ORIGINAL ARTICLE

Overview of Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Targeted Therapy and Supportive Care for Lung Cancer

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ABSTRACT

Introduction: Oral administration of ritonavir-boosted nirmatrelvir (Paxlovid) was found to be promising in the treatment of coronavirus disease 2019. The active antiviral component nirmatrelvir in Paxlovid is co-formulated with ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor. Many oral targeted therapies indicated for lung cancer are known substrates of CYP 3A4, and concurrent use with Paxlovid may lead to potential drug-drug interaction (DDI). The purpose of this review is to evaluate the potential DDI between targeted therapies and supportive care for lung cancer and ritonavir-boosted nirmatrelvir.

Methods: Drug database search in PubMed and the Food and Drug Administration was conducted to identify pharmacokinetic data on oral tyrosine kinase inhibitors (TKIs) used in NSCLC, both Food and Drug Administration approved and those in development. Metabolism pathways for various TKIs are extracted, and the impact of TKI area under the curves and maximum concentration by strong CYP 3A4 inducers and inhibitors is summarized. The most common toxicities and supportive care medications for the TKI were identified.

Results: Among EGFR and exon 20 insertion inhibitors, afatinib is least likely to be affected by CYP 3A4, followed by dacomitinib and osimertinib. Among ALK inhibitors, alectinib is the least susceptible to CYP 3A4. ROS1 inhibitors are affected by CYP 3A4 inhibition with the exception of crizotinib. Among MET inhibitors, capmatinib is substantially affected by CYP 3A4 inhibition. Drug exposure of RET inhibitors is expected to increase with CYP 3A4 inhibition, with selpercatinib being the least affected. Certain supportive care medications for lung cancer TKI may have relevant DDIs.

Conclusions: The clinical impact of the DDI between lung cancer TKI and ritonavir-boosted nirmatrelvir varies largely on the basis of the susceptibility of CYP 3A4 inhibition caused by the antiviral. Close monitoring and medication adjustments (i.e., dose changes or alternative coronavirus disease 2019 therapy) can be used to overcome DDI to ensure patient safety.

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Introduction

The Food and Drug Administration (FDA) issued an emergency use authorization for ritonavir-boosted nirmatrelvir (Paxlovid) on December 22, 2021, for the treatment of coronavirus disease 2019 (COVID-19). Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays a vital role in viral replication by cleaving the two viral polyproteins. Currently, nirmatrelvir is administered in tandem with ritonavir, a strong cytochrome P450 (CYP) 3A4 and 2D6 inhibitor, which has been previously used as a pharmacokinetic boosting agent to boost protease inhibitors used to treat human immunodeficiency virus. Coadministration of ritonavir prolongs the serum concentrations of nirmatrelvir to achieve the target therapeutic effect.[1]

The current recommended treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. Nevertheless, ritonavir-boosted nirmatrelvir comes with substantial drug-drug interactions (DDIs) owing to the ritonavir component of Paxlovid.[1] Hence, it is recommended that providers should carefully review patients' concomitant medications before prescribing ritonavir-boosted nirmatrelvir to evaluate for any potential DDIs. Ritonavir-boosted nirmatrelvir is contraindicated in patients who have recently (within 2 wk) received a strong CYP 3A4 inducer (such as rifampin or St. John's wort).[2]

Recent advances with the management of lung cancer have led to approval of a number of targeted therapies, which improves the prognosis and survival for a number of lung cancer subtypes. Among these targeted therapies are tyrosine kinase inhibitors (TKIs). TKIs are a group of medications that disrupt the downstream signal transduction pathways of protein kinases by various modes of inhibition.[3] TKI target-specific enzymes (e.g., EGFR, HER2, ALK, MET, BCR-ABL) are categorized as receptor tyrosine kinases, nonreceptor tyrosine kinases, or dual-specificity kinases. TKIs are indicated for treatment of various malignancies, from solid tumors, such as in breast cancer and NSCLC, to acute myelogenous leukemia. Furthermore, many of these targeted agents are orally available, which brings convenience to patients as they can conveniently receive this treatment in the outpatient setting. Unfortunately, many of these agents are also subjected to DDIs owing to their drug profile.[4] This has raised concerns about the safe use of ritonavir-boosted nirmatrelvir for COVID-19 infections in patients receiving concomitant oral TKI. The coadministration of these agents will increase the risk for severe toxicities associated with TKI (e.g., interstitial lung disease, pneumonitis, hepatotoxicity, QTc prolongation) owing to the pharmacokinetic-enhancing effects of ritonavir and the narrow therapeutic window of TKI. Another concern is the potential impact of oral TKI on ritonavir-boosted nirmatrelvir, which may alter the efficacy for treating the viral infection and safety of the medication. Therefore, the purpose of this review is to evaluate known pharmacokinetic profiles of common and emerging TKIs so that clinicians can make safe recommendations regarding the coadministration of ritonavir-boosted nirmatrelvir and TKI.

Materials and Methods

A search was conducted to identify oral TKIs that are used in NSCLC in August 2022, which were approved by the FDA, used in clinical practice for lung cancer on the basis of expert opinion, and those in development. A comprehensive search of FDA package inserts was conducted using the FDA drug database. For those TKIs in which FDA package inserts were not available, a literature search using PubMed was conducted to identify pharmacokinetic data. The search was conducted using brand, generic, and clinical trial-coded names of identified TKIs (e.g., gefitinib, erlotinib, afatinib, osimertinib, aumolertinib, furmonertinib, alectinib, brigatinib, lorlatinib, crizotinib, entrectinib, repotrectinib, taletrectinib, capmatinib, tepotinib, selpercatinib, pralsetinib, sotorasib, adagrasib, tucatinib, larotrectinib, cabozantinib, mobocertinib, dabrafenib, trametinib, MRTX849). The search was limited to English-language articles published between 2000 and August 2022. A manual search of clinical trial protocols was conducted for drugs in development and not currently approved by the FDA to identify the necessary information. Last, toxicities related to TKI were identified through package inserts, and the list of toxicities was cross-referenced with current National Comprehensive Cancer Network guidelines on supportive care.

Once oral TKIs and supportive care medications were identified, FDA package insert data for metabolism, excretion, pharmacokinetic induction, and inhibition were extracted (Supplementary Appendix). Data on the change of TKI area under the curve (AUC) and C_{max} on the basis of strong CYP 3A4 inducer (rifampin) and strong CYP 3A4 inhibitor (ketoconazole, itraconazole, or posaconazole) were also extracted. For those TKIs with no FDA package inserts, a search was conducted to identify international package inserts, primary literature, and protocols. Collected data were then consolidated to determine the impact of ritonavir-boosted nirmatrelvir on lung cancer TKIs and supportive care medications, including TKIs on ritonavir-boosted nirmatrelvir. Because no patients were included in this study, no consent was required.

Results

Impact of Lung Cancer TKI on Ritonavir-Boosted Nirmatrelvir

Because ritonavir-boosted nirmatrelvir is a substrate of CYP 3A4, induction or inhibition of CYP 3A4 by oral TKI can lead to a decreased or increased concentration of ritonavir-boosted nirmatrelvir. In fact, induction of ritonavir-boosted nirmatrelvir may potentially decrease its efficacy, and the concomitant use of strong CYP 3A4 inducers is contraindicated according to the emergency use authorization of the FDA. Conversely, inhibition of ritonavir-boosted nirmatrelvir can increase concentrations of the medication leading to increased risk of adverse effects (e.g., dysgeusia, diarrhea, hypertension, and myalgia) (Table 1).

EGFR Inhibitors (Gefitinib, Erlotinib, Afatinib, Osimertinib, Aumolertinib, Furmonertinib, Icotinib, Dacomitinib, Lazertinib). Oral TKIs that target EGFR typically are not inhibitors or inducers of CYP enzymes, apart from gefitinib, osimertinib, furmonertinib, sunvozertinib, and lazertinib. Gefitinib is an inhibitor of CYP 2C19 and 2D6, which can increase the concentration of ritonavir-boosted nirmatrelvir given that ritonavir is a minor substrate of CYP 2D6. Osimertinib is both an inducer and an inhibitor of CYP 3A4, though induction is dependent on the activation of pregnane X receptor. The CYP induction caused by osimertinib is minimal and likely will not result in substantial changes in the efficacy of ritonavir-boosted nirmatrelvir. Besides osimertinib, lazertinib is the only other EGFR inhibitor that inhibits CYP 3A4. Furmonertinib and sunvozertinib are inducers of CYP 3A4; however, the strength of induction is not well understood at this time.

EGFR Exon 20 Insertion (Mobocertinib, Sunvozertinib). Mobocertinib is a weak inducer and sunvozertinib is an inducer of CYP 3A4, which may lead to decreased concentrations of ritonavir-boosted nirmatrelvir. Currently, it is unknown whether reductions in concentration are clinically relevant.

HER2 ± HER4 Inhibitors (Tucatinib, Neratinib). Tucatinib is a strong inhibitor of CYP 3A4 and will increase concentrations of ritonavir-boosted nirmatrelvir, which increases the risk of its adverse effects. Neratinib is not an inhibitor or an inducer and is not expected to alter metabolism of ritonavir-boosted nirmatrelvir.

ALK Inhibitors (Alectinib, Brigatinib, Lorlatinib). Alectinib and brigatinib are neither inhibitors nor inducers of CYP 3A4. Lorlatinib is an inducer of CYP 3A4 and may reduce exposure of ritonavir-boosted nirmatrelvir.

ROS1 Inhibitors (Crizotinib, Entrectinib, Repotrectinib, Taletrectinib). Crizotinib, entrectinib, and repotrectinib are inhibitors of CYP 3A4 which may lead to increased concentrations of ritonavir-boosted nirmatrelvir and the associated adverse effects. Taletrectinib is neither an inducer nor an inhibitor of CYP 3A4. ROS1 inhibitors are not known to be inducers of CYP 3A4.

MET Inhibitors (Capmatinib, Tepotinib). Capmatinib and tepotinib are not inducers of inhibitors of CYP 3A4.

RET Inhibitors (Selpercatinib, Pralsetinib). Both selpercatinib and pralsetinib are inhibitors of CYP 3A which can lead to increased concentrations of ritonavir-boosted nirmatrelvir, increasing the potential for adverse effects. Because pralsetinib is a weak inducer of CYP 3A4, the concentrations of ritonavir-boosted nirmatrelvir may be decreased; however, the clinical relevance is currently unknown.

MEK/BRAF Inhibitors (Dabrafenib, Trametinib, Cobimetinib/Vemurafenib, Encorafenib/Binimetinib). Cobimetinib, vemurafenib, and encorafenib are all inhibitors of CYP 3A4, which can lead to increased concentrations of ritonavir-boosted nirmatrelvir, increasing the potential for adverse effects. Encorafenib and dabrafenib are inducers of CYP 3A4, which may lead to decreased concentrations of ritonavir-boosted nirmatrelvir, but the clinical impact of these interactions is currently unknown. Trametinib is not an inducer or inhibitor of CYP 3A4; thus, it is unlikely to cause any changes to ritonavir-boosted nirmatrelvir.

NTRK Inhibitor (Larotrectinib). Larotrectinib is an inhibitor of CYP 3A4, which can result in increased concentrations of ritonavir-boosted nirmatrelvir and its adverse effects when taken concomitantly.

KRAS p.G12C Mutations (Sotorasib, Adagrasib). Sotorasib is not an inducer or an inhibitor of CYP 3A4 and is unlikely to affect concentrations of ritonavir-boosted nirmatrelvir. Adagrasib, however, induces and inhibits CYP 3A4 enzymes. The clinical relevance of this interaction on ritonavir-boosted nirmatrelvir is currently unknown.

Multiple-Target TKIs (Cabozantinib, Anlotinib). Anlotinib is an inhibitor of CYP 3A4 which can result in increased concentrations of ritonavir-boosted nirmatrelvir and its adverse effects when taken

Table 1. Metabolism Profiles of Lung Cancer TKIs

	% of Dose Recovered (% Recovered Unchanged)		Metabolism			
TKIs	Feces	Urine	Major Substrate	Minor Substrate	Induces	Inhibits
EGFR inhibitors						
Gefitinib[6]	86	<4	CYP3A4	CYP2D6		CYP2C19, CYP2D6
Erlotinib[8]	83 (1)	8 (0.3)	CYP3A4	CYP1A2, CYP1A1		
Afatinib[5]	85 (74.8)	4 (3.52)	<2% Metabolized by FMO3, otherwise negligible			
Osimertinib[7]	68	14	CYP3A4		CYP3A4 (pregnane X dependent), CYP1A2	CYP3A4
Aumolertinib	Unknown	Unknown	CYP3A4			
Furmonertinib[55]	71.2	6.63	CYP3A4		CYP3A4	
Icotinib[56,57]			CYP3A4 CYP2C19	CYP3A5 CYP1A2		
Dacomitinib[9]	79 (20)	3 (<1)	CYP2D6	CYP3A4		
Lazertinib[58]	24 (unknown)	4.4 (unknown)	CYP3A4			CYP3A4
EGFR exon 20 insertion						
Mobocertinib[10]	76 (6)	4 (1)	CYP3A		CYP3A	
Sunvozertinib[59] (DZD9008)	Unspecified but largely feces and biliary route	CYP3A4 CYP3A5		CYP3A4		
ALK inhibitors						
Alectinib[60]	98 (84)	<0.5	CYP3A4			
Brigatinib[12]	65 (26.65)	25 (21.5)	CYP3A4 CYP2C8		CYP3A4	
Lorlatinib[13]	41 (9)	48 (<1)	CYP3A4	CYP2C8, CYP2C19, CYP3A5	CYP3A CYP2B6 CYP2C9	
ROS1 inhibitors						
Crizotinib[15]	63 (53)	22 (2.3)	CYP3A			CYP3A, CYP2B6
Entrectinib[14]	83 (36)	3	CYP3A4			CYP3A4
Repotrectinib[61]	Unknown	Unknown	CYP3A4		CYP3A4 CYP2B6	CYP2C8/9 CYP2C19 CYP3A4
Taletrectinib[62]	Unknown	Unknown	CYP3A4 CYP3A5			
MET inhibitors						
Capmatinib[16]	78 (42)	22 (negligible)	CYP3A4			CYP1A2
Tepotinib[63]	85 (45)	13.6 (7)	CYP3A4 CYP2C8			

(continued)

Table 1. Continued

TKIs	% of Dose Recovered (% Recovered Unchanged)		Metabolism			
	Feces	Urine	Major Substrate	Minor Substrate	Induces	Inhibits
RET inhibitors						
Selpercatinib[18]	69 (14)	24 (12)	CYP3A4			CYP3A, CYP2C8
Pralsetinib[17]	73 (66)	6 (4.8)	CYP3A4	CYP2D6, CYP1A2	CYP3A4, CYP3A5, CYP2C8, CYP2C9	CYP3A4, CYP3A5, CYP2C8, CYP2C9
KRAS p.G12C mutations						
Sotorasib[64]	74 (53)	6 (1)	CYP3A		CYP2C8, CYP2C9, CYP2B6	
Adagrasib	40.3 (predominately unchanged)	0.036 (predominately unchanged)	CYP3A4		CYP3A4	CYP2B6, CYP2C9, CYP3A4, CYP2D6
HER2 ± HER4 inhibitors						
Tucatinib[11]	86 (16)	4.1 (NA)	CYP2C8	CYP3A		CYP3A, CYP2C8
Neratinib[65]	91.1	1.13	CYP3A4			
NTRK inhibitor						
Larotrectinib[20]	58 (5)	39 (20)	CYP3A4			CYP3A4
MEK/BRAF inhibitors						
Dabrafenib[19]	71 (NA)	23 (NA)	CYP2C8 CYP3A4		CYP3A4, CYP2C9, CYP1A2, CYP2B	
Trametinib[66]	80 (<0.1)	20 (0.1)				CYP2C8
Cobimetinib[67]	76 (6.6)	17.8 (1.6)	CYP3A			CYP3A, CYP2D6
Vemurafenib[68]	94 (NA)	1 (NA)				CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
Encorafenib[69]	47 (5)	47 (2)	CYP3A4	CYP2C19	CYP2B6 CYP2C9 CYP3A4	CYP2B6, CYP2C8/9, CYP2D6 CYP3A4
Binimetinib[70]	62 (32)	31 (6.5)		CYP1A2 CYP2C19		
Multiple-target TKIs						
Cabozantinib[71]	54 (43)	27 (not detectable)	CYP3A4		CYP1A1	CYP2C8
Anlotinib[72,73]	2.2 (NA)	0.9 (NA)	CYP3A4 CYP3A5			CYP3A4 CYP2C9

NA, not applicable; TKI, tyrosine kinase inhibitor.

concomitantly. Cabozantinib is not known as an inhibitor or inducer of CYP 3A4.

Impact of Ritonavir-Boosted Nirmatrelvir on Lung Cancer TKI

Ritonavir-boosted nirmatrelvir is a strong inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A (Table 2). Currently, it is contraindicated to be co-administered with drugs that are highly dependent on CYP3A for clearance. In this section, we will review the interaction potential of ritonavir-boosted nirmatrelvir on various TKIs. Dose-attenuation information from manufacturers is summarized in Table 3.

EGFR Inhibitors (Gefitinib, Erlotinib, Afatinib, Osimertinib, Aumolertinib, Furmonertinib, Dacomitinib, Sunvozertinib, Lazertinib). Most EGFR inhibitors are major substrates of CYP3A4 with the exception of afatinib, dacomitinib, and lazertinib. Coadministration of ritonavir-boosted nirmatrelvir with EGFR inhibitors is expected to moderately increase the AUCs of these TKIs. In trials, coadministration of itraconazole and ketoconazole, strong CYP 3A4 inhibitors, increased the AUC of these TKIs between 66% and 84%.[5–9] Because the therapy duration for ritonavir-boosted nirmatrelvir is relatively short, the moderate increases in AUCs may put patients at risk for common side effects, including cutaneous adverse drug reactions, and gastrointestinal side effects, which may require monitoring.

EGFR Exon 20 Insertion (Mobocertinib, Sunvozertinib). Mobocertinib is a major substrate of CYP 3A, and coadministration with itraconazole and ketoconazole increased the AUC by 374% to 419%.[10] Strong CYP 3A4 inhibitors such as ritonavir-boosted nirmatrelvir will likely produce similar effects in the AUC and predispose patients to increased risk of adverse events (e.g., interstitial lung disease [ILD], pneumonitis, cardiac toxicity, and diarrhea). Sunvozertinib is also a major substrate of CYP 3A4; however, DDI data are limited because strong 3A4 inhibitors and inducers were excluded in trials.

HER2 ± HER4 Inhibitors (Tucatinib, Neratinib). Neratinib is a major substrate of CYP 3A4 in contrast to tucatinib, which is a minor substrate. Despite tucatinib being a minor CYP 3A4 substrate, 200 mg twice-daily administration of itraconazole increased tucatinib's AUC and C_{max} by 30%.[11] Coadministration of neratinib with ketoconazole increased the AUC by 481% and C_{max} by 321%. These increases in drug exposure can increase risk for key adverse class effects (e.g., severe diarrhea and hepatotoxicity).

ALK Inhibitors (Alectinib, Brigatinib, Lorlatinib). All ALK inhibitors are major substrates of CYP 3A4. Of note, there was no major change with alectinib in the presence of strong CYP 3A4 inhibitors and inducers. Coadministration with itraconazole increased the AUC of brigatinib and lorlatinib by 101% and 42%, respectively.[12,13] Given that ritonavir-boosted nirmatrelvir has similar or possibly higher CYP 3A4 inhibiting potential as itraconazole and posaconazole, the concomitant use of ALK inhibitors and ritonavir-boosted nirmatrelvir will result in similar supratherapeutic concentrations of ALK inhibitors and associated adverse effects (e.g., hepatotoxicity, pneumonitis, ILD, visual disturbances).

ROS1 Inhibitors (Crizotinib, Entrectinib, Repotrectinib, Taletrectinib). Both crizotinib and entrectinib are major substrates of CYP 3A4. Coadministration with ketoconazole and itraconazole has led to increased AUCs in crizotinib and entrectinib by 216% and 500%, respectively.[14,15] This makes entrectinib the most vulnerable to strong CYP 3A4 inhibition by ritonavir-boosted nirmatrelvir with the highest risk for causing adverse effects such as hepatotoxicity, QTc prolongation, ILD, and visual loss. DDI data are limited for repotrectinib and taletrectinib because strong CYP 3A4 inducers and inhibitors were excluded from trials.

MET Inhibitors (Capmatinib, Tepotinib). Capmatinib and tepotinib are both major substrates of CYP 3A4. Coadministration of itraconazole increased the AUC of capmatinib by 421%.[16] This increased drug exposure can lead to a considerable risk of adverse events (e.g., ILD, hepatotoxicity, photosensitivity). The effect of strong CYP 3A4 inhibitors on tepotinib has not been studied, but on the basis of the manufacturer's package insert, concomitant use with dual strong CYP 3A4 inhibitors and P-gp inhibitors should be avoided.

RET Inhibitors (Selpercatinib, Pralsetinib). Both selpercatinib and pralsetinib are major substrates of CYP 3A4. In clinical trials, the coadministration of itraconazole with selpercatinib and pralsetinib increased the AUCs of these agents by 133% and 251%, respectively.[17,18] Increased drug exposure can potentially lead to an increased risk of adverse effects (e.g., hepatotoxicity, QTc prolongation, hemorrhagic events, impaired wound healing).

MEK/BRAF Inhibitors (Dabrafenib, Trametinib, Cobimetinib/Vemurafenib, Encorafenib/Binimetinib). Trametinib, vemurafenib, and binimetinib are not substrates of CYP

Table 2. CYP3A4 Enzyme Interaction With Various TKIs

TKIs	Change of TKI AUC and C_{max}	
	Rifampin (Strong CYP3A4 Inducer)	Ketoconazole/Itraconazole /Posaconazole (Strong CYP3A4 Inhibition)
EGFR inhibitors		
Gefitinib	↓ AUC 58%	↑AUC 80%
Erlotinib	↓ AUC 57.6%-80%	↑AUC 66%
Afatinib	Unlikely or negligible	Unlikely or negligible
Osimertinib	↓ AUC 78%	↑ AUC 24%, ↓ C_{max} 20%
Aumolertinib	Unknown	Unknown
Furmonertinib	↓ AUC 86%, ↓ C_{max} 60%	↑ AUC 1.4× (41%), ↑ C_{max} 23%
Icotinib	Unknown	↑ AUC 67%-84%
Dacomitinib	Unknown	Unknown
Lazertinib	Unknown	Unknown
EGFR exon 20 insertion		
Sunvozertinib (DZD9008)	Strong CYP3A4 inhibitors and inducers were stopped before administration of sunvozertinib per protocol	
Mobocertinib	↓ AUC 92%	↑ AUC 374%-419%
ALK inhibitors		
Alectinib	No effects observed	
Brigatinib	↓ AUC 80%, ↓ C_{max} 60%	↑ AUC 101%, ↑ C_{max} 21%
Lorlatinib	↓ AUC 85%, ↓ C_{max} 76%	↑ AUC 42%, ↑ C_{max} 24%
ROS1 inhibitors		
Crizotinib	↓ AUC 84%, ↓ C_{max} 79%	↑ AUC 216%, ↑ C_{max} 44%
Entrectinib	↓ AUC 77%, ↓ C_{max} 56%	↑ AUC 6×, ↑ C_{max} 1.7×
Repotrectinib	Excluded from study	Excluded from study
Taletrectinib	Excluded from study	Excluded from study
MET inhibitors		
Capmatinib	↓ AUC 67%, ↓ C_{max} 56%	↑ AUC 421%, ↑ C_{max} 0%
Tepotinib	Unknown	Unknown
RET inhibitors		
Selpercatinib	↓ AUC 87%, ↓ C_{max} 70%	↑ AUC 133%, ↑ C_{max} 30%
Pralsetinib	↓ AUC 68%, ↓ C_{max} 30%	↑ AUC 251%, ↑ C_{max} 84%
KRAS p.G12C mutations		
Sotorasib	↓ AUC 51%, ↓ C_{max} 25%	
Adagrasib	↓ AUC 95%, ↓ C_{max} 88%	↑ AUC 400%, ↑ C_{max} 200%
HER2 ± HER4 inhibitors		
Tucatinib	↓ AUC 0.6×, ↓ C_{max} 0.5×	↑ AUC 1.3×, ↑ C_{max} 1.3×
Neratinib	↓ AUC 87%, ↓ C_{max} 76%	↑ AUC 481%, ↑ C_{max} 321%
NTRK inhibitor		
Larotrectinib	↓ AUC 81%, ↓ C_{max} 71%	↑ AUC 4.3×, ↑ C_{max} 2.8×
MEK/BRAF inhibitors		
Dabrafenib	↓ AUC 34%	↑ AUC 71%
Trametinib	Unknown	Unknown
Cobimetinib	↓ AUC 83%	↑ AUC 90%
Vemurafenib	↓ AUC 40%	NA
Encorafenib	Unknown	↑ AUC 200%, ↑ C_{max} 68%,
Binimetinib	Unknown	Unknown
Multiple-target TKIs		
Cabozantinib	↓ AUC 77%	↑ AUC 38%
Anlotinib	Unknown	Unknown

AUC, area under the curve; NA, not applicable; TKI, tyrosine kinase inhibitor.

3A4 and unlikely to be affected by strong CYP 3A4 inhibition by ritonavir-boosted nirmatrelvir. Dabrafenib is a major substrate of CYP 3A4 and coadministration with ketoconazole increased the AUC of dabrafenib by 71%.[19] Cobimetinib coadministration with itraconazole increased AUC by 90%. Encorafenib coadministration with

Table 3. Dose-Attenuation Recommendations Related to CYP3A4 on the basis of Package Inserts

TKIs	Dose-Attenuation Recommendations
EGFR inhibitors	
Gefitinib	• Strong CYP3A4 inducers: ↑ dose to 500 mg daily • Strong CYP3A4 inhibitors: use with caution
Erlotinib	• Strong CYP3A4 inducers: consider an alternative agent, increase dose to a maximum of 450 mg daily • Strong CYP3A4 inhibitors: use with caution
Afatinib	Not applicable
Osimertinib	• Strong CYP3A4 inducers: avoid use if possible, increase to max 160 mg daily and then resume 80 mg daily 3 wk after discontinuing inducer • Strong CYP3A4 inhibitors: no clinically relevant effect observed, use with caution
Aumolertinib	• Not available
Furmonertinib	• Strong CYP3A4 inducers: caution • Strong CYP3A4 inhibitors: generally safe and well tolerated; no strong data to suggest dose adjustment yet.
Icotinib	• Not available
Dacomitinib	• Not available
Lazertinib	• Strong CYP3A4 inducers: not well studied, avoid use if possible • Strong CYP3A4 inhibitors: not well studied. in the absence of an alternative drug, monitor closely for signs of changes in the tolerability of lazertinib (e.g., QTc prolongation, cardiotoxicity, keratitis, LFTs)
EGFR exon 20 insertion	
Mobocertinib	• Strong CYP3A inducers: avoid use • Strong CYP3A inhibitors: avoid use; if unavoidable, reduce the dose by approximately 50%.
Sunvozertinib (DZD9008)	• On the basis of in vitro data and clinical exposure, DZD9008 DDI risk is considered unlikely to cause clinically relevant hepatic drug interactions at clinically relevant concentrations through inhibition or induction of cytochrome P450 enzyme activity
ALK inhibitors	
Alectinib	Not applicable
Brigatinib	• Strong CYP3A4 inducers: avoid use; if unavoidable, increase dose by 30 mg increments once daily up to maximum of twice the original dose • Strong CYP3A4 inhibitors: avoid use; if unavoidable, decrease dose by 50%
Lorlatinib	• Strong CYP3A inducers: Contraindicated (potential risk of hepatotoxicity); discontinue strong CYP3A inducers for 3 plasma half-lives before initiating. • Strong CYP3A inhibitors: avoid use; if unavoidable, reduce starting dose from 100 mg once daily to 75 mg once daily. If starting dose is reduced to 75 mg owing to adverse reactions, then reduce further to 50 mg before starting strong CYP3A inhibitor.
ROS1 inhibitors	
Crizotinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: avoid use; if unavoidable, reduce dose to 250 mg once daily
Entrectinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: $>$ 12 yo $+$ BSA $>$ 1.5 m^2, reduce dose to 100 mg once daily if cannot be avoided; if BSA $\leq$ 1.5 m^2 avoid use
Repotrectinib	Strong CYP3A4 inducers and inhibitors were excluded from the protocol
Taletrectinib	Strong CYP3A4 inducers and inhibitors were excluded from the protocol
MET inhibitors	
Capmatinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: closely monitor for adverse reactions
Tepotinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: avoid use
RET inhibitors	
Selpercatinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: avoid use; if unavoidable, then reduce 160 mg twice daily dose to 80 mg twice daily and 120 mg twice daily dose to 40 mg twice daily

(continued)

Table 3. Continued

TKIs	Dose-Attenuation Recommendations
Pralsetinib	• Strong CYP3A4 inducers: double the dose on day 7 of the inducer until 14 d after discontinuation of inducer • Strong CYP3A4 inhibitors: avoid use; if unavoidable, then reduce 400 mg once daily to 200 mg, 300 mg once daily to 200 mg, 200 mg once daily to 100 mg
KRAS p.G12C mutations	
Sotorasib	• Strong CYP3A4 inducers: avoid use
Adagrasib	• Strong CYP3A4 inhibitors and inducers: early in study, use an alternative concomitant medication
HER2 ± HER4 inhibitors	
Tucatinib	• Strong CYP3A4 inducers: avoid use • Strong CYP2C8 inhibitors: avoid use; if unavoidable, then reduce 100 mg twice daily
Neratinib	• Strong CYP3A4 inducers: avoid use • Strong CYP3A4 inhibitors: avoid use
NTRK inhibitor	
Larotrectinib	• Strong CYP3A4 inducer: avoid use; if unavoidable, then double the dose • Strong CYP3A4 inhibitor: avoid use; if unavoidable, then reduce the dose by 50%
MEK/BRAF inhibitors	
Dabrafenib	• Strong CYP3A4 inhibitors: avoid use; if unavoidable, then monitor closely for adverse reactions
Trametinib	• n combination with dabrafenib, refer to dabrafenib labeling for dose adjustments
Cobimetinib	• Strong CYP3A4 inducers: avoid use, may decrease systemic exposure by more than 80% • Strong CYP3A4 inhibitors: avoid use, especially in patients already taking reduced doses (e.g., 40 or 20 mg daily)
Vemurafenib	• Strong CYP3A4 inducers: avoid use; if unavoidable, increase dose by 240 mg (one tablet) • Strong CYP3A4 inhibitors: avoid use, in vitro reveals as a CYP3A4 substrate but no data in vivo
Encorafenib	• Strong CYP3A4 inducers: avoid coadministration. Current data suggest auto-induction owing to reduced steady-state concentrations compared with initiation concentrations after the first dose. • Strong CYP3A4 inhibitors: reduce dose by one-third. After inhibitor has been discontinued for three to five half-lives, resume normal dose.
Binimetinib	• No clinically important drug interactions have been observed and are not a substrate of CYP3A4
Multiple-target TKIs	
Cabozantinib	• Strong CYP3A4 inducers: increase the daily dose by 20 mg • Strong CYP3A4 inhibitors: reduce the daily dose by 20 mg
Anlotinib	• Not available

BSA, body surface area; DDI, drug-drug interaction; LFT, liver function test; TKI, tyrosine kinase inhibitor.

posaconazole increased AUC by 200% and C_{max} by 68%. Increases in concentrations of these agents may pose a higher risk of adverse effects (e.g., diarrhea, nausea, fatigue, and electrolyte abnormalities).

NTRK Inhibitor (Larotrectinib). Larotrectinib is a major substrate of CYP 3A4, and coadministration with itraconazole increased the AUC of larotrectinib by 4.3 times.[20] This increase in drug exposure may magnify the risk for central nervous system adverse events (dizziness, cognitive impairment, mood disorders, sleep disturbances), fractures, and hepatotoxicity.

KRAS p.G12C Mutations (Sotorasib, Adagrasib). Sotorasib is a major substrate of CYP 3A4; however, no clinically meaningful effect on the exposure of sotorasib was observed after coadministration with itraconazole. Adagrasib is also a major substrate for CYP 3A4, and the presence of strong CYP 3A4 inhibition by itraconazole can lead to an AUC increase of 400%. There is an expected corresponding increase, but different magnitude of impact on AUC with ritonavir-boosted nirmatrelvir co-administration.

Multiple-Target TKIs (Cabozantinib, Anlotinib). Cabozantinib and anlotinib are both major substrates of

CYP 3A4. Co-administration with ketoconazole for 27 days increased AUC of cabozantinib by 38%. Data are limited on the effect of co-administration of strong CYP 3A4 inhibitors on anlotinib.

Impact of Ritonavir-Boosted Nirmatrelvir on Supportive Care Medications

Most often, patients diagnosed with having lung cancer receive supportive care medications for managing associated cancer- and treatment-induced toxicities. Patients receiving lung cancer TKI often experience nausea/vomiting, gastrointestinal toxicities (e.g., diarrhea), and dermatologic toxicities that can affect their quality of life. In this section, we will focus on the potential DDI of ritonavir-boosted nirmatrelvir on various supportive care medications.

Nausea and Vomiting. Aprepitant, prednisone, and dexamethasone are all major substrates of CYP 3A4, whereas granisetron and ondansetron are minor substrates. Co-administration of strong CYP 3A4 inhibitors with aprepitant is not recommended because it can cause an increase in serious adverse events (e.g., hypotension and bradycardia). Concomitant use of strong CYP 3A4 inhibitors with corticosteroids (e.g., dexamethasone, prednisone) should be used with caution, for a limited amount of time, and patient monitoring for side effects is recommended. The 5-HT3 inhibitors (e.g., granisetron, ondansetron) are the least affected by strong CYP 3A4 inhibitors and should be used first line before other antiemetics are considered. Adverse effects associated with 5-HT3 inhibitors include constipation, headaches, and QTc prolongation, and they may be exacerbated with concomitant ritonavir-boosted nirmatrelvir.

Gastrointestinal Toxicities. Loperamide is a minor substrate of CYP 3A4, whereas diphenoxylate/atropine is not a substrate of CYP 3A4. Co-administration of loperamide with strong CYP 3A4 inhibitors such as ritonavir has resulted in an increase of AUC from 104 ± 60 h × pmol/mL after placebo to 276 ± 68 h.[21] Patients receiving loperamide and ritonavir-boosted nirmatrelvir should be monitored for nausea and constipation. Diphenoxylate/atropine is not expected to have clinically relevant changes in AUC during co-administration with strong CYP 3A4 inhibitors.

Dermatologic Toxicities. Patients receiving TKI most often receive antibiotics, antipyretics, antihistamines, and topical agents for managing dermatologic toxicities. Within the tetracycline family, only tetracycline is expected to interact with ritonavir-boosted nirmatrelvir, as it is a minor substrate of CYP 3A4.[22] Drug exposure is not expected to change substantially with doxycycline and tetracycline during the co-administration of strong CYP 3A4 inhibitors.[22,23] Erythromycin is a major substrate of CYP 3A4, and co-administration of strong CYP 3A4 inhibitors should be avoided in patients at increased risk of adverse effects (e.g., QTc prolongation).[24] Clindamycin is a substrate of CYP 3A4 and co-administration of strong CYP 3A4 inhibitor may also increase the concentration of clindamycin.[25] Monitoring for adverse effects associated with clindamycin is recommended. Triamcinolone is a substrate of CYP 3A4, and coadministration of strong CYP 3A4 inhibitors may lead to serious glucocorticoid toxicities (e.g., iatrogenic Cushing's syndrome), even with topical administration.[26] Loratadine is most often used for managing pruritus related to oral TKIs. CYP 3A4 is not a major part of loratadine metabolism, suggesting it is safe to use in conjunction with ritonavir-boosted nirmatrelvir.[27] Last, antipyretics such as ibuprofen and acetaminophen are not metabolized by the CYP 3A4 system and thus are unaffected by concomitant ritonavir-boosted nirmatrelvir.[28,29]

Cancer-Associated Pain. Patients with lung cancer most often require analgesics to relieve their cancer-associated pain. Among opioids, tramadol, methadone, hydrocodone, oxycodone, fentanyl, and buprenorphine are major substrates of CYP3A4, and coadministration of strong CYP 3A4 inhibitors should be carefully monitored for potential adverse effects (e.g., life-threatening respiratory depression, sedation, hypotension), and a dose reduction should be considered.[30–35] Codeine is primarily metabolized to morphine by CYP 2D6 and norcodeine by CYP 3A4, and coadministration with strong CYP3A4 inhibitors may result in an increase in codeine plasma concentrations with subsequently greater metabolism by CYP 2D6 resulting in greater morphine levels; thus, a dose reduction should be considered.[36] In contrast, oxymorphone, tapentadol, morphine, and hydromorphone are not metabolized by CYP 3A4 and therefore are not expected to considerably increase plasma concentrations, suggesting they are safe to use in conjunction with ritonavir-boosted nirmatrelvir.[37–40] As mentioned previously, ibuprofen and acetaminophen, used as both antipyretics and nonopioid analgesics, are not metabolized by the CYP 3A4 system and thus are unaffected by concomitant use of ritonavir-boosted nirmatrelvir.[28,29]

Cancer-Associated Venous Thromboembolism. Direct oral anticoagulants and low molecular weight heparin are widely used and preferred to treat cancer-associated venous thromboembolisms in patients with lung cancer. Among preferred direct oral anticoagulants, apixaban

and rivaroxaban are major substrates of CYP 3A4, whereas edoxaban is not a substrate of CYP 3A4 and thus unlikely unaffected by CYP 3A4 inhibition.[41–43] If apixaban is co-administered with ritonavir-boosted nirmatrelvir, a dose reduction to 2.5 mg twice daily should be made, along with close monitoring of signs and symptoms of bleeding. There is no current dose-reduction recommendation for rivaroxaban coadministration with CYP 3A4 inhibitors; however, use should be avoided if possible, and if it is unavoidable, signs and symptoms of bleeding should be closely monitored. Enoxaparin and dalteparin are not substrates of CYP 3A4 and thus are not affected by coadministration of ritonavir-boosted nirmatelvir.[44,45] In some cases, clinicians may use dabigatran, fondaparinux, and warfarin. The R-enantiomer of warfarin is metabolized by CYP 3A4; thus, coadministration of warfarin with ritonavir-boosted nirmatrelvir is discouraged.[46] Dabigatran and fondaparinux are not metabolized by CYP 3A4 and therefore are unaffected by concomitant use of ritonavir-boosted nirmatrelvir.[45,47]

Discussion

In this review, we have identified a number of potential DDIs between lung cancer TKIs and ritonavir-boosted nirmatrelvir. Lung cancer TKIs are most often substrates of CYP 3A4, and knowing that ritonavir-boosted nirmatrelvir is a strong inhibitor of CYP 3A4, potential DDIs can occur when co-administered. Although ritonavir is a strong inhibitor of CYP 3A4, the degree of CYP 3A4 inhibition varies depending on the TKI and the dose and duration of the inhibitor. Clinical pharmacologic studies have summarized the degree of drug concentration increase. For instance, coadministration of capmatinib and itraconazole (a strong CYP 3A4 inhibitor) can result in a 421% increase in AUC, whereas coadministration of osimertinib and itraconazole only resulted in a 24% increase in AUC. Because strong CYP 3A4 inhibitors can cause changes to exposure of TKI and potentiate adverse effects, the concomitant use of such agents with TKI is not recommended and should be identified and avoided if possible. Of note, a few of the TKI are known substrates of CYP 3A4 and may potentially have increased exposure when co-administered with ritonavir-boosted nirmatrelvir; however, there is a lack of published pharmacologic studies that would allow a thorough evaluation of the impact of drug exposure owing to strong CYP 3A4 inducers or inhibitors. The current manufacturer's prescribing information does not contraindicate the concurrent use of ritonavir-boosted nirmatrelvir with CYP 3A4 inhibitors, such as in other ritonavir-based therapies, but it recommends monitoring. Nevertheless, if ritonavir-boosted nirmatrelvir must be used with potentially interacting TKI, careful monitoring for toxicities is advised.

DDIs are most often observed within oncology practice, especially with the wider use of oral TKI to treat various malignancies, such as lung cancers. Nevertheless, such interactions may also affect efficacy and safety of the various TKIs. For example, coadministration of imatinib (a drug to treat chronic myelogenous leukemia) and voriconazole (a strong CYP 3A4 inhibitor) is known to cause severe pustular eruption.[48] On the basis of the recommendation of the FDA, drugs that increase the AUC of sensitive index substrates of CYP 3A by five or more folds are considered as strong inhibitors of CYP 3A4.[49] These drugs include the various antifungals (itraconazole, ketoconazole, posaconazole, voriconazole), antibiotics (clarithromycin), diltiazem, several antivirals (ritonavir, nelfinavir, boceprevir, telaprevir), and neurologic agents, such as nefazodone. Grapefruit juice, grapefruit, and Seville oranges are also known to strongly inhibit CYP 3A4. Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates by greater than or equal to fivefold, greater than or equal to twofold to less than fivefold, and greater than or equal to 1.25-fold to less than twofold, respectively.[49] Nevertheless, the extent to which strong CYP 3A4 inhibitors affects the exposure of each TKI may vary between each drug. This article has provided an extensive review of the impact of strong CYP3A4 inhibitors that can be extrapolated to ritonavir-boosted nirmatrelvir.

Current guidelines of the National Institutes of Health stated that because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for COVID-19, DDIs resulting in increased drug exposure should not preclude the use of this medication if they can be safely managed.[1] In view of the need to initiate ritonavir-boosted nirmatrelvir for treatment of COVID-19, clinicians may choose to temporarily interrupt TKI therapies in view of the interaction. Furthermore, in view that there is an increased use of off-label prolonged therapy (as long as 10 d total) of ritonavir-boosted nirmatrelvir in clinical practice owing to COVID-19 rebound that may happen as early as day 7 (3.53%) after initiation of ritonavir-boosted nirmatrelvir,[50] prolonged treatment should be evaluated on a case-by-case scenario on the basis of risk factors and patient-specific factors to determine whether a prolonged or second 5-day course is necessary. With prolonged use of ritonavir-boosted nirmatrelvir, it is important to ensure that any modification with TKI should be continued for 3 additional days after the end of ritonavir-boosted nirmatrelvir.

Temporary reduction of TKI doses is a potential strategy for managing the drug interaction between strong CYP 3A4 inhibition. Inhibition of this enzyme

system can result in higher exposure of TKI and might allow for lower dosages to minimize adverse effects and reduce health care costs. In an open-label, crossover study, investigators compared the pharmacokinetics of monotherapy erlotinib 150 mg once daily (control arm) with erlotinib 75 mg daily plus ritonavir 200 mg daily (intervention arm).[51] The authors concluded that the pharmacokinetic exposure at a dose of 75 mg erlotinib when combined with ritonavir was similar to 150 mg erlotinib. In fact, the authors concluded that ritonavir boosting is a promising strategy to reduce erlotinib treatment costs and provides a rationale for other expensive therapies metabolized by CYP 3A4. In contrast, if the decision is to temporary hold oral TKI while patient is receiving ritonavir-boosted nirmatrelvir, it is recommended that the oral TKI should be held for 3 additional days, in view of the inhibitor effect that can last 3 additional days post-drug administration.

An alternative strategy to holding TKI or making TKI dose adjustments would be to use the other oral antiviral with emergency use authorization to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), molnupiravir. In contrast to ritonavir-boosted nirmatrelvir, molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by inducing RNA mutagenesis.[52] Molnupiravir does not require a pharmacokinetic booster (i.e., ritonavir) and is not an inhibitor or an inducer of any major human CYP enzymes; therefore, it will likely not interact with TKI by CYP enzymes.[53] With respect to efficacy, the phase 3 portion of the clinical trial (MOVe-OUT) revealed that molnupiravir had an absolute reduction of hospitalization or death by 3% and adjusted relative risk reduction of 30% compared with placebo.[54] In comparison, the phases 2 to 3 randomized clinical trial that evaluated ritonavir-boosted nirmatrelvir revealed a 5.8% absolute reduction and 89% relative risk reduction in hospitalization or death owing to SARS-CoV-2.[54]

Last, we have also observed that TKI within the same class may have different DDI potential. Providers who are newly initiating oral TKI must consider the potential risks of DDI with other medications for treatment of comorbid conditions. Nevertheless, for patients who have already been stabilized with a specific TKI, it may be challenging to switch from one TKI to another in view of the temporary DDI with ritonavir-boosted nirmatrelvir. Providers must exercise their professional judgment to decide on how best to concurrently administer ritonavir-boosted nirmatrelvir and TKI to prevent any adverse drug events. Providers should also consider consulting an oncology pharmacist to optimize the dosing strategies of the TKI.

In conclusions, with the recent advancements in COVID-19 treatments, the wide use of ritonavir-boosted nirmatrelvir may increase the risk of patients with lung cancer for unwanted morbidities owing to DDIs. In this review, we have identified a number of potential DDIs between lung cancer TKIs and ritonavir-boosted nirmatrelvir. Nevertheless, the impact of the interaction between these TKIs and ritonavir-boosted nirmatrelvir varies largely on the basis of the susceptibility of CYP 3A4 inhibition of the TKI. Clinicians must be diligent in assessing the risk of interactions before the prescribing of ritonavir-boosted nirmatrelvir in patients with lung cancer and should consider strategies to overcome DDIs and consulting an oncology pharmacist to optimize the dosing of the TKI.

CRediT Authorship Contribution Statement

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100452.

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