reflex test if ISH was initially performed, or ISH count by a second operator blinded to previous results with

new count of at least 20 cells. In the case of IHC: if score 3+ is obtained, consider the case as positive; if score 0/1+ is obtained, consider the result as negative with comment (see **); if score 2+ is obtained: perform second ISH count with operator blinded to previous results with new count of at least 20 cells including the invasion area with IHC score 2+. In the case of ISH: if the pattern of *HER2/CEP17* ratio <2 and average number of HER2 copies ≥6 is confirmed, then it is recommended to consider the test as positive; if the result of ISH counts gives a different category, experts suggest that the result should be decided according to internal procedures to define the final category.

With regards to this scenario, the 2018 recommendations point out that, based on the evidence that some cases with this pattern (group 3 according to Press et al.) present amplification of the *HER2* gene in the absence of chromosome 17 polysomy, in particular when the average number of *HER2* copies is high, experts state that these cases should continue to be classified as HER2 positive unless the IHC result is clearly negative (score 0 or 1+).[8-14]

Repeating the test on other available tissue samples may be another appropriate approach in such a scenario, and when interpretation is particularly difficult or results are debated, expert consultation may be considered as well as the use of alternative probes or other methods of genetic analysis. However, it is stressed that the use of alternative probes in this setting should not be routinely implemented as a standard due to the lack of related survival data.

** The comment suggested by the expert panel in case of negative IHC after ISH with *HER2/CEP17* ratio <2 and average number of HER2 copies ≥6 is as follows: *"Evidence is limited on the efficacy of HER2-targeted therapy in cases with HER2/CEP17 <2 in the absence of protein over-expression because these patients were not eligible in first-generation trials with patients treated with trastuzumab in the adjuvant setting. When the IHC score is 0/1+ it is recommended to consider the sample as HER2 negative."*

(Type: evidence-based; quality of evidence: intermediate; strength of recommendation: strong recommendation).

EQUIVOCAL RESULT

In the event of an equivocal test result, regardless of whether IHC or ISH is used, a reflex test should be performed using the alternative method on the same sample (ISH if the initial test was IHC and viceversa), or using the same method or the alternative method on another sample, if available. If the reflex test does not give a conclusive positive or negative result, the pathologist should review the histopathologic features and if possible discuss with the oncologist about additional HER2 tests, or act independently to facilitate a definitive diagnosis and always document any additional tests (type of test, type of sample analyzed) in the comment section of the pathological report.

IMMUNOHISTOCHEMISTRY (IHC)

The 2018 Recommendations revise the definition of this category as follows: IHC 2+, defined as "weak to moderate complete membrane staining in >10% of invasive tumor cells".

Discussion of unusual patterns of immunostaining was introduced in the legend of Figure 1 of the 2018 recommendations as follows: "Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare and if encountered should be considered IHC 2+ equivocal. As one example, some specific subtypes of breast cancers can show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2 amplified. Another example is circumferential membrane IHC staining that is intense but in # 10% of tumor cells (heterogeneous, but limited in extent)".

An equivocal test with a score of 2+ by IHC necessarily requires ISH testing.

IN SITU HYBRIDIZATION (ISH)

- With single-probe staining: average number of *HER2* copies ≥4 <6: need for further analysis;

- With dual-probe staining: *HER2/CEP17* ratio <2 and average number of *HER2* copies ≥4 <6 (group 4 according to Press et al. 5): need for further analysis.

⇨ Further analysis in case of result "average number of *HER2* copies ≥4 <6": if IHC score 2+, perform dual-probe staining and follow the recommendations for dual-probe staining;

⇨ Further analysis in case of result "*HER2/CEP17* ratio <2 and average number of HER2 copies HER2 *≥4* <6": reflex test by IHC if ISH was initially performed, or ISH count by a second operator blinded to previous results with new count of at least 20 cells. In the case of IHC: if score 3+ is obtained, consider the case as positive; if score 0/1+ is obtained, consider the result as negative with comment (see ***); if score 2+ is obtained: perform second ISH count with operator blinded to previous results with new count of at least 20 cells including the invasion area with IHC score 2+. In the case of ISH: if the pattern of *HER2/CEP17* ratio <2 and average number of HER2 copies *≥4* <6 is confirmed, then it is recommended to consider the test as negative with comment (see ***); if the result of ISH counts gives a different category, experts suggest that the result should be decided according to internal procedures to define the final category.

***The comment suggested by the expert panel in the case of a negative result following confirmation by the second operator of an ISH equivocal result is as follows: "*It is uncertain whether patients with an average of >4.0 and <6.0 HER2 signals per cell and a HER2/CEP17 ratio of <2.0 benefit from HER2-targeted therapy in the absence of protein overexpression (IHC 3+). If the specimen test result is close to the ISH ratio threshold for positive, there is a higher likelihood that repeat testing will result in different results by chance alone. Therefore, when IHC results are not 3+ positive, it is recommended that the sample be considered HER2 negative without additional testing on the same specimen*".

(Type: evidence-based; quality of evidence: intermediate; strength of recommendation: strong recommendation).

The guidelines underline how this category has been and still is problematic for both pathologists and oncologists. In the absence of a clearly positive or negative result, these cases were very often subjected to multiple tests (multiple samples analysed from the same patient) and some laboratories relied on the use of alternative probes that map regions other than chromosome 17 centromere. Many of these probes are not clinically validated and this practice has led to reports including several counts and a final result that reports the presence of *HER2* amplification if one of the counts detects a ratio >2. After careful evaluation of this practice and based on the lack of survival data, experts are opposed to the use of this approach in standard diagnostic routine.

In special cases, clinical correlations with other factors (e.g. histological grade and special histotypes) or test repetition on other specimens from the same patient may be appropriate. When interpretation is particularly difficult, or if results are debated, expert consultation may be considered as well as the use of alternative probes or other methods of genetic analysis. However, the use of alternative probes should not be standard practice in this category.

NEGATIVE TEST:

IMMUNOHISTOCHEMISTRY (IHC)

IHC 1+, defined as "faint/barely perceptible incomplete membrane staining in >10% of invasive tumor cells". IHC 0, defined as "no staining or faint/barely perceptible incomplete membrane staining in ≤10% of invasive tumor cells". Negative cases by IHC (0 and 1+) should not be routinely tested with ISH, as the expert panel was unable to identify a specific subgroup that could benefit from reflex testing if the IHC result IHC is less than 2+ *(h, Data Supplement 2: Special Issues - 2D) Consideration for Mandatory Retesting of All HER2-Negative Tests),*

IN SITU HYBRIDIZATION (ISH)

With single-probe staining: *HER2* copies <4: compare with IHC (score 0/1+) and/or with dual-probe staining;

With dual-probe staining: *HER2/CEP17* ratio <2 with average number of HER2 copies *<4*.

INDETERMINATE RESULT: this is a category already considered in 2013, which can be used if technical issues (for example: inadequate specimen handling, crush artifacts, testing failure) prevent one or both tests (IHC and ISH) from being reported as positive, negative or equivocal.

HETEROGENOUS RESULT by ISH analysis: it is specified that each population of aggregated amplified cells that are >10% of the population of tumor cells should be counted separately (*Data Supplement 7B) Heterogeneit-ASCO/CAP 2018).* The results should therefore be reported separately including HER2/CEP17 ratio, number of HER2 and CEP17 copies (if available), and the percentage of amplified cells. 2013 guidelines stated that the decision to define as clinically relevant only heterogeneity in the form of two clearly distinct tumor populations had been much debated by experts. Much more frequent are cancers with a mixture of amplified and non-amplified cells: i) in the form of single cells over a background of non-amplified cells: ii) in the form of aggregates of amplified cells interspersed with other groups of non-amplified cells. The latter two patterns are not specifically discussed further in the new 2018 recommendations, which describe more generally the identification of a population of aggregated cells with gene amplification.

REFERENCE METHODS (l Data Supplement 9: Reporting Elements for IHC and Reporting Elements for ISH): A set of data is specified in the supplements to the guidelines and must be included in the report to make it more complete and comparable over time. This must take into account the new ISH reporting methods introduced in 2018 and summarized in Table 1.[4] The clinician's *communication* with the patient remains important, as the patient should be informed of the importance of determining the biological characteristics of the tumor, of the determination of HER2 status, of the type of tissue used for analysis and the type of test, and of the importance of retesting new tumors or metastatic sites, specifying the possibility of discrepancies between tests over time and explaining that HER2 testing follow specific guidelines.

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Histopathologic features suggestive of possible HER2 test discordance
Criteria to consider*
A new HER2 test should not be ordered if the following histopathologic findings occur and the initial HER2 test was negative: Histologic grade 1 carcinoma of the following types: Infiltrating ductal or lobular carcinoma, ER and PgR positive Tubular (at least 90% pure) Mucinous (at least 90% pure) Cribriform (at least 90% pure) Adenoid cystic carcinoma (90% pure) and often triple negative
A new HER2 test should be ordered if the following histopathologic findings occur and the initial HER2 test was positive: Histologic grade 1 carcinoma of the following types: Infiltrating ductal or lobular carcinoma, ER and PgR positive Tubular (at least 90% pure) Mucinous (at least 90% pure) Cribriform (at least 90% pure) Adenoid cystic carcinoma (90% pure) and often triple negative
If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen if one of the following is observed: Tumor is grade 3 Amount of invasive tumor in the core biopsy specimen is small Resection specimen contains high-grade carcinoma that is morphologically distinct from that in the core Core biopsy result is equivocal for HER2 after testing by both ISH and IHC There is doubt about the handling of the core biopsy specimen (long ischemic time, short time in fixative, different fixative) or the test is suspected by the pathologist to be negative on the basis of testing error
* Criteria to consider if there are concerns regarding discordance with apparent histopathologic findings and possible false-negative or false-positive HER2 test result.

Mod. from Wolff A.C et al, JCO 2018

HER2 test (on invasive component) by validated IHC method

Adequate staining of external and internal tissue controls

| Circumferential membrane staining complete, intense and within >10% of tumor cells* | Membrane staining complete, weak/moderate and within >10% of tumor cells | Membrane staining incomplete, faint/barely perceptible and within >10% of tumor cells | No staining observed or membrane staining incomplete, faint/barely perceptible and within ≤10% of tumor cells |

IHC 3+ positive   IHC 2+ equivocal   IHC 1+ negative   IHC 0 negative

A reflex test (on the same sample by ISH method) or re-test (on a new sample if available, by IHC or ISH) should be requested

Algorithm 1. Algorithm to evaluate HER2 expression by immunohistochemistry (IHC) of the invasive component of a breast cancer sample.
NOTE: the final results reported assume no apparent histopathological discrepancy observed by the pathologist.
Unusual HER2 staining patterns not included in the above definitions may be encountered with IHC. In practice, such patterns are rare and should be considered "IHC 2+ equivocal".
Assessed with low-magnification lens and observed within a contiguous and homogeneous invasive cell population.
(Mod. from Wolff. A.C. et al, JCO 2018)

HER2 test (on invasive component) by validated single-probe ISH method

Adequate in situ hybridization of external and internal tissue controls

Average HER2 copy number ≥6 signals/cell*

Average HER2 copy number ≥4.0 and <6 signals/cell†

Average HER2 copy number <4.0*

Concomitant IHC 3+ classification and/or group 1 by dual-probe ISH‡

Concomitant IHC 2+ classification

Concomitant IHC 0, 1+ classification and/or group 5 by dual-probe ISH‡l

ISH positive

Perform dual-probe ISH for final result‡

ISH negative

Algorithm 2. Algorithm to evaluate HER2 amplification by in situ hybridization (ISH) of the invasive component of a breast cancer sample by single-probe ISH.
NOTE: the final results reported assume no apparent histopathological discrepancy observed by the pathologist.
*It is recommended that the concomitant immunohistochemistry (IHC) assessment becomes an integral part of interpretation of single-probe in situ hybridization results.
†Perform IHC (if not already performed) and/or dual-probe ISH using sections from the same tissue sample used for single-probe ISH test. If the IHC assessment result is "2+ equivocal", it is recommended to also perform dual-probe ISH.
‡If the initial dual-probe ISH assessment yields groups 2, 3 or 4, follow Algorithm 3.
(Mod. from Wolff. A.C. et al, JCO 2018)
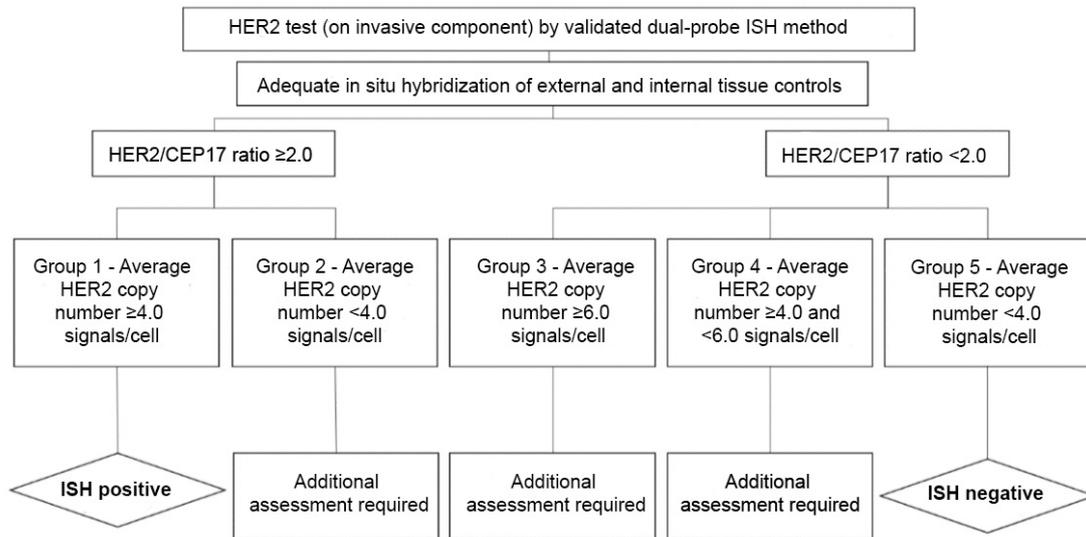
Algorithm 3. Algorithm to evaluate HER2 amplification by in situ hybridization (ISH) of the invasive component of a breast cancer sample by dual-probe ISH.
NOTE: the final results reported assume no apparent histopathological discrepancy observed by the pathologist.
As for Groups 2, 3 or 4, if not already performed, IHC should be performed on sections from the same tissue sample used for the ISH assessment, and ISH and IHC slides should be reviewed at the same time to guide the selection of ISH assessment areas. For further information on the additional assessment for groups 2, 3 or 4, refer to Wolff. A.C. et al, JCO 2018.
(Mod. from Wolff. A.C. et al, JCO 2018)

SUPPLEMENTS TO ASCO/CAP 2018 RECOMMENDATIONS[4]

Data Supplement 1: Search Strategy String and Dates
Date Supplement 2: QUOROM Diagram
Data Supplement 3: 2018 Focused Update Clinical Questions
Date Supplement 4: 2013 All Clinical Questions
Date Supplement 5: Research Survey
Data Supplement 6: Open Comment Period
Data Supplement 7: Types of Assays for Inclusion and Heterogeneity
Date Supplement 8: Pre-analytic Issues
Data Supplement 9: International Quality Assurance Program links

Annex 4. "Prescription of Molecular Multigene Prognostic Tests (MMPTs) in Breast Cancer" - Document produced in 2017 by the Italian Higher Health Council (Session L (2014-2017) Section I)

In 2017, the Higher Health Council (Session L (2014-2017) Section I) of the Italian Ministry of Health produced a document titled "Prescription of Molecular Multigene Breast Cancer Prognostic Tests", which specifies that in Italy MMPTs are not currently included among the Essential Levels of Care (LEA) and therefore are not reimbursable; they are used without reference to specific institutional rules, but according to the clinical needs of individual cases and the possibility of patients to directly cover their cost.

However, the introduction of these tests in the clinical practice as a service provided by the NHS requires regulations governing their implementation, quality and application in order to protect patients, as well as a cost analysis aiming at an effective and efficient health economics policy. The following recommendations are therefore made in this document:

1. Molecular Multigene Prognostic Tests (MMPTs) should be used to identify breast cancer patients who are not candidates for adjuvant chemotherapy, in line with international recommendations.
2. The MMPT prescription must be unique for operated breast cancer. The MMPTs most used in Italy and validated from an analytical and clinical point of view (prognostic investigation to define the recurrence risk category) are: Endopredict®, Mammaprint®, Oncotype DX®, Prosigna®.
3. Scientific societies should define the population of patients for whom MMPTs are useful, and provide specific informed consent to patients included in the MMPT-eligible population.
4. Patients excluded from the use of MMPTs:
   - Patients with triple negative breast cancer (ER-/PR-/HER2-) and HER2+ tumors.
   - Patients who cannot receive chemotherapy due to clinical or age-related reasons.
   - Cancer patients whose treatment is certain (hormone therapy vs. hormone therapy + chemotherapy) on the basis of standard prognostic parameters.
5. The Centers accredited for the performance of MMPTs must offer coverage to the population eligible for molecular testing and ensure that the time required for testing and reporting results (*turnaround time*) can ensure the start of therapy according to oncological recommendations.
6. The cost of the test must also include quality controls (intra- and inter-laboratory for the same MMPT).
7. The optimal quality of the anatomic & pathological breast cancer diagnosis and of results of immunophenotypic tests for SG, PR, HER2, Ki67 must be ensured.
8. All procedures that ensure optimal preservation of surgical breast tumor samples for diagnosing purposes must be followed, according to the "Guidelines for Tracking, Collection, Transport, Preservation and Storage of cells and tissues for diagnostic investigations of pathological anatomy" developed by the Higher Health Council in 2015 and published on the website of the Ministry of Health. (http://www.salute.gov.it/imgs/C_17_publications_2369_attached.pdf).

Annex 5 - AJJC 2017 Classification - Eighth edition

AJCC 2017 Classification (Eighth edition)
Clinical classification

Primitive tumor (T):
Tx: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: carcinoma in situ:
Tis (DCIS) Ductal carcinoma in situ
Tis (Paget) Paget disease of the nipple not associated with invasive and/or carcinoma in situ in the underlying breast parenchyma[1]
T1: tumor up to 20 mm in greatest dimension
T1mi: microinvasion ≤1 mm
T1a: tumor size between 1 mm and 5 mm (round any measurement between 1.0-1.9 mm to 2 mm)
T1b: tumor size >5 mm and ≤10 mm
T1c: tumor size >10 mm and ≤20 mm
T2: tumor >20 mm but <50 mm in greatest dimension
T3: tumor >50 mm in greatest dimension
T4: tumor of any size with direct extension to the chest wall and/or to the skin (skin ulceration or nodules)[2]
T4a: extension to the chest wall (excluding only adherence to/invasion of the pectoral muscle)
T4b: ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c: both T4a and T4b are present
T4d: inflammatory carcinoma[3]

Regional lymph nodes (N):
Nx: regional lymph nodes cannot be assessed (e.g., previously removed)
N0: no regional lymph nodes metastases (instrumental and clinical examination)
N1: metastases to movable ipsilateral axillary lymph nodes (level I-II)
cN1mi: micrometastases (approximately 200 cells, deposition greater than 0.2 mm, but none larger than 2.0 mm)[4]
N2: metastases in ipsilateral axillary nodes (level I-II) that are clinically fixed or matted; or in clinically detectable ipsilateral internal mammary nodes in the absence of clinically evident metastases in the axillary nodes
N2a: metastases in ipsilateral axillary lymph nodes (level I-II) fixed to one another or to other structures
N2b: metastases only in ipsilateral internal mammary lymph nodes and no metastases in axillary lymph nodes (level I-II)
N3: metastases in one or more ipsilateral subclavicular lymph nodes (level III axillary) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph nodes with level I-II axillary lymph node metastases; or metastases in one or more ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement
N3a: metastases in ipsilateral subclavicular lymph nodes
N3b: metastases in internal mammary and axillary lymph nodes
N3c: metastases in supraclavicular lymph nodes
Distant metastasis (M):
Mx: distant metastases cannot be ascertained (but diagnostic imaging is not required to assign category M0)
M0: no clinical or radiological evidence of distant metastases
cM0(i+): no clinical or radiological evidence of distant metastases, but deposits of tumor cells detected by molecular biology or microscopically in blood, bone marrow or other tissues other than regional lymph nodes, not exceeding 0,2 mm in a patient without signs or symptoms of metastases.

AJCC 2017 Classification (Eighth edition)
M1: distant metastases detected by typical clinical and radiological exams and/or histologically proven metastases greater than 0,2 mm (pM).

Pathological classification

pT: Primary tumor
The pathological classification of the primary tumor corresponds to the clinical classification.
pN: Regional lymph nodes [5]
pNx: regional lymph nodes cannot be assessed (e.g. not removed for pathological study or previously removed)
pN0: no regional lymph node metastases identified or isolated tumor cells (ITCs) only
Note: isolated tumor cells (ITCs) are defined as small aggregates of cells no larger than 0.2 mm or single tumor cells or a small grouping of cells with less than 200 cells in a single histological section. Isolated tumor cells can be detected by traditional histological methods or by immunohistochemical methods. Lymph nodes containing only isolated tumor cells are excluded from the total count of positive lymph nodes for N classification purposes, but should be included in the total number of lymph nodes tested.
pN0 (i-): no regional lymph node metastases by histology (standard hematoxylin & eosin staining), negative by immunohistochemistry
pN0 (i+): presence of malignant cells (ITCs) in regional lymph nodes not exceeding 0,2 mm (detected by hematoxylin & eosin staining or immunohistochemistry)
pN0 (mol-): no metastases in histologically established regional lymph nodes, RT-PCR (real time-polymerase chain reaction) negative
pN0 (mol+): RT-PCR positive but no regional lymph node metastases by histology or immunohistochemistry; no ITCs detected
pN1: micrometastases; or metastases in 1-3 ipsilateral axillary lymph nodes; and/or micrometastases or macrometastases in ipsilateral internal mammary lymph nodes detected by sentinel node biopsy but not clinically detectable[5]
pN1mi: micrometastases (aggregate of contiguous tumor cells larger than 0,2 mm and/or more than 200 cells, but no larger than 2 mm)
pN1a: metastases in 1-3 axillary lymph nodes, including at least one metastasis larger than 2 mm in greatest dimension
pN1b: metastases in internal mammary lymph nodes, excluding ITCs
pN1c: combination of pN1a and pN1b
pN2: metastases in 4-9 ipsilateral axillary lymph nodes; or in ipsilateral internal mammary lymph nodes at instrumental examinations with no axillary lymph node metastases
pN2a: metastases in 4-9 axillary lymph nodes, including at least one tumor deposit larger than 2 mm in greatest dimension
pN2b: clinically detectable[6] metastases in internal mammary lymph nodes, with or without histological confirmation, without axillary lymph node metastases
pN3: metastases in 10 or more ipsilateral axillary lymph nodes; or in ipsilateral subclavicular (level III axillary) lymph nodes; or metastases in ipsilateral internal mammary lymph nodes confirmed by imaging with metastases in one or more positive level I-II axillary lymph nodes; or metastases in more than 3 axillary lymph nodes and in internal mammary lymph nodes, with microscopic or macroscopic metastases shown by sentinel lymph node biopsy but not clinically detectable[6]; or metastases in ipsilateral supraclavicular lymph nodes
pN3a: metastases in 10 or more ipsilateral axillary lymph nodes (at least one larger than 2 mm in greatest dimension; or metastases in subclavicular lymph nodes (level III axillary lymph nodes)
pN3b: pN1a or pN2a in the presence of cN2b (ipsilateral internal mammary lymph nodes positive by imaging), or pN2a in the presence of pN1b
pN3c: metastases in ipsilateral supraclavicular lymph nodes

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[1] Carcinomas in the breast parenchyma associated with Paget's disease are classified according to the diameter and characteristics of the parenchymal disease, although Paget's disease should be noted.
[2] Invasion of the dermis alone does not allow classification of the tumor as pT4.

[3] Inflammatory carcinoma is characterized by typical skin changes involving one third or more of the breast skin. It is important to underline that inflammatory carcinoma is primarily a clinical diagnosis. The skin changes may be due to lymphedema caused by tumor emboli in lymphatic vessels, but histological findings of these embolisms are not necessary for the diagnosis of inflammatory carcinoma. Tumor emboli in lymphatics not associated with skin changes should be categorized according to tumor diameter.
[4] cN1mi is rarely used but may be appropriate in rare cases where the sentinel lymph node biopsy has been performed prior to surgery, most likely in cases treated with neoadjuvant therapy.
[5] Suffixes (sn) and (fn) should be added to category N to denote confirmation of metastases based on sentinel lymph node or FNA/core biopsy, respectively.
[6] Clinically detectable = detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and with strongly suspected malignant characteristics or presumed pathological macrometastases based on fine needle aspiration and cytological examination.

NOTE: Lobular carcinoma in situ (LCIS) is a benign entity and has been removed from TNM staging in the AJJC Manual - Eighth Edition (2017).

Staging classification for breast cancer - AJCC 2017 (eighth edition)

Stage 0	Tis	N0	M0
Stage I A	T1*	N0	M0
Stage I B	T0 T1*	N1 mi N1 mi	
Stage IIA	T0 T1* T2	N1** N1** N0	M0
Stage IIB	T2 T3	N1 N0	M0
Stage IIIA	T0 T1* T2 T3 T3	N2 N2 N2 N1 N2	M0
Stage IIIB	T4 T4 T4	N0 N1 N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mic
** T0 and T1 tumors with only lymph node micrometastases are excluded from stage II A and classified as stage I B.
- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 diagnosis should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered IV and remains IV regardless of the response to neoadjuvant therapy.
- The stage designation may change if diagnostic imaging tests reveal the presence of distant metastases, provided they were performed within four months of diagnosis in the absence of disease progression and the patient has not received neoadjuvant therapy.
- The prefixes "yc" and "yp" applied to the T and N classifications indicate staging after neoadjuvant therapy. No stage group is assigned if a complete pathological response is obtained (e.g. ypT0ypN0cM0).

2018 GUIDELINES

T	N	M	G	Her2 status*	SG status	PgR status	Prognostic Stage Group
Tis	N0	M0	1-3	Any	Any	Any	0
T1	N0	M0	1	Positive	Any	Any	AI
T1	N0	M0	1-2	Negative	Positive	Positive	AI
T1	N0	M0	2	Positive	Positive	Positive	AI
T1	N0	M0	3	Positive	Positive	Any	AI
T0-1	N1mi	M0	1	Positive	Any	Any	AI
T0-1	N1mi	M0	1-2	Negative	Positive	Positive	AI
T0-1	N1mi	M0	2	Positive	Positive	Positive	AI
T0-1	N1mi	M0	3	Positive	Positive	Any	AI
Multigene Panel** - Oncotype DX Recurrence Score <11							
T1-2	N0	M0	1-3	Negative	Positive	Any	AI
T1	N0	M0	1	Negative	Positive	Negative	IB
T1	N0	M0	1	Negative	Negative	Positive	IB
T1	N0	M0	2	Positive	Positive	Negative	IB
T1	N0	M0	2	Positive	Negative	Any	IB
T1	N0	M0	2	Negative	Negative	Positive	IB
T1	N0	M0	3	Positive	Negative	Any	IB
T1	N0	M0	3	Negative	Positive	Positive	IB
T0-1	N1mi	M0	1	Negative	Positive	Negative	IB
T0-1	N1mi	M0	1	Negative	Negative	Positive	IB
T0-1	N1mi	M0	2	Positive	Positive	Negative	IB
T0-1	N1mi	M0	2	Positive	Negative	Any	IB
T0-1	N1mi	M0	2	Negative	Negative	Positive	IB
T0-1	N1mi	M0	3	Positive	Negative	Any	IB
T0-1	N1mi	M0	3	Negative	Positive	Positive	IB
T2	N0	M0	1-3	Positive	Positive	Positive	IB
T2	N0	M0	1,2	Negative	Positive	Positive	IB
T1	N1	M0	1-3	Positive	Positive	Positive	IB
T1	N1	M0	1-2	Negative	Positive	Positive	IB
T2	N1	M0	1	Negative	Positive	Positive	IB***
T2	N1	M0	2	Positive	Positive	Positive	IB***
T0-2	N2	M0	1-2	Positive	Positive	Positive	IB***
T3	N1-2	M0	1	Positive	Positive	Positive	IB***
T3	N1-2	M0	2	Positive	Positive	Positive	IB***
T1	N0	M0	1	Negative	Negative	Negative	IIA***
T1	N0	M0	2	Negative	Negative	Negative	IIA***
T1	N0	M0	3	Negative	Positive	Negative	IIA***
T1	N0	M0	3	Negative	Negative	Positive	IIA***
T1	N0	M0	3	Negative	Negative	Negative	IIA***
T0-1	N1mi	M0	1	Negative	Negative	Negative	IIA
T0-1	N1mi	M0	2	Negative	Negative	Negative	IIA
T0-1	N1mi	M0	3	Negative	Positive	Negative	IIA
T0-1	N1mi	M0	3	Negative	Negative	Positive	IIA
T0-1	N1mi	M0	3	Negative	Negative	Negative	IIA

T0-1	N1	M0	1	Positive	Positive	Negative	IIA
T0-1	N1	M0	1-2	Positive	Negative	Any	IIA
T0-1	N1	M0	1	Negative	Positive	Negative	IIA
T0-1	N1	M0	1	Negative	Negative	Positive	IIA
T0-1	N1	M0	3	Negative	Positive	Positive	IIA
T2	N0	M0	1	Positive	Positive	Negative	IIA
T2	N0	M0	1-2	Positive	Negative	Any	IIA
T2	N0	M0	1	Negative	Positive	Negative	IIA
T2	N0	M0	1	Negative	Negative	Positive	IIA
T2	N0	M0	3	Negative	Positive	Positive	IIA
T0-2	N2	M0	1	Negative	Positive	Positive	IIA***
T3	N1-2	M0	1	Negative	Positive	Positive	IIA
T0-1	N1	M0	1	Negative	Negative	Negative	IIB
T0-1	N1	M0	2	Positive	Positive	Negative	IIB
T0-1	N1	M0	2	Negative	Positive	Negative	IIB
T0-1	N1	M0	2	Negative	Negative	Any	IIB
T0-1	N1	M0	3	Positive	Positive	Negative	IIB
T0-1	N1	M0	3	Positive	Negative	Positive	IIB
T2	N0	M0	1	Negative	Negative	Negative	IIB
T2	N0	M0	2	Positive	Positive	Negative	IIB
T2	N0	M0	2	Negative	Positive	Negative	IIB
T2	N0	M0	2	Negative	Negative	Positive	IIB
T2	N0	M0	3	Positive	Positive	Negative	IIB
T2	N0	M0	3	Positive	Negative	Any	IIB
T2	N1	M0	1	Positive	Any	Any	IIB
T2	N1	M0	1	Negative	Negative	Positive	IIB
T0-2	N2	M0	2	Negative	Positive	Positive	IIB
T0-2	N2	M0	3	Positive	Positive	Positive	IIB
T3	N1-2	M0	2	Negative	Positive	Positive	IIB
T3	N1-2	M0	3	Positive	Positive	Positive	IIB
T0-1	N1	M0	2	Negative	Negative	Negative	IIIA***
T0-1	N1	M0	3	Negative	Positive	Negative	IIIA
T0-1	N1	M0	3	Negative	Negative	Any	IIIA
T2	N0	M0	2	Negative	Negative	Negative	IIIA***
T2	N0	M0	3	Negative	Positive	Negative	IIIA***
T2	N0	M0	3	Negative	Negative	Any	IIIA***
T2	N1	M0	1	Negative	Positive	Negative	IIIA
T2	N1	M0	2	Positive	Negative	Negative	IIIA
T2	N1	M0	2	Negative	Positive	Negative	IIIA
T2	N1	M0	3	Positive	Positive	Negative	IIIA
T2	N1	M0	3	Positive	Negative	Negative	IIIA
T3	N0	M0	1	Negative	Positive	Negative	IIIA
T3	N0	M0	2	Positive	Negative	Negative	IIIA
T3	N0	M0	2	Negative	Positive	Negative	IIIA
T3	N0	M0	3	Positive	Positive	Negative	IIIA
T3	N0	M0	3	Positive	Negative	Negative	IIIA
T0-2	N2	M0	1	Positive	Positive	Negative	IIIA
T0-2	N2	M0	1	Positive	Negative	Any	IIIA
T0-2	N2	M0	1	Negative	Positive	Negative	IIIA
T0-2	N2	M0	1	Negative	Negative	Positive	IIIA

T0-2	N2	M0	2	Positive	Positive	Negative	IIIA
T0-2	N2	M0	2	Positive	Negative	Any	IIIA
T3	N1-2	M0	1	Positive	Positive	Negative	IIIA
T3	N1-2	M0	1	Positive	Negative	Any	IIIA
T3	N1-2	M0	1	Negative	Positive	Negative	IIIA
T3	N1-2	M0	1	Negative	Negative	Positive	IIIA
T3	N1-2	M0	2	Positive	Positive	Negative	IIIA
T3	N1-2	M0	2	Positive	Negative	Any	IIIA
T4	N0-2	M0	1	Negative	Positive	Positive	IIIA
Any	N3	M0	1	Negative	Positive	Positive	IIIA***
T2	N1	M0	1-2	Negative	Negative	Negative	IIIB***
T2	N1	M0	3	Negative	Positive	Negative	IIIB***
T3	N0	M0	1-2	Negative	Negative	Negative	IIIB
T3	N0	M0	3	Negative	Positive	Negative	IIIB
T0-2	N2	M0	2	Negative	Positive	Negative	IIIB
T0-2	N2	M0	2	Negative	Negative	Positive	IIIB
T0-2	N2	M0	3	Positive	Positive	Negative	IIIB
T0-2	N2	M0	3	Positive	Negative	Any	IIIB
T0-2	N2	M0	3	Negative	Positive	Positive	IIIB
T3	N1-2	M0	2	Negative	Positive	Negative	IIIB
T3	N1-2	M0	2	Negative	Negative	Positive	IIIB
T3	N1-2	M0	3	Positive	Positive	Negative	IIIB
T3	N1-2	M0	3	Positive	Negative	Any	IIIB
T3	N1-2	M0	3	Negative	Positive	Positive	IIIB
T4	N0-2	M0	1	Positive	Any	Any	IIIB
T4	N0-2	M0	2	Positive	Positive	Positive	IIIB
T4	N0-2	M0	2	Negative	Positive	Positive	IIIB
T4	N0-2	M0	3	Positive	Positive	Positive	IIIB
Any	N3	M0	1	Positive	Any	Any	IIIB
Any	N3	M0	2	Positive	Positive	Positive	IIIB
Any	N3	M0	2	Negative	Positive	Positive	IIIB
Any	N3	M0	3	Positive	Positive	Positive	IIIB
T2	N1	M0	3	Negative	Negative	Any	IIIC***
T3	N0	M0	3	Negative	Negative	Any	IIIC
T0-2	N2	M0	2	Negative	Negative	Negative	IIIC***
T0-2	N2	M0	3	Negative	Positive	Negative	IIIC***
T0-2	N2	M0	3	Negative	Negative	Any	IIIC***
T3	N1-2	M0	2	Negative	Negative	Negative	IIIC***
T3	N1-2	M0	3	Negative	Positive	Negative	IIIC***
T3	N1-2	M0	3	Negative	Negative	Any	IIIC***
T4	N0-2	M0	1	Negative	Positive	Negative	IIIC
T4	N0-2	M0	1	Negative	Negative	Any	IIIC
T4	N0-2	M0	2	Positive	Positive	Negative	IIIC
T4	N0-2	M0	2	Positive	Negative	Any	IIIC
T4	N0-2	M0	2	Negative	Positive	Negative	IIIC
T4	N0-2	M0	2	Negative	Negative	Any	IIIC
T4	N0-2	M0	3	Positive	Positive	Negative	IIIC
T4	N0-2	M0	3	Positive	Negative	Any	IIIC
T4	N0-2	M0	3	Negative	Any	Any	IIIC
Any	N3	M0	1	Negative	Positive	Negative	IIIC

Any	N3	M0	1	Negative	Negative	Any	IIIC
Any	N3	M0	2	Positive	Positive	Negative	IIIC
Any	N3	M0	2	Positive	Negative	Any	IIIC
Any	N3	M0	2	Negative	Positive	Negative	IIIC
Any	N3	M0	2	Negative	Negative	Any	IIIC
Any	N3	M0	3	Positive	Positive	Negative	IIIC
Any	N3	M0	3	Positive	Negative	Any	IIIC
Any	N3	M0	3	Negative	Any	Any	IIIC
Any	Any	M1	1-3	Any	Any	Any	IV

*In cases where Her2 status is defined as equivocal by ISH (FISH or CISH) according to the ASCO/CAP 2013 guidelines, it should be considered as negative

**If Oncotype DX is not performed or not available, or if the Recurrence Score is ≥ 11 for patients with T1-2 N0 M0 Her2 negative ER positive tumors, the Prognostic Stage Group should be assigned based on the anatomic categories and biomarkers indicated above. Oncotype DX is the only multigene panel included in the prognostic classification, since it is supported by Level 1 prospective data in patients with Recurrence Score < 11.

***Indicates a stage where the use of the prognostic grade and factors results in a skip >1 stage from the Anatomic stage (e.g. from Anatomic stage IIB to Prognostic stage IB)