



A Review of CYP3A Drug-Drug Interaction Studies: Practical Guidelines for Patients Using Targeted Oral Anticancer Drugs

Laura Molenaar-Kuijsten^{1*}, Dorieke E. M. Van Balen¹, Jos H. Beijnen^{1,2}, Neeltje Steeghs³ and Alwin D. R. Huitema^{1,4,5}

¹Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek, Amsterdam, Netherlands, ²Department of Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands, ³Department of Medical Oncology and Clinical Pharmacology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek, Amsterdam, Netherlands, ⁴Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, ⁵Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

OPEN ACCESS

Edited by:

Caroline Flora Samer,
Geneva University Hospitals (HUG),
Switzerland

Reviewed by:

Chakradhara Rao Satyanarayana
Uppugunduri,
Université de Genève, Switzerland
Roland Wolf,
University of Dundee, United Kingdom

*Correspondence:

Laura Molenaar-Kuijsten
l.kuijsten@nki.nl

Specialty section:

This article was submitted to
Pharmacogenetics and
Pharmacogenomics,
a section of the journal
Frontiers in Pharmacology

Received: 22 February 2021

Accepted: 06 August 2021

Published: 30 August 2021

Citation:

Molenaar-Kuijsten L, Van Balen DEM, Beijnen JH, Steeghs N and Huitema AD (2021) A Review of CYP3A Drug-Drug Interaction Studies: Practical Guidelines for Patients Using Targeted Oral Anticancer Drugs. *Front. Pharmacol.* 12:670862. doi: 10.3389/fphar.2021.670862

Many oral anticancer drugs are metabolized by CYP3A. Clinical drug-drug interaction (DDI) studies often only examine the effect of strong CYP3A inhibitors and inducers. The effect of moderate or weak inhibitors or inducers can be examined using physiologically based pharmacokinetic simulations, but data from these simulations are not always available early after approval of a drug. In this review we provide recommendations for clinical practice on how to deal with DDIs of oral anticancer drugs if only data from strong CYP3A inhibitors or inducers is available. These recommendations were based on reviewed data of oral anticancer drugs primarily metabolized by CYP3A and approved for the treatment of solid tumors from January 1st, 2013 to December 31st, 2015. In addition, three drugs that were registered before the new EMA guideline was issued (i.e., everolimus, imatinib, and sunitinib), were reviewed. DDIs are often complex, but if no data is available from moderate CYP3A inhibitors/inducers, a change in exposure of 50% compared with strong inhibitors/inducers can be assumed. No *a priori* dose adaptations are indicated for weak inhibitors/inducers, because their interacting effect is small. In case pharmacologically active metabolites are involved, the metabolic pathway, the ratio of the parent to the metabolites, and the potency of the metabolites should be taken into account.

Keywords: drug interaction, cytochrome P450 enzyme, CYP3A inhibitor, CYP3A inducer, cancer, kinase inhibitor

INTRODUCTION

Oral targeted anticancer drugs are important drugs for the treatment of cancer. Most oral anticancer drugs are metabolized by CYP3A; therefore, patients are at risk for drug-drug interactions (DDI). Because many of these drugs show an exposure-efficacy and an exposure-toxicity relationship, a change in exposure to these drugs can be highly relevant (Verheijen et al., 2017; Groenland et al., 2019). This change in exposure as a consequence of a DDI could result in adverse events if exposure is increased, or treatment failure if exposure is decreased (in case of prodrugs vice versa).

DDI studies are performed before registration of a drug, based on the metabolism of the drug and following the recommendations of the EMA and FDA (Food and Drug Administration. Center for Drug

Evaluation and Research, 2009; Food and Drug Administration. Center for Drug Evaluation and Research, 2020a; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2014a). These studies use strong CYP3A inhibitors (e.g., itraconazole or ketoconazole) and inducers (e.g., rifampin) since the guidelines of the EMA and FDA advise a worst-case approach. Subsequently, the effects of moderate and weak inhibitors or inducers are extrapolated from these data using physiologically based pharmacokinetic (PBPK) simulations (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015a; Food and Drug Administration. Center for Drug Evaluation and Research, 2020a). In short, conducting a PBPK simulation consists of three steps: model development, model verification, and model application. First a physiologically based model is built for the substrate and interacting drug (for the latter also the SimCYP library can be used), including for example PK data. Secondly, the models are verified, e.g., by simulating a concentration-time profile and comparing it with the data from clinical studies. Subsequently, the two models are linked and drug-drug interactions can be simulated. Before the effects of moderate and weak inhibitors and inducers can be predicted, first the models should be verified using data from clinical DDI studies with strong inhibitors and inducers. The use of PBPK models is described in several guidelines of the FDA (Food and Drug Administration. Center for Drug Evaluation and Research, 2018; Food and Drug Administration. Center for Drug Evaluation and Research, 2020a; Food and Drug Administration. Center for Drug Evaluation and Research, 2020b). There is, however, a critical problem with the above described DDI studies performed before drug approval. Despite the fact that moderate and weak inhibitors and inducers are far more frequently used than the strong CYP3A inhibitors and inducers, clinical data on moderate and weak inhibitors and inducers is often lacking. This problem is partly overcome by the, increasingly performed, PBPK simulations. But, data from these PBPK simulations are not always available early after approval of a drug. This is for example the case for drugs that are conditionally approved, as is the case for, for instance, larotrectinib, and lorlatinib (Food and Drug Administration, 2017; Food and Drug Administration, 2018; Chen et al., 2020; Patel et al., 2020).

To determine which drugs might influence the metabolism of oral anticancer drugs, the Flockhart Table can be consulted (Flockhart, 2007). The Flockhart Table displays drugs that inhibit or induce specific CYP enzymes, for example CYP3A (Flockhart, 2007). The interacting drugs are placed in groups according to the inhibition or induction capacity, and are classified in broad ranges. Weak inhibitors increase the AUC by ≥ 1.25 – <2 -fold, moderate inhibitors by ≥ 2 – <5 -fold, and strong inhibitors by ≥ 5 -fold (Flockhart, 2007; Food and Drug Administration. Center for Drug Evaluation and Research, 2020a). Weak inducers decrease the AUC by ≥ 20 – $<50\%$, moderate inducers by ≥ 50 – $<80\%$, and strong inducers by $\geq 80\%$ (Food and Drug Administration, 2020a).

The aim of this review was to provide recommendations for clinical practice on how to deal with DDIs of oral anticancer drugs if only data from strong CYP3A inhibitors or inducers is available. To achieve this goal, we compared results from DDI

studies with strong inhibitors or inducers with results with moderate or weak inhibitors or inducers, to extrapolate results to clinical practice and formulate an advice on how to deal with DDIs for which data is lacking.

METHODS

Oral anticancer drugs, used for the treatment of solid tumors, were selected based on their metabolism and year of approval. On January 1st, 2013, the EMA guideline on the investigation of DDIs came into effect (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015b). To allow several years of follow-up after approval, in which clinical DDI studies with these drugs might be conducted, an inclusion cut-off in December 2015 was chosen. Therefore, all drugs primarily metabolized by CYP3A and approved for the treatment of solid tumors from January 1st, 2013 to December 31st, 2015 were selected. In addition, we included three drugs that were registered before the new EMA guideline was issued (i.e., everolimus, imatinib, and sunitinib), to illustrate how DDI studies were performed with the prior guideline. An overview of the drug selection is shown in **Figure 1**. Firstly, the US FDA Clinical Pharmacology and Biopharmaceutics Review and the Summary of Product Characteristics of these drugs were studied for data on DDI studies. Second, PubMed was searched using the search terms (drug name) AND [drug-drug interaction (study)] OR (drug name of most used potent inhibitor and inducer). Furthermore, citation snowballing was used to find other articles of interest. The articles, including case reports, in which no AUCs were reported, or in which the dose of the victim drug was different between the control group and group with combination treatment, and *in vitro* studies were excluded. We searched the articles for the change in AUC (preferably the $AUC_{0-\infty}$) of the victim drug in combination with the studied CYP3A inhibitor or inducer, compared with administration of the victim drug alone. We visualized this by making graphs using the ratios of adjusted means of the combination versus the victim drug alone, whereby the victim drug alone was rated as 100% exposure. The studied inhibitors and inducers were grouped according to their interaction potential, which was reported in the reviewed articles and checked with the Flockhart Table (Flockhart, 2007).

RESULTS

Table 1 gives a summary of the DDI studies of the twelve selected oral anticancer drugs. In **Table 2** a detailed overview of the results is shown. The results are described for the drugs without active metabolites first and for the drugs with active metabolites thereafter.

Drugs Without Active Metabolites Ceritinib

When the strong CYP3A inhibitor ketoconazole was combined with a single-dose of ceritinib, the $AUC_{0-\infty}$ of ceritinib increased by 190% ($n = 19$) (Food and Drug Administration,

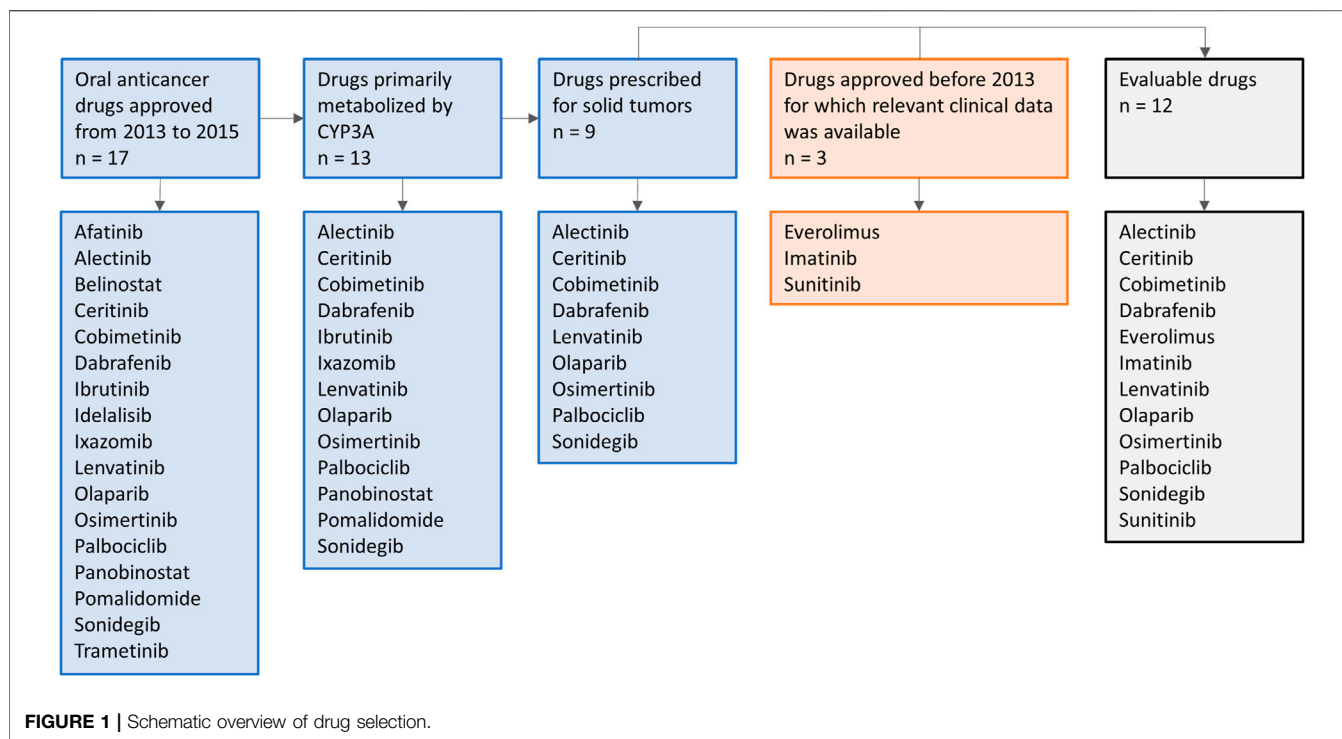


FIGURE 1 | Schematic overview of drug selection.

TABLE 1 | Summary table of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug	Effect CYP3A inhibitors ^a			Effect CYP3A inducers ^a		
	Strong	Moderate	Weak	Strong	Moderate	Weak
Alectinib ^b	36% ↑			18.4% ↓		
Ceritinib	118.5% ↑ (51–186)	37% ↑		68.5% ↓ (67–70)	43% ↓	
Cobimetinib	572% ↑	280.5% ↑ (226–335)	3% ↑	83% ↓	72% ↓	13% ↓
Dabrafenib	71% ↑			34% ↓		
• Hydroxy-dabrafenib	82% ↑			30% ↓		
• Desmethyl-dabrafenib	68% ↑			73% ↑		
• Carboxy-dabrafenib	16% ↓					
Everolimus	1,430% ↑	220% ↑ (74–340)		63% ↓		
Imatinib	18.5% ↑ (–3.1–40.1)			73.3% ↓ (72.5–74)		37.1% ↓ (30.2–44)
• N-desmethyl-imatinib	16.75% ↑ (–5–38.5)			10.8% ↓ (9.8–11.7)		4.1% ↑
Lenvatinib	14.5% ↑			6.2% ↑ (–18.2–30.6)		
Olaparib	161% ↑ (152–170)	115% ↑ (98–126)	1.5% ↑ (1–2)	79% ↓ (71–87)	57.3% ↓ (53–60)	0% ↓
Osimertinib	24.2% ↑			78.5% ↓	42% ↓	0% ↓
Palbociclib	86.8% ↑	40% ↑ (38–42)	0.4% ↑ (0.3–0.4)	85.2% ↓	35% ↓ (32–38)	
Sonidegib	122.8% ↑ (42–253)	98% ↑ (36–179)		76.6% ↓ (66–88)	49% ↓ (29–65)	
Sunitinib ^c	51% ↑	11% ↑		46% ↓		

^aReported as percentage of AUC change, if multiple DDI studies were performed the mean AUC change and range are reported.

^bSum of alectinib and M4.

^cSum of sunitinib and SU12662, except for the moderate inhibitor.

2014a). In a PBPK study the effect of ketoconazole on steady-state exposure of ceritinib was simulated. Steady-state exposure increased by 51% (Food and Drug Administration, 2014a). The difference between the effect of ketoconazole on single-dose and steady-state ceritinib concentrations can be explained by the auto-inhibition of CYP3A4 by ceritinib. Hereby, the fraction of ceritinib metabolized by CYP3A4 will be decreased at steady-state concentrations, thus the effect of a strong inhibitor will be smaller. (Food and Drug

Administration, 2014a). The moderate inhibitor fluconazole increased the steady-state exposure of ceritinib by 37% in a PBPK simulation (Food and Drug Administration, 2014a). The strong CYP3A inducer rifampin decreased the AUC_{0-∞} of single-dose ceritinib by 70% (n = 19) and it was predicted to decrease the AUC on steady-state by 67%. In a simulation study, the moderate inducer efavirenz decreased the AUC of ceritinib by approximately half with 43% (Food and Drug Administration, 2014a).

TABLE 2 | Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
Alectinib (2015)	CYP3A	ALK	46%	Dose proportional exposure	Posaconazole (strong CYP3A inhibitor)	AUC _{0-∞} 75% ↑ (90% CI 57–95) M4 AUC _{0-∞} 24.9% ↓ (90% CI 12.3–35.6) Sum alectinib and M4 AUC _{0-∞} 36% ↑ (90% CI 24–49)	Be careful when combining alectinib with strong inhibitors of CYP3A	Clinical trial	Food and Drug Administration (2015a) and Morcos et al. (2017)
					Rifampin (strong CYP3A inducer)	AUC _{0-∞} 73.2% ↓ (90% CI 69.9–76.2) M4 AUC _{0-∞} 79% ↑ (90% CI 58–102) Sum alectinib and M4 AUC _{0-∞} 18.4% ↓ (90% CI 9.9–26)	Be careful when combining alectinib with strong inducers of CYP3A	Clinical trial	Food and Drug Administration (2015a) and Morcos et al. (2017)
Ceritinib (2014)	CYP3A	ALK	74%	Nonlinear PK	Ketoconazole (strong CYP3A inhibitor)	Single dose AUC _{0-∞} 186% ↑ (90% CI 146–233) Steady-state AUC 51% ↑ (90% CI 43–59)	Avoid coadministration of strong CYP3A inhibitors or reduce the dose of ceritinib to 150 mg QD	Clinical trial PBPK simulation	Food and Drug Administration (2014a)
					Fluconazole (moderate CYP3A inhibitor)	AUC 37% ↑ (90% CI 31–42)		PBPK simulation	Food and Drug Administration (2014a)
					Rifampin (strong CYP3A inducer)	Single dose AUC _{0-∞} 70% ↓ (90% CI 61–77) Steady-state AUC 67% ↓ (90% CI 64–70)	Avoid coadministration of strong CYP3A inducers	Clinical trial PBPK simulation	Food and Drug Administration (2014a)
Cobimetinib (2015)	CYP3A	MEK	61%	Dose proportional exposure	Efavirenz (moderate CYP3A inducer)	AUC 43% ↓ (90% CI 38–48)		PBPK simulation	Food and Drug Administration (2014a)
					Itraconazole (strong CYP3A inhibitor)	AUC _{0-∞} 572% ↑ (90% CI 464–702)	Avoid coadministration of strong and moderate CYP3A inhibitors or reduce the dose of cobimetinib to 20 mg QD (short term use)	Clinical trial	Food and Drug Administration (2014b)
					Erythromycin (moderate CYP3A inhibitor)	AUC 335% ↑		PBPK simulation	Food and Drug Administration (2014b) and Budha et al. (2016)
					Diltiazem (moderate CYP3A inhibitor)	AUC 226% ↑		PBPK simulation	Food and Drug Administration (2014b) and Budha et al. (2016)
					Fluvoxamine (weak CYP3A inhibitor)	AUC 3% ↑		PBPK simulation	Food and Drug Administration (2014b) and Budha et al. (2016)
					Rifampin (strong CYP3A inducer)	AUC 83% ↓	Avoid coadministration of strong and moderate CYP3A inducers	PBPK simulation	Food and Drug Administration (2014b) and Budha et al. (2016)
					Efavirenz (moderate CYP3A inducer)	AUC 72% ↓		PBPK simulation	Food and Drug Administration (2014b) and Budha et al. (2016)
Vemurafenib (weak CYP3A inducer)	AUC _{0-24h} 13% ↓		Clinical trial	Food and Drug Administration (2014b)					

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
Dabrafenib (2013)	CYP2C8/ CYP3A	BRAF	38%	Dose proportional exposure at single dose, but less than dose-proportional after repeat twice daily dosing (likely due to auto-induction)	Ketoconazole (strong CYP3A inhibitor)	AUC _{0-12h} 71% ↑ (90% CI 55–90) Hydroxy-dabrafenib AUC _{0-12h} 82% ↑ (90% CI 61–105) Desmethyl-dabrafenib AUC _{0-12h} 68% ↑ (90% CI 47–93) Carboxy-dabrafenib AUC _{0-12h} 16% ↓ (90% CI 4–27)	Be careful when combining dabrafenib with strong inhibitors of CYP3A	Clinical trial	Food and Drug Administration (2012), Suttle et al. (2015), and European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2018)
					Rifampin (strong CYP3A inducer)	AUC 34% ↓ Desmethyl-dabrafenib AUC 30% ↓ Carboxy-dabrafenib AUC 73% ↑	Avoid coadministration of CYP3A inducers	Clinical trial	European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2018)
Everolimus (2003)	CYP3A/P-gp	mTOR	36%	Dose proportional exposure	Ketoconazole (strong CYP3A inhibitor)	AUC _{0-∞} 1,430% ↑ (90% CI 1020–2,150)	Avoid coadministration of strong CYP3A inhibitors. Avoid coadministration of moderate CYP3A inhibitors or reduce the dose of everolimus to 2.5 or 5 mg QD	Clinical trial	Kovarik et al. (2005b) and Food and Drug Administration (2008) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP); Kovarik et al. (2005c) and Food and Drug Administration (2008)
					Erythromycin (moderate CYP3A inhibitor)	AUC _{0-∞} 340% ↑ (90% CI 250–440)		Clinical trial	
					Verapamil (moderate CYP3A inhibitor)	AUC _{0-∞} 250% ↑ (90% CI 210–290)	Clinical trial	(European Medicines Agency Committee for Medicinal Products For Human Use (CHMP); Kovarik et al., (2005a) and Food and Drug Administration (2008)	
Everolimus (2003)	CYP3A/P-gp	mTOR	36%	Dose proportional exposure	Imatinib (moderate CYP3A inhibitor)	AUC 270% ↑	Avoid coadministration of strong CYP3A inhibitors. Avoid coadministration of moderate CYP3A inhibitors or reduce the dose of everolimus to 2.5 or 5 mg QD	Clinical trial	European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2006)
					Cyclosporine (moderate CYP3A inhibitor)	Neoral [®] AUC _{0-∞} 168% ↑ (90% CI 122–224) Sandimmune [®] AUC _{0-∞} 74% ↑ (90% CI 49–104)		Clinical trial	

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
					Rifampin (strong CYP3A inducer)	AUC 63% ↓ (90% CI 54–70)	Avoid coadministration of strong CYP3A inducers or increase the dose of everolimus to 10 or 20 mg QD	Clinical trial	(European Medicines Agency Committee for Medicinal Products For Human Use (CHMP); Kovarik et al. (2002a) and Food and Drug Administration (2008)
Imatinib (2001)	CYP3A	KIT, PDGFR, Bcr-Abl	40–60%	Dose proportional exposure	Ketoconazole (strong CYP3A inhibitor)	Single dose AUC _{0–∞} 40.1% ↑ (90% CI 31–49.9) N-desmethylimatinib AUC _{0–∞} 5% ↓ (90% CI –3–12.5)	Be careful when combining imatinib with inhibitors of CYP3A	Clinical trial	Food and Drug Administration, (2008); European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2006) Van Erp et al. (2007)
					Ritonavir (strong CYP3A inhibitor)	Steady-state AUC _{0–24h} 3.1% ↓ (90% CI –12.5–16.5) N-desmethylimatinib AUC _{0–24h} 38.5% ↑ (90% CI 15.9–65.6)		Clinical trial	
					Rifampin (strong CYP3A inducer)	AUC _{0–∞} 74% ↓ (90% CI 71–76) N-desmethylimatinib AUC _{0–∞} 11.7% ↓ (90% CI 3.3–19.4)	Avoid coadministration of strong CYP3A inducers	Clinical trial	Bolton et al. (2004) and European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2006) Wen et al. (2006)
Imatinib (2001)	CYP3A	KIT, PDGFR, Bcr-Abl	40–60%	Dose proportional exposure	Enzyme-inducing antiepileptic drugs (EIAEDs; e.g., carbamazepine, oxcarbazepine and phenytoin) (mixed potency; carbamazepine and phenytoin are potent inducers; oxcarbazepine is a weak inducer) St John's Wort (weak CYP3A inducer)	AUC _{0–∞} 72.5% ↓ N-desmethylimatinib AUC _{0–∞} 9.8% ↓ Study 1 AUC _{0–∞} 30.2% ↓ (90% CI 25–34.9) N-desmethylimatinib AUC _{0–72h} 4.1% ↑ (90% CI –8.4–18.3) Study 2 AUC _{0–∞} 44% ↓ (90% CI 30–54)	Avoid coadministration of strong CYP3A inducers	Clinical trial	Frye et al. (2004) Smith et al. (2004)

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
Lenvatinib (2015)	CYP3A	VEGFR	36–78%	Dose proportional exposure	Itraconazole (strong CYP3A inhibitor)	AUC _{0-∞} 14.5% ↑ (90% CI 8.5–20.9)	None	Clinical trial	Food and Drug Administration (2015b) and Shumaker et al. (2015)
					Rifampin (strong CYP3A inducer)	Single dose AUC _{0-∞} 30.6% ↑ (90% CI 22.7–39) Multiple doses AUC _{0-∞} 18.2% ↓ (90% CI 8.7–26.7)		Clinical trial	Shumaker et al. (2014) and Food and Drug Administration (2015b)
Olaparib (2014)	CYP3A	PARP	38%	Dose-proportionality cannot be concluded based on available PK data	Itraconazole (strong CYP3A inhibitor)	Study 1; tablet AUC _{0-∞} 170% ↑ (90% CI 144–197) Study 2; capsule AUC 152% ↑ (95% CI 139–167)	Reduce dose of olaparib to 150 mg BID when combined with strong CYP3A inhibitors and reduce dose to 200 mg BID when combined with moderate CYP3A inhibitors (tablets)	Clinical trial	Food and Drug Administration (2014c) and Dirix et al. (2016)
					Fluconazole (moderate CYP3A inhibitor)	Study 1; tablet AUC 126% ↑ (95% CI 115–130) Study 2; tablet AUC 121% ↑ (95% CI 114–128) Study 2; capsule AUC 98% ↑ (95% CI 92–105)		PBPK simulation PBPK simulation PBPK simulation	Food and Drug Administration (2014c) Pilla Reddy et al. (2019)
Olaparib (2014)	CYP3A	PARP	38%	Dose-proportionality cannot be concluded based on available PK data	Fluvoxamine (weak CYP3A inhibitor)	Tablet AUC 2% ↑ (95% CI 1–2) Capsule AUC 1% ↑ (95% CI 1–2)	Reduce dose of olaparib to 150 mg BID when combined with strong CYP3A inhibitors and reduce dose to 200 mg BID when combined with moderate CYP3A inhibitors (tablets)	PBPK simulation	Pilla Reddy et al. (2019)
					Rifampin (strong CYP3A inducer)	Study 1; tablet AUC _{0-∞} 87% ↓ (90% CI 84–89) Study 2; capsule AUC 71% ↓ (95% CI 69–73)		Clinical trial	Food and Drug Administration, (2014c); Dirix et al. (2016)
					Efavirenz (moderate CYP3A inducer)	Study 1; tablet AUC 59% ↓ (95% CI 58–62) Study 2; tablet AUC 60% ↓ (95% CI 57–62) Study 2; capsule AUC 53% ↓ (95% CI 50–56)		PBPK simulation PBPK simulation PBPK simulation	Food and Drug Administration, (2014c) Pilla Reddy et al. (2019)
					Dexamethasone (weak CYP3A inducer)	Tablet AUC 0 (95% CI –1–0) Capsule AUC 0 (95% CI –1–0)		PBPK simulation	Pilla Reddy et al. (2019)

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References	
Osimertinib (2015)	CYP3A	EGFR	37%	Dose proportional exposure	Itraconazole (strong CYP3A inhibitor)	AUC _{0-∞} 24.2% ↑ (90% CI 14.6–34.5) AZ5104 AUC _{0-∞} 8.3% ↑ (90% CI –5.6–24.2) AZ7550 AUC 51% ↓ (90% CI 45–56.3)	None	Clinical trial	European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016a) and Vishwanathan et al. (2018)	
					Rifampin (strong CYP3A inducer)	AUC _{0-24h} 78.5% ↓ (90% CI 76.2–80.5) AZ5104 AUC _{0-24h} 81.2% ↓ (90% CI 78.8–83.4) AZ7550 AUC _{0-24h} 29.8% ↑ (19.1–41.4)	Avoid coadministration of strong and moderate CYP3A inducers	Clinical trial		European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016a) and Vishwanathan et al. (2018)
					Efavirenz (moderate CYP3A inducer) Dexamethasone (weak CYP3A inducer)	AUC 42% ↓ (95% CI 40–44) AUC 0.001% ↓ (95% CI 0.001–0.001)		PBPK simulation PBPK simulation		Reddy et al. (2018)
Palbociclib (2015)	CYP3A	CDK4/6	29%	Dose proportional exposure	Itraconazole (strong CYP3A inhibitor)	AUC _{0-∞} 86.8% ↑ (90% CI 72.9–101.9)	Avoid coadministration of strong CYP3A inhibitors or reduce dose of palbociclib to 75 mg QD	Clinical trial	Food and Drug Administration (2014d) and European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016b) Yu et al. (2017)	
					Diltiazem (moderate CYP3A inhibitor)	AUC _{0-216h} 42% ↑		PBPK simulation		
					Verapamil (moderate CYP3A inhibitor)	AUC _{0-216h} 38% ↑		PBPK simulation		
					Fluvoxamine (weak inhibitor)	AUC _{0-216h} 0.4% ↑		PBPK simulation		
					Fluoxetine (weak CYP3A inhibitor)	AUC _{0-216h} 0.3% ↑		PBPK simulation		
Palbociclib (2015)	CYP3A	CDK4/6	29%	Dose proportional exposure	Rifampin (strong CYP3A inducer)	AUC _{0-∞} 85.2% ↓ (90% CI 81.4–88.2)	Avoid coadministration of strong CYP3A inducers	Clinical trial	Food and Drug Administration (2014d) Yu et al. (2017)	
					Efavirenz (moderate CYP3A inducer)	AUC _{0-168h} 38% ↓		PBPK simulation		
					Modafinil (moderate CYP3A inducer)	AUC _{0-∞} 32% ↓	Avoid coadministration of strong CYP3A inducers	Clinical trial		European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016b)

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
Sonidegib (2015)	CYP3A	Smooth-ened	CL/F 67% V/F 213%	Dose proportional exposure with doses up to 400 mg, with higher dose less than proportional (due to dose-dependent absorption)	Ketoconazole (strong CYP3A inhibitor)	<u>Study 1; healthy subjects</u> AUC _{0-240h} 125% ↑ (90% CI 78–186)	Reduce dose of sonidegib to 200 mg every other day when combined with strong CYP3A inhibitors	Clinical trial	European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), (2015c), and Food and Drug Administration (2015d) Food and Drug Administration (2015d) and Einolf et al. (2017)
					<u>Study 2; cancer patients, sonidegib 1 day, ketoconazole 14 days</u> AUC _{0-24h} 42% ↑ (90% CI 39–45) <u>Study 2; sonidegib 120 days, ketoconazole 120 days</u> AUC _{0-24h} 253% ↑ (90% CI 231–276) <u>Study 2; sonidegib 133 days, ketoconazole 14 days</u> AUC _{0-24h} 101% ↑ (90% CI 92–111) <u>Study 2; sonidegib QOD 133 days, ketoconazole 14 days</u> AUC _{0-24h} 93% ↑ (90% CI 84–102)	PBPB simulation			
Sonidegib (2015)	CYP3A	Smooth-ened	CL/F 67% V/F 213%	Dose proportional exposure with doses up to 400 mg, with higher dose less than proportional (due to dose-dependent absorption)	Erythromycin (moderate CYP3A inhibitor)		<u>Sonidegib 1 day, erythromycin 14 days</u> AUC _{0-24h} 36% ↑ (90% CI 33–39) <u>Sonidegib 120 days, erythromycin 120 days</u> AUC _{0-24h} 179% ↑ (90% CI 76–361) <u>Sonidegib 133 days, erythromycin 14 days</u> AUC _{0-24h} 79% ↑ (90% CI 71–86)	Reduce dose of sonidegib to 200 mg every other day when combined with strong CYP3A inhibitors	PBPB simulation
					Rifampin (strong CYP3A inducer)	<u>Study 1; healthy subjects</u> AUC _{0-240h} 72.4% ↓ (90% CI 65.1–78.1)	Avoid coadministration of strong CYP3A inducers, but if necessary, consider to increase the dose to 400–800 mg		

(Continued on following page)

TABLE 2 | (Continued) Detailed overview of the results of DDI studies performed with the reviewed oral oncolytic drugs.

Drug (year of market approval)	(Primary) metabolism	Target Verheijen et al. (2017)	Inter-patient variability (%CV)	Dose-linearity	DDI study with (interaction potential)	Change in AUC	Recommendations Summary of product Characteristics	Type of trial	References
						<p>Study 2; cancer patients, sonidegib 1 day, rifampin 14 days AUC_{0-24h} 66% ↓ (90% CI 63–68)</p> <p>Study 2; sonidegib 120 days, rifampin 120 days AUC_{0-24h} 88% ↓ (90% CI 87–89)</p> <p>Study 2; sonidegib 133 days, rifampin 14 days AUC_{0-24h} 80% ↓ (90% CI 78–82)</p>		PBPK simulation	Food and Drug Administration (2015d) and Einolf et al. (2017)
Sonidegib (2015)	CYP3A	Smoothened	CL/F 67% V/F 213%	Dose proportional exposure with doses up to 400 mg, with higher dose less than proportional (due to dose-dependent absorption)	Efavirenz (moderate CYP3A inducer)	<p>Sonidegib 1 day, efavirenz 14 days AUC_{0-24h} 29% ↓ (90% CI 26–31)</p> <p>Sonidegib 120 days, efavirenz 120 days AUC_{0-24h} 65% ↓ (90% CI 62–67)</p> <p>Sonidegib 133 days, efavirenz 14 days AUC_{0-24h} 53% ↓ (90% CI 50–56)</p>	Avoid coadministration of strong CYP3A inducers, but if necessary, consider to increase the dose to 400–800 mg	PBPK simulation	Food and Drug Administration (2015d) and Einolf et al. (2017)
Sunitinib (2006)	CYP3A	VEGFR	40%	Dose proportional exposure	<p>Ketoconazole (strong CYP3A inhibitor)</p> <p>Grapefruit juice (moderate CYP3A inhibitor)</p> <p>Rifampin (strong CYP3A inducer)</p>	<p>Sum sunitinib and SU12662 AUC_{0-∞} 51% ↑</p> <p>AUC_{0-24h} 11% ↑</p> <p>Sum sunitinib and SU12662 AUC_{0-∞} 46% ↓</p>	<p>Reduce dose of sunitinib to 37.5 mg QD in GIST and MRCC patients and to 25 mg QD in pancreatic/NET patients when combined with strong CYP3A inhibitors</p> <p>Increase the dose of sunitinib in steps of 12.5 mg with a maximum of 87.5 mg QD when combined with CYP3A inducers</p>	<p>Clinical trial</p> <p>Clinical trial</p> <p>Clinical trial</p>	<p>Food and Drug Administration (2005)</p> <p>Van Erp et al. (2011)</p> <p>Food and Drug Administration (2005)</p>

Cobimetinib

Figure 2 shows the results of the DDI studies conducted with cobimetinib. It can be seen that CYP3A based DDIs have a large influence on the exposure to cobimetinib. The strong inhibitor itraconazole increased the $AUC_{0-\infty}$ of cobimetinib by almost 600% ($n = 15$) (Food and Drug Administration, 2014b). The moderate CYP3A inhibitors erythromycin and diltiazem increased the AUC by around 300% in a PBPK simulation, which is half the effect of strong inhibitors, while weak inhibitors had no effect (Food and Drug Administration, 2014b; Budha et al., 2016). The effect of rifampin on the exposure of cobimetinib was studied in a PBPK simulation study instead of a clinical trial, which is in contrast with most DDI studies performed with rifampin. In this simulation the AUC of cobimetinib decreased by 83% when combined with rifampin (Food and Drug Administration, 2014b). Furthermore, the effect of the moderate CYP3A inducer efavirenz was studied in a PBPK simulation and a decrease in AUC of 72% was predicted (Food and Drug Administration, 2014b; Budha et al., 2016). The weak inducer vemurafenib showed a decrease in AUC_{0-24h} of only 13% in a clinical trial ($n =$ unknown) (Food and Drug Administration, 2014b).

Everolimus

The strong inhibitor ketoconazole increased the $AUC_{0-\infty}$ of everolimus by 1,430% ($n = 12$) (Kovarik et al., 2005b; Food and Drug Administration, 2008). Therefore, it is not recommended to coadminister strong CYP3A4 inhibitors with everolimus (Food and Drug Administration, 2008). The effect size of moderate inhibitors was around 25% compared with ketoconazole (increase in exposure of 340% for erythromycin ($n = 16$), 250% for verapamil ($n = 16$), 270% for imatinib ($n =$ unknown), and 121% as average for two different cyclosporin formulations ($n = 12$) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP); Kovarik et al., 2002a; Kovarik et al., 2002b; Kovarik et al., 2005a; Kovarik et al., 2005c; Kovarik et al., 2006). Rifampin decreased the AUC of everolimus by 63% ($n = 12$) (Kovarik et al., 2002a). The effect of the moderate inhibitors was small compared with the strong inhibitor ketoconazole. An explanation for this finding is that ketoconazole also inhibits P-glycoprotein (P-gp), which influences the pharmacokinetics (PK) of everolimus in addition to CYP3A (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2014; Ravaud et al., 2014).

Lenvatinib

Lenvatinib is for more than 80% metabolized by CYP3A to different metabolites *in vitro*. Furthermore, *in vitro* data suggests that lenvatinib is a substrate for P-gp. But *in vivo*, oxidation by aldehyde oxidase and glutathione conjugation play an important role in the metabolism of lenvatinib, next to the metabolism *via* CYP3A (Food and Drug Administration, 2015b). Since the potency of lenvatinib is at least 20 times higher than of the metabolites, the metabolites were considered inactive (Shumaker et al., 2014; Food and Drug Administration, 2015b). The strong CYP3A inhibitor ketoconazole increased the

$AUC_{0-\infty}$ of lenvatinib by 15% ($n = 18$) (Food and Drug Administration, 2015b; Shumaker et al., 2015). The strong CYP3A inducer rifampin decreased the $AUC_{0-\infty}$ of lenvatinib by 18% when multiple doses were given ($n = 15$) (Shumaker et al., 2014; Food and Drug Administration, 2015b). In contrast, a single dose of rifampin increased the $AUC_{0-\infty}$ of lenvatinib by 31%. Shumaker et al. explained this by a presystemic inhibition of P-gp, which is consistent with the study of Rietman et al. who described that rifampin can inhibit the efflux of drugs into the intestinal lumen (Rietman et al., 2011; Shumaker et al., 2014). The marginal effects of ketoconazole and rifampin on the lenvatinib AUC suggest that the role of CYP3A in the metabolism of lenvatinib is small. In addition, the effects of ketoconazole and rifampin on the AUC of lenvatinib could also be caused by inhibition and induction of P-gp, because both ketoconazole and rifampin have an effect on P-gp (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2014b; Food and Drug Administration, 2015b).

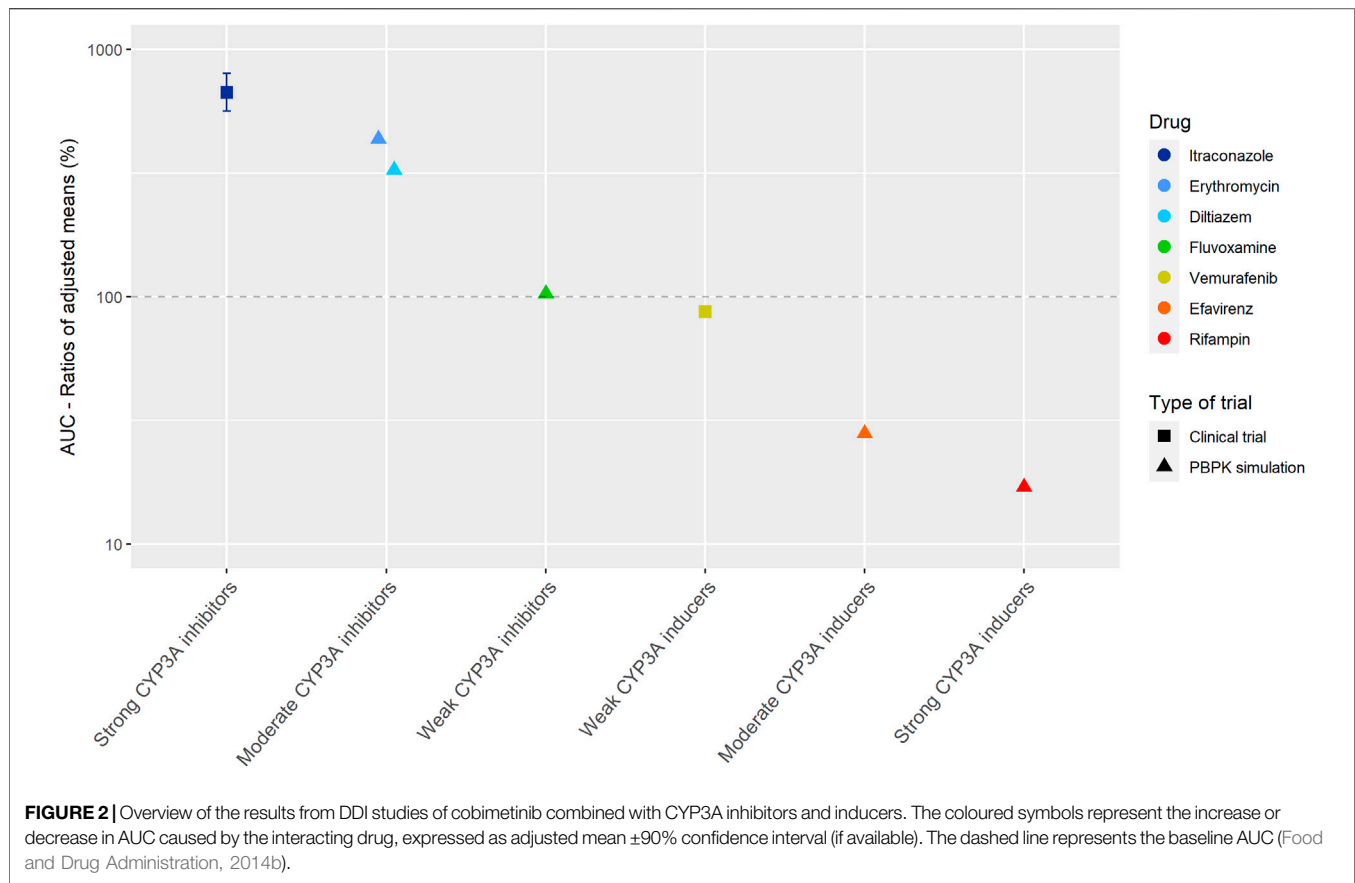
Olaparib

Clinical DDI studies investigated the influence of itraconazole and rifampin on the AUC of olaparib administered as tablets (Food and Drug Administration, 2014c; Dirix et al., 2016). In PBPK simulations, the effect of inhibitors and inducers on the AUC of olaparib formulated as capsules was simulated. The effect on olaparib tablets and capsules were predicted to be similar (Pilla Reddy et al., 2019).

The strong CYP3A inhibitor itraconazole increased the $AUC_{0-\infty}$ of olaparib by 170% ($n = 59$) (Food and Drug Administration, 2014c; Dirix et al., 2016). The moderate inhibitor fluconazole increased the AUC of olaparib with an average of 115% in three PBPK simulations (Food and Drug Administration, 2014c; Pilla Reddy et al., 2019). Furthermore, the weak inhibitor fluvoxamine, was simulated to have no effect on the AUC of olaparib (Pilla Reddy et al., 2019). Rifampin, a strong CYP3A inducer, decreased the olaparib $AUC_{0-\infty}$ by 87% ($n = 22$) (Food and Drug Administration, 2014c). The moderate inducer efavirenz decreased the AUC of olaparib by approximately 75%, compared with rifampin, with a decrease of 60% in a PBPK simulation (Pilla Reddy et al., 2019). The weak inducer dexamethasone, was simulated to have no effect on the AUC of olaparib (Pilla Reddy et al., 2019).

Palbociclib

Figure 3 shows the results of the DDI studies performed with palbociclib. The strong inhibitor itraconazole increased the palbociclib $AUC_{0-\infty}$ by 87% ($n = 12$) (Food and Drug Administration, 2014d; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015b). The moderate CYP3A inhibitors diltiazem and verapamil were simulated to increase the AUC_{0-216h} of palbociclib by half compared with itraconazole, with an increase of 40% (Food and Drug Administration, 2014d; Yu et al., 2017). No effect of the weak inhibitors fluvoxamine and fluoxetine on the AUC_{0-216h} of palbociclib was predicted in a simulation study (Yu et al., 2017). Moderate CYP3A inducers decreased the palbociclib AUC by approximately half compared with strong CYP3A inducers. The strong inducer rifampin decreased the $AUC_{0-\infty}$ of palbociclib by



85% ($n = 14$) (Food and Drug Administration, 2014d). The moderate inducer efavirenz decreased the AUC_{0-168h} by 38% in a simulation study and modafinil decreased the $AUC_{0-\infty}$ by 32% in a clinical trial ($n = 14$) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2016b; Yu et al., 2017).

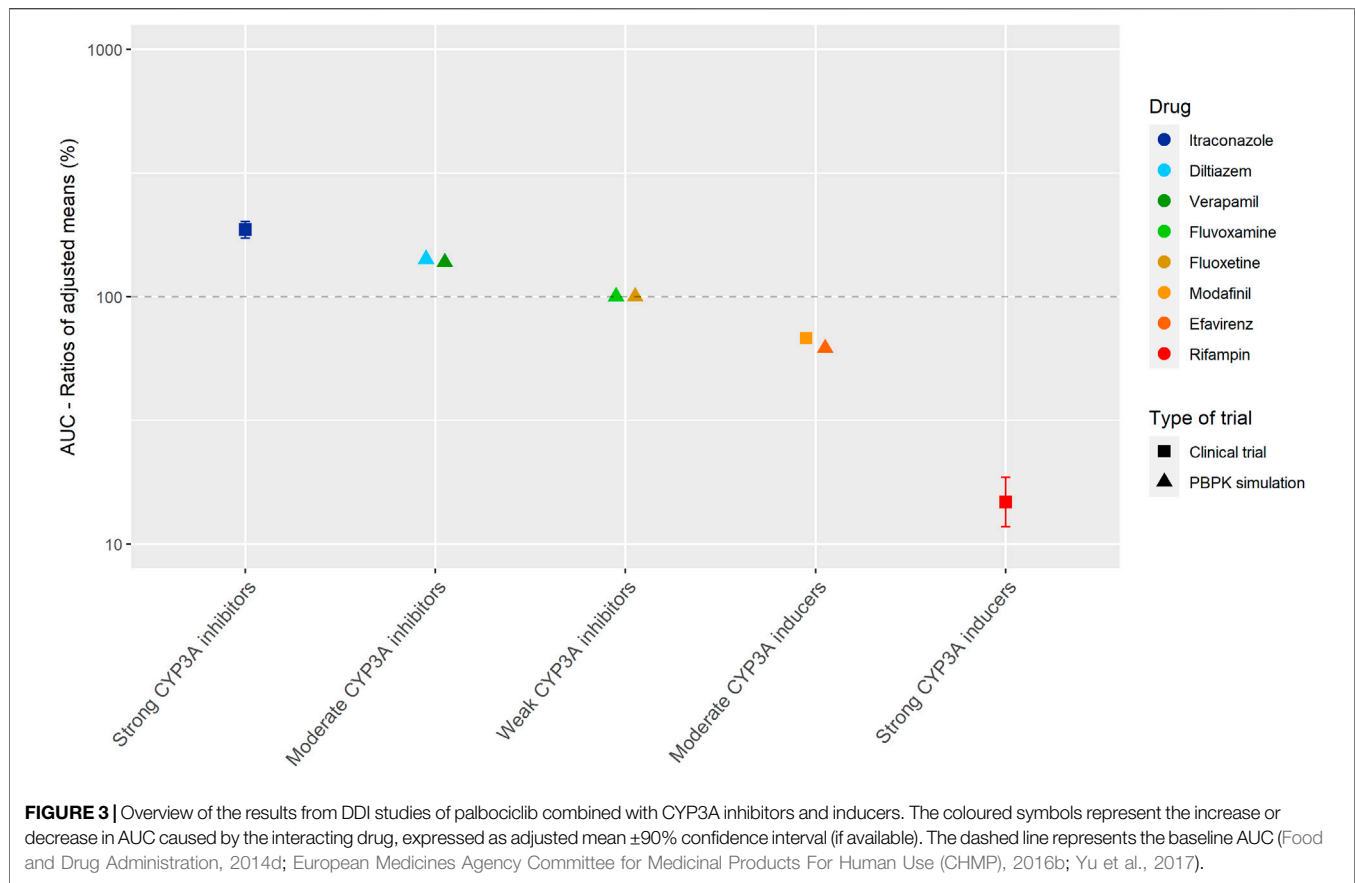
Sonidegib

In a clinical trial with healthy subjects, the strong CYP3A inhibitor ketoconazole increased the AUC_{0-240h} of sonidegib 800 mg by 125% (same was simulated for sonidegib 200 mg) (parallel study; $n = 16$ in control group and $n = 15$ in combination group) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015c; Food and Drug Administration, 2015d; Einolf et al., 2017). Ketoconazole was simulated to increase the AUC_{0-24h} of sonidegib given as a single dose by 42% in cancer patients (Food and Drug Administration, 2015d; Einolf et al., 2017). The smaller effect of ketoconazole in cancer patients, can be explained by a decreased hepatic clearance with an elimination half-life of 28 days in cancer patients, and 10 days in healthy subjects (Food and Drug Administration, 2015d). After long-term exposure to sonidegib, ketoconazole was simulated to increase the AUC_{0-24h} by 101–253%, dependent on the duration of combined use (Food and Drug Administration, 2015d; Einolf et al., 2017).

The moderate CYP3A inhibitor erythromycin increased the AUC_{0-24h} of sonidegib given as a single dose by 36% (Food and Drug Administration, 2015d; Einolf et al., 2017). The AUC_{0-24h} of sonidegib given long-term was increased by 79–179%, dependent on the duration of combined use with erythromycin (Food and Drug Administration, 2015d; Einolf et al., 2017). Compared with the simulations for ketoconazole, according to the same treatment schedule, the increases in sonidegib AUC were more than half.

In a clinical trial with healthy subjects, the strong CYP3A inducer rifampin decreased the AUC_{0-240h} of sonidegib 800 mg by 72.4% (same was simulated for sonidegib 200 mg) (parallel study; $n = 16$ in control group and $n = 16$ in combination group) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015c; Food and Drug Administration, 2015d; Einolf et al., 2017). Rifampin was simulated to decrease the AUC_{0-24h} of sonidegib given as a single dose by 66% in cancer patients (Food and Drug Administration, 2015d; Einolf et al., 2017). The smaller decrease in cancer patients can be explained by a decreased hepatic clearance. The AUC_{0-24h} of sonidegib was decreased by 80–88% when sonidegib given long-term and rifampin were combined, dependent on the duration of combined use (Food and Drug Administration, 2015d; Einolf et al., 2017).

The moderate CYP3A inducer efavirenz was simulated to decrease the AUC_{0-24h} of sonidegib given as a single dose by



29% (Food and Drug Administration, 2015d; Einolf et al., 2017). Efavirenz decreased the AUC_{0-24h} of sonidegib given long-term by 53–65%, dependent on the duration of combined use (Food and Drug Administration, 2015d; Einolf et al., 2017). Compared with the simulations of rifampin, according to the same treatment schedule, a decrease of approximately 70% was seen in sonidegib steady-state AUC.

To summarize, the interacting effect on sonidegib is influenced by the patient population and duration of therapy with sonidegib and the interacting agent.

Drugs With Active Metabolites

Alectinib

Alectinib is mainly metabolized by CYP3A to the active metabolite M4. Alectinib and M4 show a similar potency and plasma protein binding *in vitro* (Fowler et al., 2017; Morcos et al., 2017). Therefore, the sum of alectinib and M4 concentration was reported as the pharmacologically active exposure in the DDI studies with posaconazole and rifampin (Morcos et al., 2017).

Figure 4 shows the results of the DDI studies performed with alectinib. The strong inhibitor posaconazole increased the exposure to the sum of alectinib and M4 by 36% ($n = 17$) (Food and Drug Administration, 2015a; Morcos et al., 2017). The strong inducer rifampin decreased the sum of exposure by 18% ($n = 24$) (Food and Drug Administration, 2015a; Morcos

et al., 2017). Based on the small effects of posaconazole and rifampin, the effects of other CYP3A inhibitors and inducers on the exposure of alectinib and M4 were considered clinically irrelevant.

Dabrafenib

Dabrafenib is partially metabolized to active metabolites. It is firstly oxidized by CYP enzymes to hydroxy-dabrafenib, which is further oxidized to carboxy-dabrafenib. Carboxy-dabrafenib is converted to desmethyl-dabrafenib *via* a non-enzymatic process or excreted in urine or bile. Subsequently, desmethyl-dabrafenib is oxidized to other metabolites (Bershas et al., 2013). Dabrafenib auto-induces its metabolism *via* CYP3A4 (Food and Drug Administration, 2012). Hydroxy-dabrafenib and desmethyl-dabrafenib show a similar potency and may contribute to the clinical activity of dabrafenib, on the other hand carboxy-dabrafenib does not relevantly contribute to the activity (Suttle et al., 2015).

The strong inhibitor ketoconazole increased the AUC_{0-12h} of dabrafenib and the metabolites hydroxy-dabrafenib and desmethyl-dabrafenib by 71, 82, and 68%, respectively, while the AUC_{0-12h} of carboxy-dabrafenib decreased by 16% ($n = 16$) (Suttle et al., 2015; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2018). In the DDI study with the strong inducer rifampin the opposite was seen, the AUCs of dabrafenib and desmethyl-dabrafenib decreased by 34

and 30%, respectively, and the AUC of the inactive carboxy-dabrafenib increased by 73% ($n = 23$) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2018). These results for both parent and metabolites when combined with a strong inhibitor versus a strong inducer were as expected because the conversion of dabrafenib, hydroxy-dabrafenib, and desmethyl-dabrafenib is mediated by CYP enzymes and thus influenced by inhibitors and inducers of CYP3A. On the contrary, the non-enzymatic conversion of carboxy-dabrafenib is not affected by CYP3A inhibitors and inducers (Bershas et al., 2013). The comparable or even higher increase in AUC for hydroxy-dabrafenib and desmethyl-dabrafenib compared to the parent, indicates higher involvement of CYP3A in elimination of the metabolites compared to their production (Suttle et al., 2015; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2018).

Imatinib

Imatinib is mainly metabolized by CYP3A. Other CYP enzymes play a minor role. Auto-inhibition of CYP3A by imatinib was shown *in vitro*, but no *in vivo* data is available (Food and Drug Administration, 2001). The main metabolite is N-desmethylinatinib also known as CGP 74588. N-desmethylinatinib is as potent as the parent compound *in vitro*. The exposure to N-desmethylinatinib is approximately 10% compared to the exposure to imatinib, therefore the effect of the metabolite is considered clinically irrelevant (Peng et al., 2005; Whirl-Carrillo et al., 2012).

Ketoconazole in combination with a single dose of imatinib increased the imatinib $AUC_{0-\infty}$ by 40% ($n = 14$) (Food and Drug Administration, 2001; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2006). Ritonavir combined with imatinib, at imatinib steady-state, decreased the imatinib AUC_{0-24h} by 3% ($n = 11$) (Van Erp et al., 2007). According to the Flockhart Table, ritonavir and ketoconazole share the same interaction potential (Flockhart, 2007). But ritonavir is also an inhibitor of CYP2D6 and inducer of CYP2C19 (Flockhart, 2007), which both play a minor role in the metabolism of imatinib (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2006; Whirl-Carrillo et al., 2012). Especially the induction of CYP2C19 could be an explanation for the difference seen between the effects of ketoconazole and ritonavir. Furthermore, the difference could be caused by a shift to alternative elimination routes when imatinib is administered chronically, especially because auto-inhibition of CYP3A was shown *in vitro* (Food and Drug Administration, 2001). The two described hypotheses are supported by the *in vitro* experiment of Van Erp et al. which showed that ritonavir completely inhibited the metabolism of imatinib *via* CYP3A, but in human liver microsomes by only 50% (Van Erp et al., 2007). In DDI studies with CYP3A inducers large effects of the drugs rifampin and enzyme-inducing antiepileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine and phenytoin on imatinib AUC were seen. The strong inducer rifampin decreased the

$AUC_{0-\infty}$ of imatinib by 74% ($n = 14$) (Bolton et al., 2004; European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2006). EIAEDs (mixed potency; carbamazepine and phenytoin are potent inducers, oxcarbazepine is a weak inducer (Riva et al., 1996)) decreased the $AUC_{0-\infty}$ of imatinib by 72.5% ($n = 50$; $n = 27$ in EIAED group and $n = 23$ in non-EIAED group) (Wen et al., 2006). The effect of St John's Wort on imatinib exposure was smaller with an average decrease of 37% in 2 studies ($n = 12$ in study Frye et al.; $n = 10$ in study Smith et al.) (Frye et al., 2004; Smith et al., 2004). To summarize, DDI studies with mostly strong CYP3A inhibitors and inducers were performed. The effects of these drugs on imatinib were variable. This can be due to differences in study design, characteristics of the interacting drugs and also the inter-individual variability of 40–60% will have an effect (Food and Drug Administration, 2001).

Osimertinib

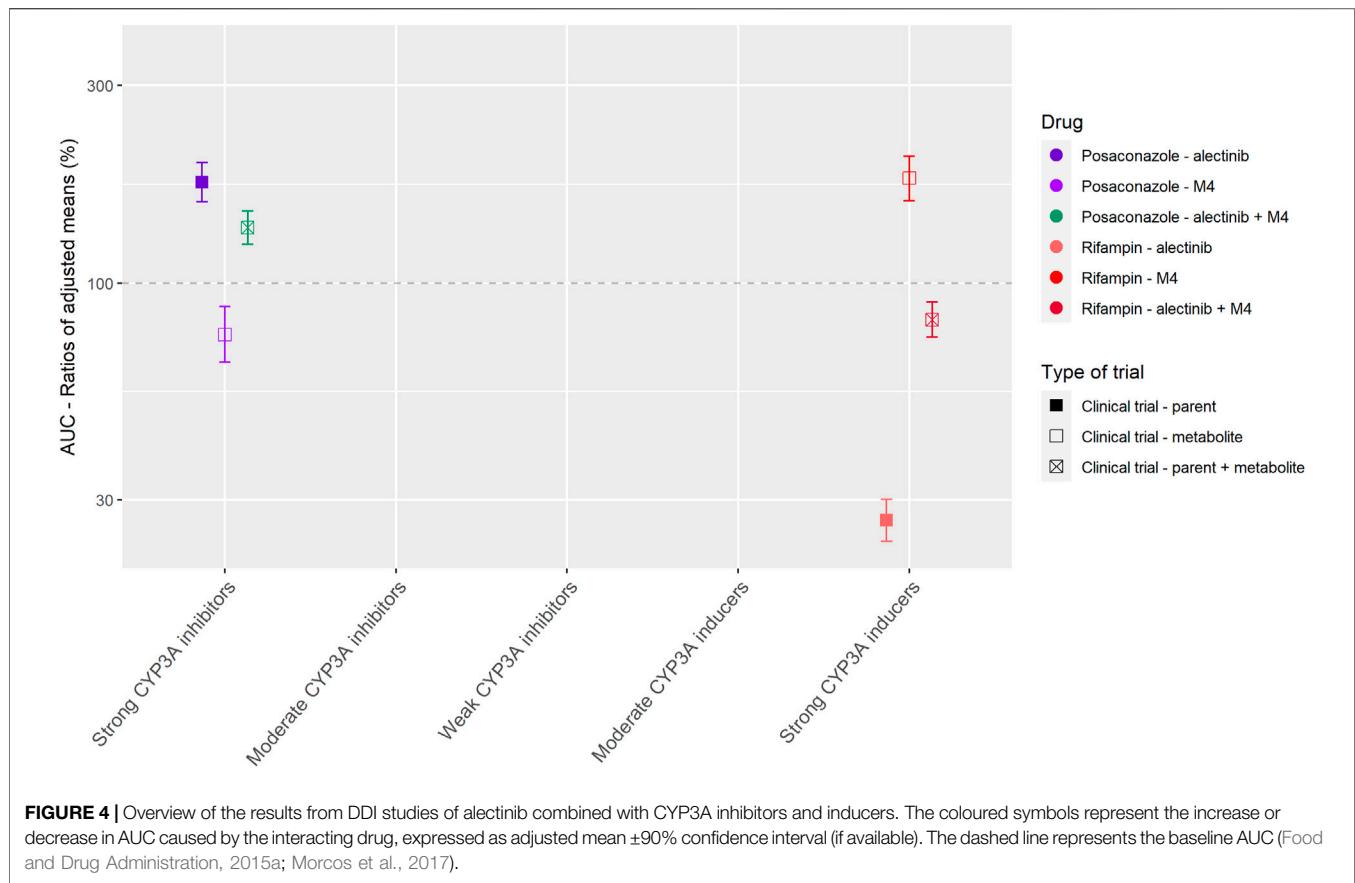
Osimertinib is converted into different metabolites by predominantly CYP3A, among which the active metabolites AZ5104 and AZ7550. The exposure to the active metabolites is, however, less than 10% of the total drug exposure, therefore the effects of the metabolites are considered clinically irrelevant (Vishwanathan et al., 2018). Next to the metabolism by CYP3A, in *in vitro* studies CYP1A2, CYP2A6, CYP2C9, CYP2E1 also play a minor role in the metabolism of osimertinib (Dickinson et al., 2016; Vishwanathan et al., 2018). *In vitro* studies also showed that osimertinib is an inhibitor of CYP3A, but no *in vivo* data is available (Food and Drug Administration, 2015c).

The strong inhibitor itraconazole increased the $AUC_{0-\infty}$ of osimertinib by 24% ($n = 38$) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015a; Vishwanathan et al., 2018). On the other hand, the effect of rifampin on osimertinib exposure was large, rifampin decreased the AUC_{0-24h} by 78.5% ($n = 32$) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2016a; Vishwanathan et al., 2018). The moderate inducer efavirenz was simulated to decrease the exposure by approximately 50% compared with rifampin, with a decrease in AUC of 42% (Reddy et al., 2018). Dexamethasone, a weak CYP3A inducer, had no effect on the AUC of osimertinib in a PBPK simulation (Reddy et al., 2018).

The presence of a clinically relevant effect for the interaction of osimertinib with rifampin, while it was lacking for the interaction between osimertinib and itraconazole, could be explained by the fact that rifampin induces multiple enzymes and transporters, and that, next to CYP3A, other CYP enzymes play a role in the metabolism of osimertinib (Vishwanathan et al., 2018). For the drugs tivozanib and ixazomib, also a clinically relevant effect was shown for rifampin, while it was lacking for a CYP3A inhibitor (Cotreau et al., 2015; Gupta et al., 2018; Vishwanathan et al., 2018).

Sunitinib

Sunitinib is metabolized by CYP3A to the active metabolite SU12662, which is equally potent (Food and Drug



Administration, 2005). SU12662 is metabolized further by CYP3A and transported by P-gp (Heath et al., 2011).

The strong inhibitor ketoconazole increased the sum of the $AUC_{0-\infty}$ of sunitinib and SU12662 only by 51% ($n = 27$) (Food and Drug Administration, 2005). Grapefruit juice, a moderate CYP3A inhibitor, increased the AUC_{0-24h} of sunitinib by 11%, which was considered negligible ($n = 8$) (Van Erp et al., 2011). In this study only the AUC of sunitinib was measured and not the AUC of the metabolite SU12662. Grapefruit juice mainly inhibits intestinal CYP3A with little effect on hepatic CYP3A, while ketoconazole inhibits both (Saito et al., 2005). In addition, the small increase in AUC could be explained by the fact that in the study with ketoconazole (Food and Drug Administration, 2005), only a single dose of sunitinib was administered in contrast to the multiple dosing in the grapefruit juice study (Van Erp et al., 2011), which could lead to a shift to other metabolic pathways. The strong CYP3A inducer rifampin reduced the sum of the $AUC_{0-\infty}$ of sunitinib and SU12662 by 46% ($n = 28$) (Food and Drug Administration, 2005).

DISCUSSION

Most currently used oral targeted anticancer drugs have a narrow therapeutic range. Furthermore, most of these drugs are substrates of CYP3A and are, therefore, prone to DDIs with

inhibitors or inducers of CYP3A. It is of crucial importance for clinical practice to have guidelines on how to deal with these DDIs in cases where data is lacking, which might be the case early after drug approval. This study reviewed the literature for DDI studies performed with twelve oral anticancer drugs. Based on this data, we formulated recommendations for clinical practice on how to deal with DDIs of oral anticancer drugs when only data from strong inducers or inhibitors is available.

In our approach, we extrapolated results from dedicated DDI studies with strong inhibitors and inducers to clinical practice. Since the extrapolation of the effects of CYP3A inhibitors and inducers is more complex in the presence of active metabolites, separate recommendations are given for the drugs metabolized to inactive and with active metabolites. The recommendations are summarized in a flowchart (Figure 5). When interested in a victim drug without active metabolites, start in the left of the figure in the upper blue box. Follow the flowchart depending on the characteristics (inhibitor or inducer; interaction potential) of the drug you are interested in. The last box will show you our recommendation regarding the interaction. When interested in a victim drug with active metabolites, start in the right of the figure in the upper orange box. When the metabolite contributes less than 10% to total drug exposure or less than 50% to total drug effect, the presence of an active metabolite can be neglected. Therefore, the part of the flowchart for drugs without active metabolites can be followed. If the metabolite has a relevant

contribution to total drug exposure and effect, the part of the flowchart for drugs without active metabolites can be followed, using the sum of parent and metabolite, or assessing the effect of parent and metabolite separately.

For the studied drugs without active metabolites, **Tables 1** and **2** show that the effect of moderate CYP3A inhibitors on the AUC is roughly approximate to 50% of the effect of the strong inhibitors. The same effect can be seen for moderate inducers in comparison with strong inducers. Furthermore, it can be noted that weak inhibitors and inducers had marginal effects on the exposure of the studied drugs. In **Figures 2** and **3**, these results are visualized for the drugs cobimetinib and palbociclib, which gives a good representation of the effects seen for all seven drugs without active metabolites (the **Supplementary Material** shows figures for the other drugs).

Regarding drug selection for this review we made the following decisions. Drugs which have been approved for solid tumors from January 1st, 2013 to December 31st, 2015, and three drugs (everolimus, imatinib, sunitinib) authorized before 2013 based on the availability of relevant clinical data were selected. This resulted in a selection of twelve drugs. This was decided since 1) no difference is to be expected in quality of PBPK simulations performed in early years (2013–2015) compared to later years, and 2) the results of all twelve analyzed drugs in this review roughly indicate the same direction on the extrapolation of the effects of DDI studies. For the twelve drugs selected in our analysis, only for sunitinib and palbociclib a clinical trial was performed with a moderate CYP3A inhibitor and inducer, respectively. Also for the seven drugs that were approved after 2015 and met the inclusion criteria regarding metabolism and indication (abemaciclib, brigatinib, entrectinib, larotrectinib, lorlatinib, neratinib, and ribociclib) no clinical DDI studies with moderate inhibitors/inducers, but only PBPK simulations were performed (or no DDI studies at all). Furthermore, we decided to focus on oral anticancer drugs in our review. However, our recommendations are probably also applicable to other drugs metabolized by CYP3A.

It is important to take into account the following, regarding our recommendations. First, a large variability in the PK after multiple doses occurred in the studied drugs, with a range of 23–78%. Similarly, Verheijen et al. showed that there is a high inter-individual variability in the exposure to kinase inhibitors (Verheijen et al., 2017). This is also reflected by the large variability in the effect of CYP3A inhibitors and inducers for some drugs. Possibly, this variability in exposure could partly be explained by the highly variable CYP3A4 activity among patients, which is for 60–90% genetically determined (Özdemir et al., 2000; Westlind-Johnsson et al., 2003). For example, the CYP3A4*22 polymorphism has been described, resulting in a two-fold increase of the formation of a non-functional variant of CYP3A4 (Wang et al., 2011). If the CYP3A4 activity is decreased by a genetic polymorphism, the magnitude of the effect of a CYP3A inhibitor will theoretically be decreased. Furthermore, caution should be taken while using the flowchart for drugs in which auto-induction or -inhibition plays a role and drug-drug interaction studies are not performed on steady-state, or for drugs with nonlinear dose-

exposure relationships. In these cases it might not be possible to extrapolate results from DDI studies with strong inhibitors and inducers, or dose recommendations based on these results. While interpreting the results of this review it is necessary to bear in mind this large variability in PK, and the exceptions in which our recommendations might not be applicable.

Next to the results of the drugs without active metabolites, **Tables 1** and **2** show that for drugs that have active metabolites the results are less straightforward. As a visual example **Figure 4** was made, which shows the effect of interacting drugs on the AUC of the parent drug alectinib and its active metabolite (similar figures are presented in the **Supplementary Material** for the other studied drugs). There are three factors to take into account while interpreting the results of DDI studies with drugs with active metabolites. Firstly, the metabolic pathway is important. For example, in case of dabrafenib not only the parent, but also two of the active metabolites are metabolized by CYP3A, whereas the third metabolite is converted non-enzymatically. This results in an effect of CYP3A inhibitors and inducers on both parent and some of the metabolites, but not all of them. Secondly, the ratio between parent and metabolites should be taken into account. As a cut-off value a contribution of less than 10% of the metabolite to total drug exposure could be used. This is in line with the EMA recommendation to characterize metabolites structurally that contribute to more than 10% of the AUC of a drug in *in vitro* studies (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015b). An example of a drug with an active metabolite which contributes to less than 10% of total drug exposure is osimertinib. Thirdly, the potency of the metabolites plays an important role. A cut-off value of 50% contribution to the total drug effect can be used when considering the relevance of the contribution of an active metabolite. This cut-off value is supported by the EMA (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015b). Shown by the recommendation to conduct an *in vivo* DDI study not only for drugs where enzymes contribute to at least 25% of the overall elimination but also for drugs with pharmacologically active metabolites which contribute to 50% or more of the effect of the drug (and enzymes are involved in the formation or elimination of these metabolites) (European Medicines Agency Committee for Medicinal Products For Human Use (CHMP), 2015b). For example, if a metabolite is as potent as the parent drug, the effect of an interacting drug on the sum of parent and metabolite might be reported as measure of total drug activity, as was done in the case of alectinib and sunitinib.

A practical example for the drug palbociclib is given. The assumption of an effect of 50% in comparison to that of strong inhibitors and inducers can be used to extrapolate the advice of the manufacturer. In case of palbociclib, the standard dose is 125 mg once daily (QD). The manufacturer recommends to reduce the dose of palbociclib to 75 mg (QD) if combination with a strong CYP3A inhibitor cannot be avoided. In combination with a moderate CYP3A inducer it could be considered to reduce the dose with 50% compared with the

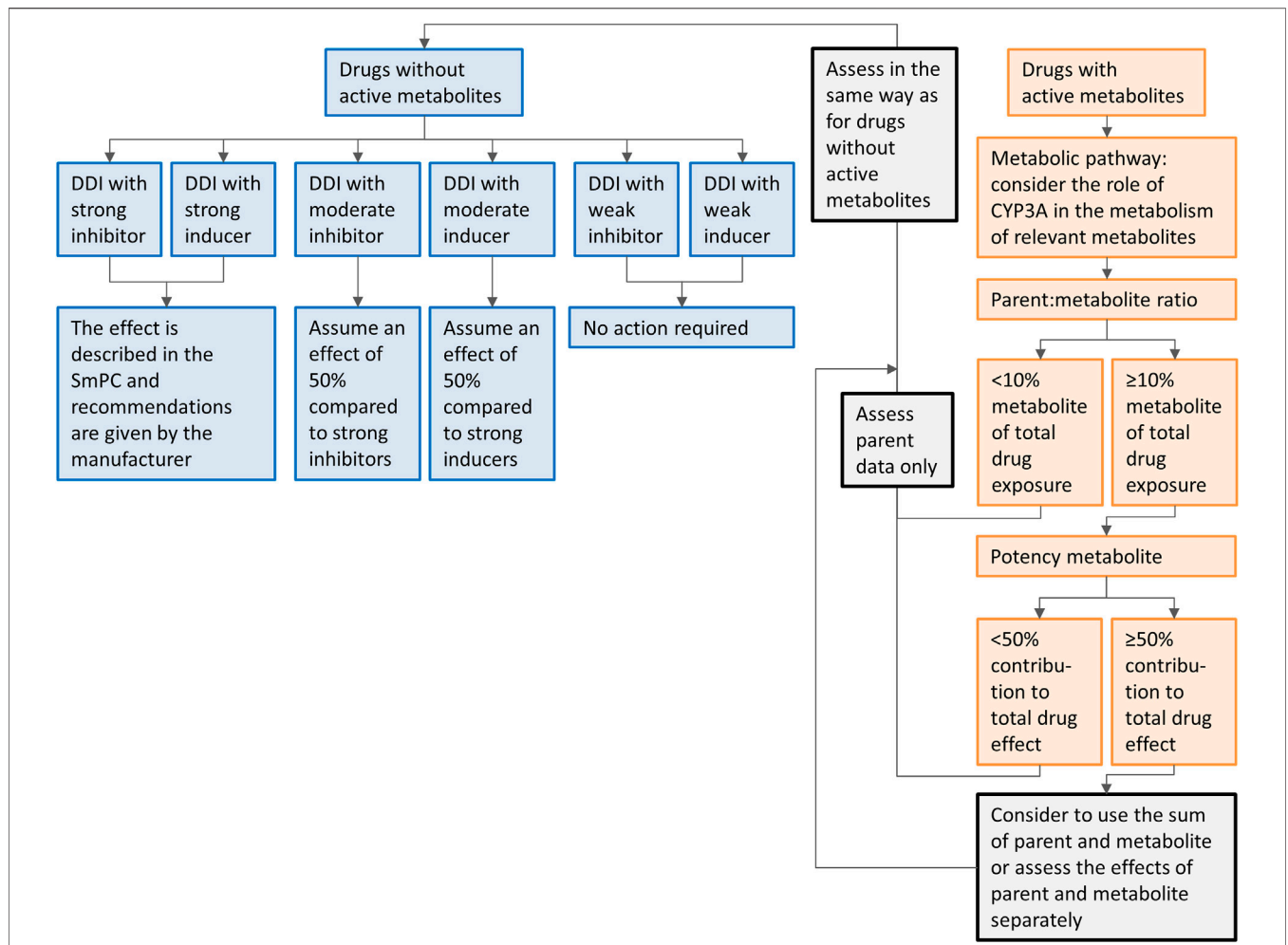


FIGURE 5 | Flowchart of the recommendations on how to handle DDIs for oral anticancer drugs metabolized by CYP3A if only clinical data from strong CYP3A inhibitors or inducers is available. Caution should be taken while using the flowchart for drugs in which auto-induction or -inhibition plays a role and drug-drug interaction studies are not performed on steady-state, or for drugs with nonlinear dose-exposure relationships.

reduction in combination with strong inhibitors. This would result in a dose of 100 mg QD (Food and Drug Administration, 2014d). A reason to reduce the dose of palbociclib is that a higher palbociclib exposure is associated with increased toxicity, specifically a larger decrease in absolute neutrophil count when compared with baseline. However, the limited data available on exposure-response and exposure-toxicity relationships could be a consideration to start with the standard starting dose and decrease the dose in case toxicity occurs (Flaherty et al., 2012; Food and Drug Administration, 2014d; Verheijen et al., 2017).

After initiation of therapy with oral anticancer drugs in a reduced or increased dose, attainment of adequate drug exposure could be monitored by means of Therapeutic Drug Monitoring. Many of the oral anticancer drugs show an exposure-efficacy and an exposure-toxicity relationship, the strength of the evidence for these relationships is and recommendations for target plasma trough levels are discussed by Verheijen et al. (Verheijen et al., 2017).

CONCLUSION

In conclusion, DDIs are often very complex and dependent on multiple factors. But, if only data from strong CYP3A inhibitors or inducers is available, in case of drugs without active metabolites, a change in exposure of 50% for moderate inhibitors/inducers compared with strong inhibitors/inducers can be assumed. We therefore recommend to start with a 50% dose reduction compared with the advised reduction in combination with strong inhibitors, and with a 50% dose increase compared to the advised increase in combination with strong and inducers.

Since an effect of weak CYP3A inhibitors on the AUC of oral anticancer drugs is small in the twelve reviewed drugs, *a priori* dose adaptations are not indicated.

In the presence of active metabolites, the response on DDIs should be based on the metabolic pathway, the exposure to the metabolites compared with the parent drug and to the potency of the metabolites. Options are to ignore the presence of a metabolite (for example when a metabolite is not

pharmacologically active or contributes minimal to the exposure of the drug) or to use the sum of the parent and metabolite (at least do this when parent and metabolite are equally potent).

AUTHOR CONTRIBUTIONS

LM-K, NS, and AH contributed to conception and design of the review. LM-K wrote the review, and designed figures and tables.

REFERENCES

- Bershas, D. A., Ouellet, D., Mamaril-Fishman, D. B., Nebot, N., Carson, S. W., Blackman, S. C., et al. (2013). Metabolism and Disposition of Oral Dabrafenib in Cancer Patients: Proposed Participation of Aryl Nitrogen in Carbon-Carbon Bond Cleavage via Decarboxylation Following Enzymatic Oxidation. *Drug Metab. Dispos.* 41, 2215–2224. doi:10.1124/dmd.113.053785
- Bolton, A. E., Peng, B., Hubert, M., Krebs-Brown, A., Capdeville, R., Keller, U., et al. (2004). Effect of Rifampicin on the Pharmacokinetics of Imatinib Mesylate (Gleevec, STI571) in Healthy Subjects. *Cancer Chemother. Pharmacol.* 53, 102–106. doi:10.1007/s00280-003-0722-9
- Budha, N. R., Ji, T., Musib, L., Eppler, S., Dresser, M., Chen, Y., et al. (2016). Evaluation of Cytochrome P450 3A4-Mediated Drug-Drug Interaction Potential for Cobimetinib Using Physiologically Based Pharmacokinetic Modeling and Simulation. *Clin. Pharmacokinet.* 55, 1435–1445. doi:10.1007/s40262-016-0412-5
- Chen, J., Xu, H., Pawlak, S., James, L. P., Peltz, G., Lee, K., et al. (2020). The Effect of Rifampin on the Pharmacokinetics and Safety of Lorlatinib: Results of a Phase One, Open-Label, Crossover Study in Healthy Participants. *Adv. Ther.* 37, 745–758. doi:10.1007/s12325-019-01198-9
- Cotreau, M. M., Siebers, N. M., Miller, J., Strahs, A. L., and Slichenmyer, W. (2015). Effects of Ketoconazole or Rifampin on the Pharmacokinetics of Tivozanib Hydrochloride, a Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor. *Clin. Pharmacol. Drug Dev.* 4, 137–142. doi:10.1002/cpdd.145
- Dickinson, P. A., Cantarini, M. V., Collier, J., Frewer, P., Martin, S., Pickup, K., et al. (2016). Metabolic Disposition of Osimertinib in Rats, Dogs, and Humans: Insights into a Drug Designed to Bind Covalently to a Cysteine Residue of Epidermal Growth Factor Receptor. *Drug Metab. Dispos.* 44, 1201–1212. doi:10.1124/dmd.115.069203
- Dirix, L., Swaisland, H., Verheul, H. M. W., Rottey, S., Leunen, K., Jerusalem, G., et al. (2016). Effect of Itraconazole and Rifampin on the Pharmacokinetics of Olaparib in Patients with Advanced Solid Tumors: Results of Two Phase I Open-Label Studies. *Clin. Ther.* 38, 2286–2299. doi:10.1016/j.clinthera.2016.08.010
- Einolf, H. J., Zhou, J., Won, C., Wang, L., and Rebello, S. (2017). A Physiologically-Based Pharmacokinetic Modeling Approach to Predict Drug-Drug Interactions of Sonidegib (LDE225) with Perpetrators of CYP3A in Cancer Patients. *Drug Metab. Dispos.* 45, 361–374. doi:10.1124/dmd.116.073585
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2018). Dabrafenib European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf (Accessed September 19, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP). (2014a). Everolimus European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/afinitor-epar-product-information_en.pdf (Accessed September 19, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2015b). Guideline on the Investigation of Drug Interactions. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf (Accessed May 14, 2020).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2015a). Guideline on the Investigation of Drug Interactions. 1–59. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf (Accessed May 14, 2020).

All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.670862/full#supplementary-material>

- guideline-investigation-drug-interactions-revision-1_en.pdf (Accessed May 14, 2020).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2006). Imatinib European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/glivec-epar-product-information_en.pdf (Accessed September 19, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2014b). Ketoconazole HRA European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/ketoconazole-hra-epar-product-information_en.pdf (Accessed September 19, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016a). Osimertinib European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf (Accessed September 20, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2016b). Palbociclib European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf (Accessed September 20, 2019).
- European Medicines Agency Committee for Medicinal Products For Human Use (CHMP) (2015c). Sonidegib European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/odomzo-epar-product-information_en.pdf (Accessed June 2, 2020).
- Flaherty, K. T., Lorusso, P. M., Demichele, A., Abramson, V. G., Courtney, R., Randolph, S. S., et al. (2012). Phase I, Dose-Escalation Trial of the Oral Cyclin-dependent Kinase 4/6 Inhibitor PD 0332991. *Administered Using a 21-Day Schedule Patients Adv. Cancer* 18, 568–577. doi:10.1158/1078-0432.CCR-11-0509
- Flockhart, D. A. (2007). Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana Univ. Sch. Med. Available at: <https://drug-interactions.medicine.iu.edu> (Accessed September 3, 2019).
- Food and Drug Administration (2015a). Center for Drug Evaluation and Research Alectinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2014a). Center for Drug Evaluation and Research Ceritinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2014b). Center for Drug Evaluation and Research Cobimetinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206192Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2012). *Center for Drug Evaluation and Research Dabrafenib Clinical Pharmacology and Biopharmaceutics Review* Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202806Orig1s000ClinPharmR.pdf (Accessed July 20, 2021).
- Food and Drug Administration (2008). Center for Drug Evaluation and Research Everolimus Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2001). Center for Drug Evaluation and Research Imatinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-335_Gleevec_biopharmr_P1.pdf (Accessed September 19, 2019).

- Food and Drug Administration (2018). Center for Drug Evaluation and Research Larotrectinib Multi-Discipline Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210861Orig1s000_211710Orig1s000MultidisciplineR.pdf (Accessed December 14, 2020).
- Food and Drug Administration (2015b). Center for Drug Evaluation and Research Lenvatinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206947Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2017). Center for Drug Evaluation and Research Lorlatinib Multi-Discipline Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210868Orig1s000MultidisciplineR.pdf (Accessed December 14, 2020).
- Food and Drug Administration (2014c). Center for Drug Evaluation and Research Olaparib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2015c). Center for Drug Evaluation and Research Osimertinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000ClinPharmR.pdf (Accessed July 12, 2021).
- Food and Drug Administration (2014d). Center for Drug Evaluation and Research Palbociclib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207103Orig1s000ClinPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration (2015d). Center for Drug Evaluation and Research Sonidegib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205266Orig1s000ClinPharmR.pdf (Accessed May 25, 2020).
- Food and Drug Administration (2005). Center for Drug Evaluation and Research Sunitinib Clinical Pharmacology and Biopharmaceutics Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938_S000_Sutent_BioPharmR.pdf (Accessed September 20, 2019).
- Food and Drug Administration. Center for Drug Evaluation and Research (2009). Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications Guidance for Industry Draft Guidance. 1–29. Available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (Accessed May 14, 2020).
- Food and Drug Administration. Center for Drug Evaluation and Research (2020a). Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry. Available at: <https://www.fda.gov/media/134581/download> (Accessed June 11, 2020).
- Food and Drug Administration. Center for Drug Evaluation and Research (2018). Physiologically Based Pharmacokinetic Analyses — Format and Content. Available at: <https://www.fda.gov/media/101469/download> (Accessed July 8, 2021).
- Food and Drug Administration. Center for Drug Evaluation and Research (2020b). Vitro Drug Interaction Studies — Cytochrome P450 Enzyme and Transporter Mediated Drug Interactions. Available at: <https://www.fda.gov/media/134582/download> (Accessed July 9, 2021).
- Fowler, S., Morcos, P. N., Cleary, Y., Martin-Facklam, M., Parrott, N., Gertz, M., et al. (2017). Progress in Prediction and Interpretation of Clinically Relevant Metabolic Drug-Drug Interactions: a Minireview Illustrating Recent Developments and Current Opportunities. *Curr. Pharmacol. Rep.* 3, 36–49. doi:10.1007/s40495-017-0082-5
- Frye, R. F., Fitzgerald, S. M., Lagattuta, T. F., Hruska, M. W., and Egorin, M. J. (2004). Effect of St John's Wort on Imatinib Mesylate Pharmacokinetics. *Clin. Pharmacol. Ther.* 76, 323–329. doi:10.1016/j.cpt.2004.06.007
- Groenland, S. L., van Nuland, M., Verheijen, R. B., Schellens, J. H. M., Beijnen, J. H., Huitema, A. D. R., et al. (2019). Therapeutic Drug Monitoring of Oral Antihormonal Drugs in Oncology. *Clin. Pharmacokinet.* 58, 299–308. doi:10.1007/s40262-018-0683-0
- Gupta, N., Hanley, M. J., Venkatakrishnan, K., Bessudo, A., Rasco, D. W., Sharma, S., et al. (2018). Effects of Strong CYP3A Inhibition and Induction on the Pharmacokinetics of Izaxomib, an Oral Proteasome Inhibitor: Results of Drug-Drug Interaction Studies in Patients with Advanced Solid Tumors or Lymphoma and a Physiologically Based Pharmacokinetic Ana. *J. Clin. Pharmacol.* 58, 180–192. doi:10.1002/jcph.988
- Heath, E. I., Blumenschein, G. R., Cohen, R. B., Lorusso, P. M., Loconte, N. K., Kim, S. T., et al. (2011). Sunitinib in Combination with Paclitaxel Plus Carboplatin in Patients with Advanced Solid Tumors: Phase I Study Results. *Cancer Chemother. Pharmacol.* 68, 703–712. doi:10.1007/s00280-010-1536-1
- Kovarik, J. M., Beyer, D., Bizot, M. N., Jiang, Q., Allison, M. J., and Schmoeder, R. L. (2005a). Pharmacokinetic Interaction between Verapamil and Everolimus in Healthy Subjects. *Br. J. Clin. Pharmacol.* 60, 434–437. doi:10.1111/j.1365-2125.2005.02434.x
- Kovarik, J. M., Beyer, D., Bizot, M. N., Jiang, Q., Shenouda, M., and Schmoeder, R. L. (2005b). Blood Concentrations of Everolimus Are Markedly Increased by Ketoconazole. *J. Clin. Pharmacol.* 45, 514–518. doi:10.1177/0091270005275368
- Kovarik, J. M., Beyer, D., Bizot, M. N., Jiang, Q., Shenouda, M., and Schmoeder, R. L. (2005c). Effect of Multiple-Dose Erythromycin on Everolimus Pharmacokinetics. *Eur. J. Clin. Pharmacol.* 61, 35–38. doi:10.1007/s00228-004-0866-5
- Kovarik, J. M., Beyer, D., and Schmoeder, R. L. (2006). Everolimus Drug Interactions: Application of a Classification System for Clinical Decision Making. *Biopharm. Drug Dispos.* 27, 421–426. doi:10.1002/bdd
- Kovarik, J. M., Hartmann, S., Figueiredo, J., Rouilly, M., Port, A., and Rordorf, C. (2002a). Effect of Rifampin on Apparent Clearance of Everolimus. *Ann. Pharmacother.* 36, 981–985. doi:10.1345/aph.1A384
- Kovarik, J. M., Kalbag, J., Figueiredo, J., Rouilly, M., O'Bannon, L., and Rordorf, C. (2002b). The Journal of Clinical Differential Influence of Two Cyclosporine Formulations on Everolimus Pharmacokinetics: A Clinically Relevant. *J. Clin. Pharmacol.* 42, 95–99. doi:10.1177/0091270002042001011
- Morcos, P. N., Cleary, Y., Guerini, E., Dall, G., Bogman, K., De Petris, L., et al. (2017). Clinical Drug-Drug Interactions through Cytochrome P450 3A (CYP3A) for the Selective ALK Inhibitor Alectinib. *Clin. Pharmacol. Drug Dev.* 6, 280–291. doi:10.1002/cpdd.298
- Özdemir, V., Kalow, W., Tang, B. K., Paterson, A. D., Walker, S. E., Endrenyi, L., et al. (2000). Evaluation of the Genetic Component of Variability in CYP3A4 Activity: A Repeated Drug Administration Method. *Pharmacogenetics* 10, 373–388. doi:10.1097/00008571-200007000-00001
- Patel, M., Chen, J., McGrory, S., O'Gorman, M., Nepal, S., Ginman, K., et al. (2020). The Effect of Itraconazole on the Pharmacokinetics of Lorlatinib: Results of a Phase I, Open-Label, Crossover Study in Healthy Participants. *Invest. New Drugs* 38, 131–139. doi:10.1007/s10637-019-00872-7
- Peng, B., Lloyd, P., and Schran, H. (2005). Clinical Pharmacokinetics of Imatinib. *Clin. Pharmacokinet.* 44, 879–894. doi:10.2165/00003088-200544090-00001
- Pilla Reddy, V., Bui, K., Scarfe, G., Zhou, D., and Learoyd, M. (2019). Physiologically Based Pharmacokinetic Modeling for Olaparib Dosing Recommendations: Bridging Formulations, Drug Interactions, and Patient Populations. *Clin. Pharmacol. Ther.* 105, 229–241. doi:10.1002/cpt.1103
- Ravaud, A., Urva, S. R., Grosch, K., Cheung, W. K., Anak, O., and Sellami, D. B. (2014). Relationship between Everolimus Exposure and Safety and Efficacy: Meta-Analysis of Clinical Trials in Oncology. *Eur. J. Cancer* 50, 486–495. doi:10.1016/j.ejca.2013.11.022
- Reddy, V. P., Walker, M., Sharma, P., Ballard, P., and Vishwanathan, K. (2018). Development, Verification, and Prediction of Osimertinib Drug-Drug Interactions Using PBPK Modeling Approach to Inform Drug Label. *CPT Pharmacometrics Syst. Pharmacol.* 7, 321–330. doi:10.1002/psp4.12289
- Reitman, M. L., Chu, X., Cai, X., Yabut, J., Venkatasubramanian, R., Zajic, S., et al. (2011). Rifampin's Acute Inhibitory and Chronic Inductive Drug Interactions: Experimental and Model-Based Approaches to Drug-Drug Interaction Trial Design. *Clin. Pharmacol. Ther.* 89, 234–242. doi:10.1038/clpt.2010.271
- Riva, R., Albani, F., and Contin, M. (1996). Pharmacokinetic Interactions between Antiepileptic Drugs. Clinical Considerations. *Clin. Pharmacokinet.* 31, 470–493. doi:10.2165/00003088-199631060-00005
- Saito, M., Hirata-Koizumi, M., Matsumoto, M., Urano, T., and Hasegawa, R. (2005). Undesirable Effects of Citrus Juice on the Pharmacokinetics of Drugs: Focus on Recent Studies. *Drug Saf.* 28, 677–694. doi:10.2165/00002018-200528080-00003

- Shumaker, R., Aluri, J., Fan, J., Martinez, G., Thompson, G. A., and Ren, M. (2015). Effects of Ketoconazole on the Pharmacokinetics of Lenvatinib (E7080) in Healthy Participants. *Clin. Pharmacol. Drug Dev.* 4, 155–160. doi:10.1002/cpdd.140
- Shumaker, R. C., Aluri, J., Fan, J., Martinez, G., Thompson, G. A., and Ren, M. (2014). Effect of Rifampicin on the Pharmacokinetics of Lenvatinib in Healthy Adults. *Clin. Drug Investig.* 34, 651–659. doi:10.1007/s40261-014-0217-y
- Smith, P. F., Bullock, J. M., Booker, B. M., Haas, C. E., Berenson, C. S., and Jusko, W. J. (2004). Erratum: The Influence of St. John's Wort on the Pharmacokinetics and Protein Binding of Imatinib Mesylate. *Pharmacotherapy* 24 (1508-1514), 11. doi:10.1592/phco.24.16.1508.50958
- Smittle, A. B., Grossmann, K. F., Ouellet, D., Richards-Peterson, L. E., Aktan, G., Gordon, M. S., et al. (2015). Assessment of the Drug Interaction Potential and Single- and Repeat-Dose Pharmacokinetics of the BRAF Inhibitor Dabrafenib. *J. Clin. Pharmacol.* 55, 392–400. doi:10.1002/jcph.437
- Van Erp, N. P., Baker, S. D., Zandvliet, A. S., Ploeger, B. A., Den Hollander, M., Chen, Z., et al. (2011). Marginal Increase of Sunitinib Exposure by Grapefruit Juice. *Cancer ChemotherPharmacol.* 67, 695–703. doi:10.1007/s00280-010-1367-0
- Van Erp, N. P., Gelderblom, H., Karlsson, M. O., Li, J., Zhao, M., Ouwkerk, J., et al. (2007). Influence of CYP3A4 Inhibition on the Steady-State Pharmacokinetics of Imatinib. *Clin. Cancer Res.* 13, 7394–7400. doi:10.1158/1078-0432.CCR-07-0346
- Verheijen, R. B., Yu, H., Schellens, J. H. M., Beijnen, J. H., Steeghs, N., and Huitema, A. D. R. (2017). Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. *Clin. Pharmacol. Ther.* 102, 765–776. doi:10.1002/cpt.787
- Vishwanathan, K., Dickinson, P. A., So, K., Thomas, K., Chen, Y. M., De Castro Carpeño, J., et al. (2018). The Effect of Itraconazole and Rifampicin on the Pharmacokinetics of Osimertinib. *Br. J. Clin. Pharmacol.* 84, 1156–1169. doi:10.1111/bcp.13534
- Wang, D., Guo, Y., Wrighton, S. A., Cooke, G. E., and Sadee, W. (2011). Intronic Polymorphism in CYP3A4 Affects Hepatic Expression and Response to Statin Drugs. *Pharmacogenomics J.* 11, 274–286. doi:10.1038/tpj.2010.28
- Wen, P. Y., Yung, W. K. A., Lamborn, K. R., Dahia, P. L., Wang, Y., Peng, B., et al. (2006). Phase I/II Study of Imatinib Mesylate for Recurrent Malignant Gliomas: North American Brain Tumor Consortium Study 99-08. *Clin. Cancer Res.* 12, 4899–4907. doi:10.1158/1078-0432.CCR-06-0773
- Westlind-Johnsson, A., Malmebo, S., Johansson, A., Otter, C., Andersson, T. B., Johansson, I., et al. (2003). Comparative Analysis of CYP3A Expression in Human Liver Suggests Only a Minor Role for CYP3A5 in Drug Metabolism. *Drug Metab. Dispos.* 31, 755–761. doi:10.1124/dmd.31.6.755
- Whirl-Carrillo, M., McDonagh, E., Hebert, J., Gong, L., Sangkuhl, K., Thorn, C., et al. (2012). Pharmacogenomics Knowledge for Personalized Medicine. *Clin. Pharmacol. Ther.* Available at: <https://www.pharmgkb.org/pathway/PA164713427/overview>.
- Yu, Y., Loi, C.-M., Hoffman, J., and Wang, D. (2017). Physiologically Based Pharmacokinetic Modeling of Palbociclib. *J. Clin. Pharmacol.* 57, 173–184. doi:10.1002/jcph.792
- Conflict of Interest:** JB: Modra Pharmaceuticals; NS: AB Science, Abbvie, Actuate Therapeutics, Amgen, Array, AstraZeneca/MedImmune, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Cantargia, Cytovation, Deciphera, Genentech/Roche, GlaxoSmithKline, Incyte, InterRNA, Lilly, Merck Sharp & Dohme, Merus, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Takeda; AH: Pfizer, Roche, Novartis, Merus.
- The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
- Copyright © 2021 Molenaar-Kuijsten, Van Balen, Beijnen, Steeghs and Huitema. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.