Management of Nirmatrelvir/Ritonavir (Paxlovid™) Drug-Drug Interactions in Oncology

Paxlovid™ oral tablets consist of a combination of nirmatrelvir and ritonavir co-packaged for use in the treatment of COVID-19. Ritonavir is a protease inhibitor but is not active against SARS-CoV-2, and is administered as a “boosting agent” to slow the metabolism of nirmatrelvir. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The use of ritonavir presents challenges with respect to drug-drug interactions which can potentially impact the efficacy of nirmatrelvir/ritonavir, as well as the safety of coadministered medications. Firstly, nirmatrelvir and ritonavir are substrates of CYP3A4 and are contraindicated in patients taking CYP3A-inducers (current or recent use in last 14-days) since this may significantly decreased concentrations of nirmatrelvir/ritonavir and potential treatment failure. Secondly, ritonavir acts as a potent inhibitor of CYP3A4, P-gp and other CYP isoenzymes and transporters, which may lead to supratherapeutic concentrations for medications that are highly dependent on CYP3A4-mediated metabolism and potentially serious or life-threatening reactions.

A summary of potential drug-drug interactions for medications used in oncology can be found in the table on the proceeding page. There may be some slight variance from the product monograph based upon pharmacokinetic drug principles, the specific dose and duration of nirmatrelvir/ritonavir therapy, and characteristics of individual medications. In oncology, it is common practice to hold certain medications such as cytotoxic chemotherapy, some tyrosine kinase inhibitors (TKIs), cyclin-dependent kinase (CDK) inhibitors, and poly (ADP-ribose) polymerase (PARP) inhibitors during acute infections – including COVID-19. Dose adjustment of many chemotherapeutic agents is problematic due to the need for obtaining a new prescription with temporary new dosing instructions, arranging delivery of specialized chemotherapy agents and then resuming therapy at regular doses. For these medications, the preferred course of action is to hold therapy during treatment with nirmatrelvir/ritonavir. Consultation with an oncology prescriber/pharmacist is therefore recommended and decisions to hold or dose-adjust should be made in conjunction with the patient's oncology team.

The table is not all-inclusive nor all-comprehensive, focussing on the most clinically significant interactions. Therefore, prescribers and pharmacists are encouraged to consult the product monograph, and other resources, such as the guidance document *Nirmatrelvir/Ritonavir: What Prescribers and Pharmacists Need to Know* and the University of Liverpool COVID-19 Drug Interactions Checker.

Drug	Recommendation	Comments
Abemaciclib (Verzenio)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, for patients who have not previously had dose reduction for toxicity, consider a dose reduction to 50 mg once daily with close monitoring for toxicity.	Cyclin-dependent kinase inhibitors are generally held for acute infection. Abemaciclib AUC increased over 3-fold when coadministered with clarithromycin.
Abiraterone	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	In a clinical drug interaction study, ketoconazole 400 mg x 6 days had no impact on abiraterone PK on day 4. Abiraterone was well tolerated.
Acalabrutinib	Hold acalabrutinib and start nirmatrelvir/ritonavir 24 hours after the last acalabrutinib dose. Restart acalabrutinib 2 days after completing nirmatrelvir/ritonavir.	Acalabrutinib AUC increased 5-fold when coadministered with itraconazole.
Afatinib	Drug interaction not likely to be clinically relevant if afatinib and the first daily dose of nirmatrelvir/ritonavir are administered simultaneously. Continue with standard dosing and monitor for toxicity.	Afatinib AUC increased 1.5-fold when administered 1 hour after ritonavir. When ritonavir and afatinib are administered simultaneously or when afatinib is administered 6 hours prior to ritonavir, there was no significant impact on AUC. *Wind et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. Clin Drug Investig. 2014;34(3):173-82.*
Alectinib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Alectinib and its active metabolite (M4) are metabolized primarily by CYP3A4. Co-administration of strong CYP3A4 inhibitor is anticipated to increase alectinib exposure and decrease M4 exposure. In pharmacokinetic studies with posaconazole, a strong CYP3A4 inhibitor, combined exposure of alectinib and M4 was impacted to a minor extent.
Alpelisib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Alpelisib AUC was predicted to increase almost 1.2-fold with administration of ritonavir 100 mg bid using a physiologically-based PK model. *European Medicine Agency Assessment Report: Piqray®.* https://www.ema.europa.eu/en/documents/assessment-report/piqray-epar-public-assessment-report_en.pdf
Anastrozole	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Metabolism to hydroxyanastrozole primarily via CYP3A4 and glucuronidation to anastrozole N-glucuronide by UGT1A4. These metabolites are pharmacologically inactive. Potential for increased anastrozole concentrations via CYP3A4 inhibition by ritonavir. Clinical significance unknown.
Apalutamide (Erleada)	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Coadministration has not been studied. Apalutamide is a strong inducer of CYP3A4 (92% decrease in AUC of midazolam).

Drug	Recommendation	Comments
Avapritinib	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Predicted 6-fold increase in avapritinib AUC when co-administered with itraconazole. Given long avapritinib half-life (32-57 hours), interaction is unlikely to be mitigated by holding avapritinib.
Axitinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by 50% if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Axitinib AUC increased 2-fold when coadministered with ketoconazole.
Azacitidine	No interaction expected.	Azacitidine has no known induction or inhibition effects on cytochrome P450 enzymes and does not undergo P450 mediated metabolism.
Bevacizumab	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as bevacizumab is metabolized via proteolytic catabolism.
Bexarotene	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Coadministration has not been studied. Bexarotene is a moderate CYP3A4 inducer and may decrease exposure to nirmatrelvir/ritonavir.
Bicalutamide	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	A number of clinical studies show the magnitude of any inhibition is unlikely to be of clinical significance for the majority of substances metabolised by CYP P450.
Binimetinib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Coadministration has not been studied. A clinically significant PK interaction is not expected with short duration of co-administration as binimetinib is primarily metabolized by UGT1A1.
Bortezomib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, may consider co-administration with close monitoring for bortezomib related toxicity.	Bortezomib is generally held during acute infection. Bortezomib AUC increased almost 1.4-fold when coadministered with ketoconazole.
Bosutinib (Bosulif)	Hold bosutinib and start nirmatrelvir/ritonavir 24 hours after the last bosutinib dose. Restart bosutinib 2 days after completing nirmatrelvir/ritonavir.	Bosutinib AUC increased almost 9-fold when coadministered with ketoconazole.
Brigatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by 50% if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Brigatinib AUC increased 2-fold when coadministered with itraconazole.

Drug	Recommendation	Comments
Cabozantinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by 20 mg if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Cabozantinib AUC increased almost 1.4-fold when coadministered in the presence of steady-state ketoconazole 400mg daily.
Capecitabine	No interaction expected.	Coadministration has not been studied but based on metabolism and clearance, a clinically significant interaction is not expected.
Capmatinib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Capmatinib AUC increased 1.4-fold when coadministered with itraconazole. No effect on the capmatinib Cmax was noted.
Cedazuridine/ Decitabine	No interaction expected.	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is not expected.
Ceritinib (Zykadia)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing ceritinib dose by 33% if used concomitantly and monitor for toxicity.	Canadian monograph recommends to avoid concomitant use. However, US monograph suggests reducing dose by 33%, rounded to nearest 150 mg dosage strength. Zykadia (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205755s016lbl.pdf Decision to hold or dose-adjust ceritinib should be made in conjunction with the patient's oncologist. Ceritinib AUC increased 3-fold when single dose coadministered with ketoconazole.
Chlorambucil	No interaction expected.	Coadministration has not been studied and little is known about chlorambucil metabolism in humans. Based on available data, a clinically significant interaction is not expected.
Cobimetinib (Cotellic)	Hold cobimetinib and start nirmatrelvir/ritonavir 24 hours after the last cobimetinib dose. Restart cobimetinib 2 days after completing nirmatrelvir/ritonavir.	Cobimetinib AUC increased almost 7-fold when coadministered with ketoconazole.
Crizotinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by at least 50% if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Crizotinib AUC increased 3.2-fold when coadministered with ketoconazole.

Drug	Recommendation	Comments
Cyclophosphamide	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Based on metabolism and clearance, clinically relevant interaction is not expected with short course of nirmatrelvir/ritonavir. Activation of cyclophosphamide (major pathway) to 4-hydroxycyclophosphamide is catalyzed by CYPs 2B6 (major), 2C9 and 3A4. Inactivation (minor, 10%) to the neurotoxic metabolite is performed mainly by CYP3A4.
Cytarabine	No interaction expected.	Coadministration has not been studied, but no PK interaction is expected as cytarabine is primarily metabolized via cytidine deaminase.
Dabrafenib (Tafinlar)	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Dabrafenib is a moderate to strong in vivo inducer of CYP3A4. Coadministration may decrease exposure to nirmatrelvir/ritonavir.
Dacomitinib	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely based on metabolism and clearance.
Darolutamide	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for daralutamide related toxicity and interrupt therapy or consider dose reduction if necessary.	Darolutamide AUC increased 1.7-fold when coadministered with itraconazole. Given darolutamide is relatively well tolerated, empiric dose adjustment is not suggested.
Dasatinib (Sprycel)	Chronic phase chronic myelogenous leukemia (CML): Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dasatinib dose to 20 to 40 mg if used concomitantly and monitor for toxicity. Accelerated or blast phase CML: Do not coadminister; use alternate COVID-19 therapy.	Dasatinib AUC increased 5-fold when coadministered with ketoconazole.
Degarelix	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as degarelix is metabolized via peptide hydrolysis.

Drug	Recommendation	Comments
Dexamethasone	High dose (≥20 mg daily): Reduce dexamethasone dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Low dose (<20 mg daily): Continue with usual dose during nirmatrelvir/ritonavir.	Dexamethasone AUC increased almost 3-fold when coadministered with voriconazole. Li M, Zhu L, Chen L et al. Assessment of drug-drug interactions between voriconazole and glucocorticoids. J Chemother. 2018;30(5):296-303. doi: 10.1080/1120009X.2018.1506693. Potential for risk of dexamethasone toxicity with high doses (≥20 mg daily). Clinically significant interaction is not expected with dexamethasone at low doses, including when used for COVID-19 treatment.
Duvelisib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose to 15 mg BID if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir. Note: if patient is already receiving 15 mg BID due to previous reduction for toxicity, do not coadminister and consider alternate COVID-19 therapy if unable to hold.	Depending on disease volume, abrupt discontinuation of duvelisib may result in disease flare in patients with CLL. Based on physiologically-based PK modeling and simulation, the increase in exposure to duvelisib is estimated to be almost 2-fold at steady state when concomitantly used with strong CYP3A4 inhibitors.
Enasidenib	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Enasidenib induces CYP3A4. The clinical significance of this potential drug interaction is unknown at this time. Given lack of available data regarding magnitude of induction potential, suggest not to coadminister due to potential to decrease in nirmatrelvir/ritonavir.
Encorafenib (Braftovi)	Hold encorafenib and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing encorafenib dose as follows and monitoring for toxicity: If taking 450 mg per day: reduce to 150 mg daily. If taking 150 to 300 mg per day: reduce dose to 75 mg daily. Resume usual encorafenib dose 2 days after completing nirmatrelvir/ritonavir.	Encorafenib AUC increased 3-fold when coadministered with posaconazole.
Entrectinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose to 100 mg daily if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Entrectinib AUC increased 6-fold when coadministered with itraconazole.

Drug	Recommendation	Comments
Enzalutamide (Xtandi)	Contraindicated (use within past 8 weeks). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Enzalutamide is a strong CYP3A4 inducer and may reduce concentrations of nirmatrelvir/ritonavir. Given long terminal half-life of enzalutamide (~6 days), enzyme induction is expected to persist. A physiologically-based pharmacokinetic model predicts that CYP3A4 activity does not return to baseline until at least 8 weeks after enzalutamide discontinuation. *Narayanan et al. Application of a "Fit for Purpose" PBPK Model to Investigate the CYP3A4 Induction Potential of Enzalutamide. Drug Metab Lett. 2016;10(3):172-179.*
Erdafitinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for erdafitinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Erdafitinib AUC increased 1.3-fold when coadministered with itraconazole.
Erlotinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose in 50 mg decrements if toxicity occurs. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Coadministration of erlotinib and ketoconazole led to 86% increase in erlotinib AUC.
Etoposide	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for etoposide related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Co-administration has not been studied. Etoposide is metabolized by CYP3A4 and undergoes P-gp medicated transport, therefore coadministration with nirmatrelvir/ritonavir theoretically may increase etoposide exposure.
Everolimus	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Everolimus AUC increased 15-fold when coadministered with ketoconazole. Given long terminal half-life (30 hours), holding everolimus is unlikely to mitigate effects of this interaction.
Exemestane	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Exemestane is metabolized by CYP3A4, but coadministration with ketoconazole did not result in clinically significant changes in exemestane exposure.
Fedratinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose to 200 mg daily depending on indication, tolerability, and previously planned dose and monitor for toxicity. Discontinue fedratinib if the patient is unable to tolerate a dose of 200mg daily.	Fedratinib AUC is predicted to increase by 2.5-fold when coadministered with ritonavir 100 mg BID based on physiologically-based PK modeling simulations.
Fludarabine	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as fludarabine is metabolized via non-CYP P450 pathways.

Drug	Recommendation	Comments
Flutamide	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for increased/decreased flutamide concentrations secondary to inhibition of CYP3A4 or induction of CYP1A2 by lopinavir/ritonavir; clinical significance is unknown. Monitor for flutamide efficacy and toxicity. Studies show the principal role of CYP1A2 is in the metabolism of flutamide to 2-hydroxyflutamide (active metabolite).
Fostamatinib (Tavalisse)	No dose-adjustment is required, HOWEVER, monitor for toxicity including diarrhea, hypertension, hepatotoxicity, and neutropenia. If significant toxicity occurs, consider interruption of fostamatinib with reintroduction 2 days after completing nirmatrelvir/ritonavir.	Fostamatinib active metabolite AUC increased 2-fold when administered with ketoconazole.
Fulvestrant	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Results from a clinical study with ketoconazole (400 mg daily), a potent inhibitor of CYP3A4, indicate that there is no clinically relevant change in the PK of an 8 mg IV dose of fulvestrant. Fulvestrant is a minor substrate of CYP 3A4; dosage adjustments are not considered necessary during co-administration with CYP 3A4 inhibitors or inducers.
Gefitinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for gefitinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	In healthy volunteers, gefitinib AUC increased 1.8-fold when coadministered with itraconazole. In a developed physiologically-based PK model, steady state gefitinib concentrations were simulated in a virtual population of 50 individuals receiving gefitinib 250 mg daily with and without darunavir 800 mg/ritonavir 100 mg daily, efavirenz 600 mg daily, or etravirine 200 mg twice daily. Gefitinib AUC was increased 5.5-fold when coadministered with darunavir/ritonavir, and was still increased by 2.79-fold after halving the gefitinib dose to 125 mg daily. However, these concentrations were still considered to be within the therapeutic range. Some references recommend reducing gefitinib to 125mg daily, however, note that gefitinib is a hazardous drug, so handling safety in splitting tablets should be considered.
Gilteritinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for gilteritinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Gilteritinib AUC increased 2.2-fold when coadministered with itraconazole.

Drug	Recommendation	Comments
Glasdegib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for glasdegib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Glasdegib AUC increased 2.4-fold when coadministered with ketoconazole dosed at 400 mg once daily for 7 days in healthy volunteers.
Goserelin	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as goserelin is metabolized via non-CYP P450 pathways.
Hydroxyurea	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as hydroxyurea is metabolized via non-CYP P450 pathways.
Ibrutinib (Imbruvica)	Consider alternate COVID-19 therapy. Alternatively, consider holding ibrutinib and starting nirmatrelvir/ritonavir 12 hours after the last ibrutinib dose. Restart ibrutinib 2 days after completing nirmatrelvir/ritonavir.	Ibrutinib AUC increased 26-fold when coadministered with ketoconazole. It may be dangerous to interrupt therapy in patients with high volume chronic lymphocytic leukemia or mantle cell lymphoma due to disease flare and/or cytokine release.
Idelalisib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for idelalisib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Idelalisib AUC increased 1.8-fold when coadministered with ketoconazole.
Imatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for imatinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Imatinib AUC increased 1.4-fold when coadministered with ketoconazole. In another pharmacokinetic study of 11 cancer patients, coadministration with ritonavir (600 mg for 3 days) did not alter imatinib (400 mg to 800 mg daily for at least 2 months) steady-state concentrations, but did increase exposure to the imatinib metabolite (CGP74588) 1.4-fold.
Infigratinib	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Infigratinib AUC increased 7-fold when coadministered with multiple doses of itraconazole. BHS697 (active metabolite) increased almost 3-fold when coadministered with multiple doses of itraconazole. Given long terminal half-life of parent drug (33 hours), holding infigratinib is unlikely to mitigate effects of this interaction.

Drug	Recommendation	Comments
Isotretinoin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for isotretinoin related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Coadministration has not been studied. Ritonavir could potentially increase isotretinoin concentrations by inhibition of CYP2C8 and CYP3A4. However, plasma retinoid concentrations in one patient treated with isotretinoin were substantially lower after the start of antiviral therapy (indinavir/ ritonavir 800/800 mg daily dose + zidovudine/lamivudine). This was unexpected and the reason is unclear.
Ivosidenib	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Ivosidenib induces CYP3A4 and is itself a substrate of CYP3A4. Simulations suggest that concomitant use of ivosidenib (500 mg once daily) and the sensitive CYP3A substrate midazolam (single 5-mg dose) decreases AUC and peak plasma concentration of midazolam by 83 and 74%, respectively. Given long terminal half-life of ivosidenib (~2-5 days), enzyme induction is expected to persist. Ivosidenib AUC increased 2.7-fold when coadministered with itraconazole.
Ixazomib	No interaction expected	Coadministration with strong CYP3A4 and CYP1A2 inhibitors will likely not result in clinically significant interactions.
Lanreotide	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Product monograph mentions somatostatin analogues might decrease metabolic clearance of compounds metabolized by CYP 450 enzymes, which might be due to suppression of growth hormone. Paxlovid is a CYP 3A4 substrate.
Lapatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose lapatinib dose from 1250mg to 500mg daily if used concomitantly and monitor for toxicity. A 7-day washout period is recommended before the lapatinib dose is readjusted upwards.	Lapatinib AUC increased 3.6-fold when coadministered with ketoconazole.
Larotrectinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing larotrictinib dose by 50% if used concomitantly and monitor for toxicity. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Larotrectinib AUC increased 4.3-fold when coadministered with itraconazole.
Lenalidomide (Revlimid)	No interaction expected.	Lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. Hence, coadministration of cytochrome P450 substrates or inhibitors with lenalidomide is not likely to result in clinically relevant drug-drug interactions.

Drug	Recommendation	Comments
Lenvatinib	No interaction expected.	Lenvatinib may be co-administered without dose adjustment with CYP3A inhibitors and CYP3A inducers. Avoid coadministration of lenvatinib with other drugs known to prolong the QT interval because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including torsade de pointes.
Letrozole (Femara)	Drug interaction not likely to be clinically relevant. Continue with standard dosing. Monitor for letrozole related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Coadministration has not been studied. Letrozole is metabolised by CYP3A4 and CYP2A6 to carbinol, an inactive metabolite. Coadministration could potentially increase letrozole concentrations and thus increase the occurrence of side effects. A clinical interaction study with cimetidine (a non-specific inhibitor of CYP2C19 and CYP3A4) indicated that coadministration with letrozole does not result in a clinically significant drug interaction
Leuprolide	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as leuprolide is metabolized via peptide hydrolysis.
Lomustine	Drug interaction not likely to be clinically relevant. Continue with standard dosing. Monitor for lomustine related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Coadministration has not been studied. Potential for increased lomustine exposures with CYP2D6 inhibitors; ritonavir is a weak inhibitor of CYP2D6. Clinical significance unknown.
Lorlatinib (Lorbrena)	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Lorlatinib induces CYP3A4 and is itself a substrate of CYP3A4. Lorlatinib 150 mg orally once daily for 15 days decreased the AUC by 64% of a single oral 2 mg dose of midazolam. Given long terminal half-life of lorlatinib (~24 hours), enzyme induction is expected to persist.
Melphalan	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as melphalan is metabolized via chemical hydrolysis.
Mercaptopurine	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as mercaptopurine is metabolized via non-CYP P450 pathways.
Methotrexate	No interaction expected. Monitor for methotrexate related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as methotrexate is metabolized via non-CYP P450 pathways.

Drug	Recommendation	Comments
Midostaurin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by 50% of ideal dose if used concomitantly and monitor for toxicity. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Midostaurin AUC increased 10.4-fold when coadministered with ketoconazole. Monitor closely for increased toxicities especially during the first week of consecutive midostaurin administration in the advanced systemic mastocytosis population, and during first week of midostaurin administration in each cycle of chemotherapy in the AML population.
Mitotane (Lysodren)	Contraindicated (use within past 3-6 months). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Coadministration has not been studied. Mitotane is a strong inducer of CYP3A4. Given long terminal half-life of mitotane (18 to 159 days), enzyme induction is expected to persist.
Mobocertinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Mobocertinib AUC increased 6.3-fold when coadministered with itraconazole.
Neratinib (Nerlynx)	Hold neratinib and start nirmatrelvir/ritonavir 24 hours after the last neratinib dose. Restart neratinib 2 days after completing nirmatrelvir/ritonavir.	Neratinib AUC increased 4.8-fold when administered with ketoconazole.
Nilotinib (Tasigna)	Chronic phase chronic myelogenous leukemia (CML): Hold nilotinib if possible, and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider dose reduction to 400 mg PO daily and monitor for toxicity. Accelerated or blast phase CML: Do not coadminister, consider alternate COVID-19 therapy.	Nilotinib AUC increased 3-fold when administered with ketoconazole.
Nilutamide	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as nilutamide is metabolized via non-CYP P450 pathways.
Niraparib	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as niraparib is metabolized via non-CYP P450 pathways.
Octreotide	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Somatostatin analogues may decrease the clearance of compounds metabolized by CYP3A4 through the suppression of growth hormone. Concurrent use of octreotide with substrates of CYP3A4 should be done cautiously, particularly if the substrate drug has a low therapeutic index.

Drug	Recommendation	Comments
Olaparib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing olaparib tablet dose to 100 mg twice daily, or reducing olaparib capsule dose to 150 mg twice daily. Monitor for olaparib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Olaparib AUC increased 2.7-fold when coadministered with itraconazole.
Osimertinib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Osimertinib AUC increased 1.2-fold when coadministered with itraconazole. Given the inter-patient variability of 46% in the osimertinib exposure in the population PK analysis, this change of 24% is not clinically significant. Due to the dose proportional, linear and time independent PK of osimertinib, the effect of a strong CYP3A4 inhibitor at steady state is likely to be similar to that seen after a single dose. Hence, CYP3A4 inhibitors are unlikely to affect the exposure of Osimertinib.
Palbociclib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing palbociclib dose to 75 mg daily and monitor for toxicity. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Palbociclib AUC increased almost 1.9-fold when coadministered with itraconazole.
Panobinostat	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing to 10 mg or interrupt therapy as necessary and monitor for toxicity. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Panobinostat AUC increased almost 1.8-fold when coadministered with ketoconazole.
Pazopanib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose to 400 mg or interrupt therapy as necessary and monitor for toxicity. Reduce dose further if necessary. Do not use doses higher than 400mg. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Pazopanib AUC increased 1.7-fold when coadministered with ketoconazole. More adverse events were observed when pazopanib was administered in combination with ketoconazole than when pazopanib was administered alone, which included cases of severe hypertension. In the presence of a strong CYP3A4 and P-gp inhibitor, a dose reduction to 400 mg daily may result in systemic exposure higher than that observed after administration of 800 mg pazopanib daily alone. In a minority (25%) of patients the dose of 400 mg pazopanib daily in the presence of ketoconazole resulted in systemic exposure greater than the highest systemic exposure observed after administration of 800 mg pazopanib daily alone.

Drug	Recommendation	Comments
Pemigatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose as follows: If taking 13.5 mg daily for the first 14 days of each cycle, decrease the pemigatinib dose to 9 mg; If taking 9 mg daily for the first 14 days of each cycle, decrease the pemigatinib dose to 4.5 mg. Monitor for pemigatinib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Pemigatinib AUC increased almost 1.9-fold when coadministered with itraconazole.
Pexidartinib	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Coadministration has not been studied. Pexidartinib is a moderate CYP3A4 inducer and may decrease exposure to nirmatrelvir/ritonavir. Additionally, pexidartinib AUC increased 1.7-fold when coadministered with itraconazole.
Pomalidomide	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Pomalidomide AUC increased 1.2-fold when coadministered with ketoconazole.
Ponatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose as follows: If taking 45 mg daily, reduce to 30 mg daily; If taking 30 mg daily, reduce to 15 mg daily; If taking 15 mg daily, reduce to 10 mg daily. If taking 10 mg daily, do not use nirmatrelvir/ritonavir. avoid concomitant use with strong CYP3A4 inhibitors. Monitor for ponatinib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Ponatinib AUC increased 1.8-fold when coadministered with ketoconazole.
Pralsetinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose as follows: If taking 400 mg or 300 mg daily, reduce to 200 mg daily; If taking 200 mg daily, reduce to 100 mg once daily. Monitor for pralsetinib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Pralsetinib AUC increased 3.5-fold when coadministered with itraconazole.
Procarbazine	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Coadministration has not been studied. Procarbazine is metabolized to azoprocarbazine by CYP450 (mainly CYP2B and 1A) and monoamine oxidase. Ritonavir could potentially decrease procarbazine concentrations due to induction of CYPs 2B and 1A.

Drug	Recommendation	Comments
Regorafenib	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Regorafenib AUC increased 1.3-fold when coadministered with ketoconazole. However, the AUC of both the active M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) metabolites decreased by 93%.
Relugolix	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If coadministration is unavoidable, take relugolix at least 6 hours prior to the P-gp inhibitor and monitor patients more frequently for adverse reactions. Treatment with relugolix may be interrupted for up to two weeks if a short course of treatment with a P-gp inhibitor is required. Monitor for relugolix related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir. However, if treatment with relugolix is interrupted for more than 7 days, resume administration of relugolix with a 360 mg loading dose on the first day, followed by 120 mg once daily.	Relugolix AUC increased 6.2-fold when coadministered with erythromycin (P-gp and moderate CYP3A inhibitor).
Ribociclib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose to 200 mg daily; however, there are no clinical data with this dose adjustment. Monitor for ribociclib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Ribociclib AUC increased 3.2-fold when coadministered with ritonavir.
Ripretinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for ripretinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Ripretinib AUC increased 2-fold when coadministered with itraconazole. The AUC of the active metabolite, DP-5439, also increased 2-fold in the presence of itraconazole.
Rucaparib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for rucaparib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary.	Coadministration has not been studied. Potential for increased rucaparib exposures with CYP2D6 inhibitors; ritonavir is a weak inhibitor of CYP2D6. In vitro, rucaparib is metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Clinical significance unknown.
Ruxolitinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dose by 50% if used concomitantly and monitor for toxicity. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Ruxolitinib AUC increased 1.9-fold when coadministered with ketoconazole.

Drug	Recommendation	Comments
Selinexor	Hold and start nirmatrelvir/ritonavir 24 hours after the last selinexor dose. Restart selinexor 2 days after completing nirmatrelvir/ritonavir.	Coadministration has not been studied. Selinexor is metabolized by CYP3A4, multiple UDP-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs). Selinexor is not a CYP3A4, CYP1A2, or CYP2B6 inducer. In vivo implications are not known.
Selpercatinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir Alternatively, consider reducing dose from 120 mg twice daily to 40 mg twice daily, or from 160 mg twice daily to 80 mg twice daily. Monitor for selpercatinib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Selpercatinib AUC increased 2.3-fold when coadministered with itraconazole.
Sonidegib	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Sonidegib AUC increased 2.2-fold when coadministered with ketoconazole. The magnitude of exposure change was estimated to be even higher following repeated doses of sonidegib and with continuous dosing of ketoconazole. Given long half-life (28 days), holding sonidegib is unlikely to mitigate effects of this interaction.
Sorafenib	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Sorafenib is metabolized to a moderate extent by CYP3A4 and UGT1A9, UGT1A1. Sorafenib AUC was minimally changed when coadministered with ketoconazole. However, concentrations of the active N-oxide metabolite (which accounts for only 9 to 16% of circulating metabolites and is thought to be generated by CYP3A4), were substantially decreased by ketoconazole. In another small study of 10 patients with HIV and Kaposi sarcoma, when sorafenib 200mg daily was coadministered with ritonavir, the sorafenib AUC was 28% lower compared with the sorafenib AUC in 2 patients who received sorafenib 200 mg twice daily alone. Concentrations of the active N-oxide metabolite were 74% lower in the ritonavir group. The study had to be terminated early due to poor tolerance, which could possibly be related to inhibition of CYP3A4 by ritonavir leading to the formation of more toxic metabolites.
Sotorasib	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Sotorasib is a moderate CYP3A4 inducer and may reduce concentrations of nirmatrelvir/ritonavir.

Drug	Recommendation	Comments
Sunitinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing sunitinib dose to a minimum of 37.5mg daily for 4 weeks on treatment, then 2 weeks off when treating gastrointestinal stromal tumor (GIST) or renal cell carcinoma (RCC). Decrease the sunitinib dose to a minimum of 25mg daily when treating pancreatic neuroendocrine tumor (PNET). Sunitinib dose may be reduced in 12.5 mg per day increments down to 25 mg per day in patients receiving CYP3A4 inhibitors. Monitor for sunitinib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Sunitinib and its primary active metabolite's AUC increased 1.5-fold when coadministered with ketoconazole.
Talazoparib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, if coadministration with a strong P-gp inhibitor is unavoidable, the dose should be reduced to the next lower dose. Monitor for talazoparib related toxicity if used concomitantly and interrupt therapy if necessary. Restart previous dose 2 days after completion of nirmatrelvir/ritonavir.	Talazoparib AUC increased 1.5-fold when coadministered with itraconazole. Talazoparib is a major substrate of P-gp.
Tamoxifen	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Some data suggest that tamoxifen may induce CYP metabolizing enzymes, although the clinical impact of this induction effect is not well established. Serum concentrations of letrozole (a CYP3A4 and 2D6 substrate) were decreased 38% in 12 female patients following 6 weeks of concomitant administration of tamoxifen. Additionally, ritonavir may increase tamoxifen parent concentration due to inhibition of CYP3A4 and decrease of the active metabolites (4-hydroxytamoxifen and endoxifen) due to potential moderate inhibition of CYP2D6 by ritonavir. The clinical significance of these interactions with short duration of use is expected to be low.
Temozolomide	No interaction expected.	Clearance of temozolomide should not be affected to a clinically meaningful degree by interaction of concurrent medications with specific isozymes of CYP450 nor would administration of temozolomide alter by competitive inhibition the metabolism of other drugs.

Drug	Recommendation	Comments
Tepotinib (Tepmetko)	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	The mechanism for the predicted interaction is inhibition of the CYP3A4-mediated metabolism of tepotinib and inhibition of P-gp mediated efflux of tepotinib. Coadministration had no clinically significant effect on the pharmacokinetics of midazolam (sensitive CYP3A substrate).
Thalidomide	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as thalidomide is metabolized via non-enzymatic hydrolysis.
Trametinib	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as trametinib is metabolized via deacetylation (alone or with mono-oxygenation) or in combination with glucuronidation biotransformation pathways; ≥75% unchanged drug in plasma.
Trifluridine and Tipiraci	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as thalidomide is metabolized via non-CYP P450 pathways. Trifluridine, tipiracil and its metabolite FTY did not inhibit or induce CYP3A4, 1A2 or 2B6 in vitro studies.
Triptorelin	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as thalidomide is metabolized possibly via degradation by peptidases.
Tucatinib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Tucatinib AUC was minimally changed when coadministered with itraconazole.
Umbralisib	Contraindicated (use within past 14 days). Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Coadministration has not been studied. Umbralisib is a CYP3A4 inducer and may reduce concentrations of nirmatrelvir/ritonavir. Umbralisib inhibits CYP2C8, CYP2C9, CYP2C19, and CYP3A4, but does not inhibit CYP1A2, CYP2B6, and CYP2D6. Given long terminal half-life of umbralisib (~91 hrs), enzyme induction is expected to persist.
Vandetanib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, monitor for vandetanib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary. Restart 2 days after completing nirmatrelvir/ritonavir.	Vandetanib AUC increased 1.1-fold when coadministered with itraconazole.

Drug	Recommendation	Comments
Vemurafenib	Hold and start nirmatrelvir/ritonavir 24 hours after the last vemurafenib dose. Alternatively, monitor for vemurafenib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary. Restart 2 days after completing nirmatrelvir/ritonavir.	Vemurafenib AUC increased 1.4-fold when coadministered with itraconazole. Terminal half-life ~57 hours.
Venetoclax (Venclexta)	Contraindicated. Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Venetoclax AUC increased almost 8-fold when coadministered with ritonavir 50mg once daily. This effect is expected to be more pronounced with ritonavir 100mg twice daily. Concomitant use of strong CYP3A inhibitors, such as ritonavir, with venetoclax may increase the risk of tumor lysis syndrome.
Vinblastine	Vinblastine may be held in the context of acute infection. Restart vinblastine at least 2 days after completing nirmatrelvir/ritonavir. Alternatively, vinblastine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vinblastine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Vinblastine AUC increased up to 1.6-fold when administered with boosted protease inhibitors. CYP3A4 inhibitors, including ritonavir, may increase the risk for autonomic and peripheral neurotoxicity and neutropenia.
Vincristine	Vincristine may be held in the context of acute infection. Restart vincristine no sooner than 2 days after completing nirmatrelvir/ritonavir. Alternatively, vincristine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vincristine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Increased rates of hematologic toxicity and neuropathy (including autonomic neuropathy) have been reported with concomitant use of boosted protease inhibitors and vincristine.
Vismodegib	Drug interaction not likely to be clinically relevant. Continue with standard dosing.	Vismodegib is not an inducer of CYP1A2, CYP2B6 or CYP3A. Vismodegib is a substrate of CYP2C9, CYP3A4 and P-gp in vitro. Vismodegib AUC was minimally changed when coadministered with itraconazole.
Vorinostat	No interaction expected.	Coadministration has not been studied. A clinically significant pharmacokinetic interaction is unlikely as vorinostat is metabolized via glucuronidation (UGT2B17) and hydrolysis followed by B oxidation (non CYP-mediated).

Drug	Recommendation	Comments
Zanubrutinib	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing zanubrutinib dose to 80 mg daily. Monitor for zanubrutinib related toxicity if used concomitantly and interrupt therapy or consider dose reduction if necessary. If grade 3 toxicity to zanubrutinib occurs (e.g., febrile neutropenia, thrombocytopenia with bleeding, neutropenia for 10 days or longer, etc.), interruption of zanubrutinib therapy should occur. Resume previous dose 2 days after completing nirmatrelvir/ritonavir.	Zanubrutinib AUC increased 3.8-fold when coadministered with itraconazole. Terminal half-life 2-4 hours.

AUC = Area under the curve; CYP = Cytochrome P450

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