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Clinically relevant drug interactions with multikinase inhibitors: a review

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Abstract: Multikinase inhibitors (MKIs), including the tyrosine kinase inhibitors (TKIs), have rapidly become an established factor in daily (hemato)-oncology practice. Although the oral route of administration offers improved flexibility and convenience for the patient, challenges arise in the use of MKIs. As MKIs are prescribed extensively, patients are at increased risk for (severe) drug–drug interactions (DDIs). As a result of these DDIs, plasma pharmacokinetics of MKIs may vary significantly, thereby leading to high interpatient variability and subsequent risk for increased toxicity or a diminished therapeutic outcome. Most clinically relevant DDIs with MKIs concern altered absorption and metabolism. The absorption of MKIs may be decreased by concomitant use of gastric acid-suppressive agents (e.g. proton pump inhibitors) as many kinase inhibitors show pH-dependent solubility. In addition, DDIs concerning drug (uptake and efflux) transporters may be of significant clinical relevance during MKI therapy. Furthermore, since many MKIs are substrates for cytochrome P450 isoenzymes (CYPs), induction or inhibition with strong CYP inhibitors or inducers may lead to significant alterations in MKI exposure. In conclusion, DDIs are of major concern during MKI therapy and need to be monitored closely in clinical practice. Based on the current knowledge and available literature, practical recommendations for management of these DDIs in clinical practice are presented in this review.

Keywords: cytochrome P450 enzyme, drug–drug interaction, drug transporters, gastric acid suppression, metabolism, multikinase inhibitor

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Introduction

Although cancer is still the leading cause of death among men and women worldwide, novel treatment options are rapidly evolving. In order to improve treatment efficacy and minimize toxicity more specific targets have been identified. One of the most promising classes of targeted anticancer agents are the multikinase inhibitors (MKIs), including the tyrosine kinase inhibitors (TKIs). MKIs target specific tyrosine kinases within the tumor cell, where they play a key role in signal transduction, gene transcription, and DNA synthesis.[1] MKIs like osimertinib (for lung cancer) and cabozantinib (for kidney cancer) rapidly gained a place in standard of care treatment for multiple or new indications [e.g. regorafenib in primary liver cancer, after earlier approvals for gastrointestinal stromal tumor (GIST) and colorectal cancer].

MKIs include both small molecule MKIs and large molecule MKIs. In this review we will solely focus on the small molecule MKIs. Small molecule MKIs are administered orally, which gives them a clear advantage over conventional chemotherapy in terms of flexibility and patient convenience. Many MKIs show a narrow therapeutic window, whereas intra- and interpatient exposure is highly variable and multifactorial.[2–4] Also factors like food, beverages, lifestyle, and pharmacogenetic polymorphisms may alter MKI bioavailability significantly.[5] For example, as MKIs are predominately metabolized through phase I (e.g. CYP enzymes) or phase II enzymes

(e.g. UPD-glucuronyltransferases) or almost exclusively by phase II enzymes (e.g. in the case of afatinib), this makes them highly prone for drug–drug interactions (DDIs) involving drug metabolism.[6] Moreover, since cancer patients often use multiple drugs concomitantly with their anticancer therapy, they are even more at risk for DDIs, compared with other patient groups.[7]

DDIs can be classified as pharmacodynamic or pharmacokinetic.[8] Pharmacokinetic DDIs are defined as drug interactions regarding drug absorption, metabolism, distribution and elimination leading to altered plasma concentrations of a drug and possible unfavorable outcomes (e.g. increased toxicity and reduced treatment efficacy). A pharmacodynamic interaction is the altered response in terms of toxicity and efficacy when two or more drugs affect similar molecular targets (e.g. membrane receptors). Pharmacodynamic DDIs can be additive, antagonistic or synergistic. For instance, epidermal growth factor receptor (EGFR) kinase inhibitors often show synergistic antitumor effects when combined with chemotherapy.[9]

Both the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) present guidelines for the interpretation of DDIs. However, because of discrepancies between recommendations, currently no clear general consensus for the management of DDIs is available. Therefore, the management of DDIs is challenging for clinicians and the need for a general consensus is urgent.

This review article presents an overview of known pharmacokinetic DDIs regarding orally taken MKIs currently approved by the US FDA and EMA. Moreover, if possible, practical recommendations are given for the management of DDIs during MKI therapy in clinical practice.

Methods

We conducted a search in *PubMed* and the *Embase* databases for English language studies published until 2 July 2018 for randomized clinical trials, observational studies, and reviews about US FDA and EMA-approved MKIs. We used the following search MESH terms: '(Drug interactions) OR (Drug combination) AND (Drug name)'. In *Embase*, we used 'clinical studies', 'humans' and 'only in English' as additional search limits. The search results were manually screened for relevance. In addition, all MKI (US FDA and EMA) assessment reports were screened on the latest updates regarding DDIs in the scientific updates available at the EMA and US FDA website until 2 July 2018. We included clinical drug–drug interaction studies in human and preclinical pharmacokinetic studies investigating possible interactions. We excluded studies which did not focus on pharmacokinetics or drug interactions. Clinical relevance of the interaction was scored on the basis of the US FDA-classification of the effect of drug interactions and the level of available evidence as a 'major', 'moderate' or 'minor' interaction. If there was no clinical pharmacokinetic study performed, the interaction potential was estimated on the basis of the inhibitory concentration or pKa and the advice in the assessment reports.[10]

Absorption

Intragastric pH

The absorption of MKIs can be significantly affected by altered intragastric pH. When intragastric pH is elevated (e.g. due to proton pump inhibitors; PPIs), the MKI solubility, bioavailability, and eventually treatment efficacy may be significantly influenced (Figure 1).[8,11–13] The impact of this 'pH effect' is highly variable per MKI and the clinical relevance of the DDI between MKIs and acid-suppressive agents (e.g. PPIs, H_2-antagonists and antacids) must be assessed on an individual basis. A complete overview can be found in Table 1.[14–35]

Indecisive guidelines and the fact that 20–30% of all cancer patients have an indication for the use of acid-suppressive agents (ASAs) complicate the management of this DDI.[36] The general consensus is, if possible, to avoid the combination between MKIs and ASAs.[37] However, if there is a distinct indication for an ASA (e.g. Barrett's esophagus), a clear and practical advice to manage the DDI between MKIs and ASAs is essential to safeguard optimal MKI therapy. Based on the pharmacokinetics and pharmacodynamics of both MKIs and ASAs, practical advice can be given for the management of the DDI between MKIs and PPIs, H_2-antagonists (H_2As) and antacids (see Figure 1 and Table 1).[13] This advice may be extrapolated to newly introduced MKIs with a known or suspected drug interaction with gastric suppressive agents

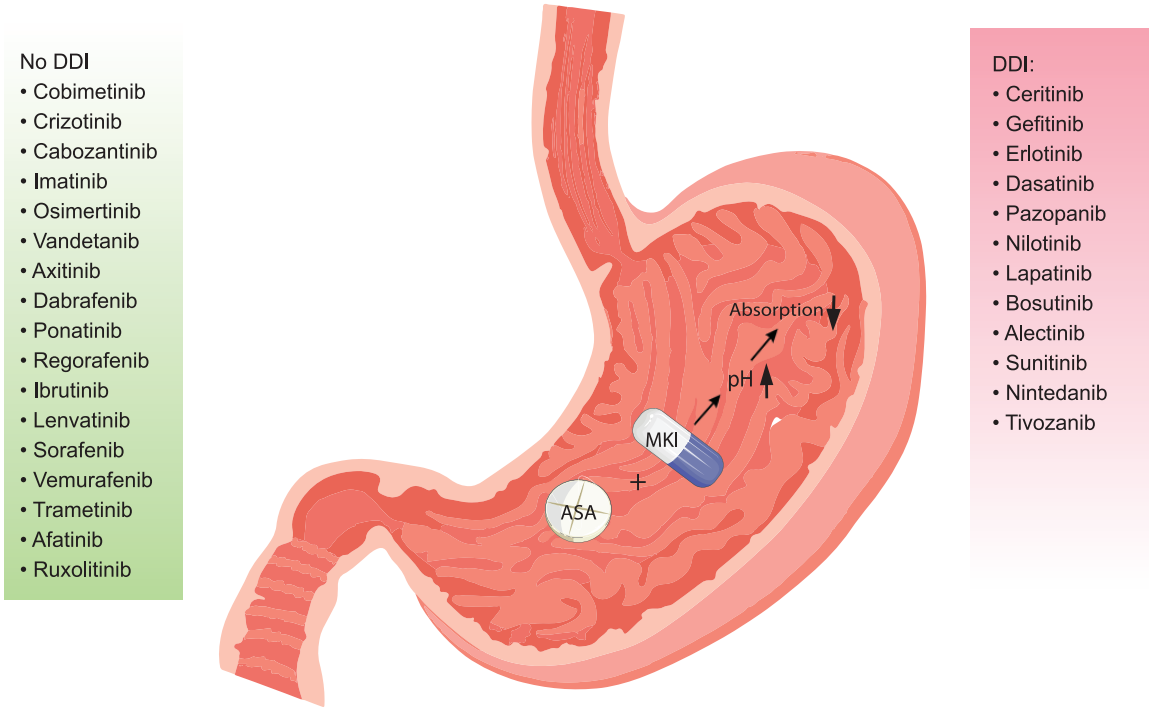

Figure 1. Working mechanism of the drug–drug interaction with an ASA: MKIs are arranged according to the clinical relevance and magnitude of the interaction in a descending order, with the most relevant interactions on top of the list. A PPI increases stomach pH after intake and thereby decreases absorption of MKIs and therefore bioavailability of MKIs.
ASA, acid-suppressive agent; DDI, drug–drug interaction; MKI, multikinase.

and thus with a great impact of the 'pH effect' as mentioned in Figure 1 and Table 1.

MKIs and PPIs. Since PPIs do not elevate intragastric pH over the full 24 h-range, a window of relatively low intragastric pH may be used to manage the DDI.[38] If there is a hard indication for PPI use, MKIs should be taken at least 2 h before the PPI in the morning in a once-daily regimen, since MKIs can be absorbed completely within this window.[13,38] Another possibility is to administer a MKI with an acidic beverage such as cola (pH = 2.5) to manage the DDI, since the acidic beverage temporarily decreases stomach pH resulting in better MKI solubility and absorption.[23] Furthermore, the influence of other acidic beverages [e.g. sprite (pH = 3.4) or orange juice (pH = 3.3)] on the absorption of MKIs has not been studied yet.

MKIs and H_2-antagonists. Since most H_2-antagonists show a short plasma half-life and are administered in a twice daily regimen (e.g. ranitidine), MKIs should be taken at least 2 h before or 10 h after the H_2-antagonist intake according to US FDA and EMA guidelines.[14,15]

Management MKIs and antacids. Antacids are relatively short-acting agents (e.g. magnesium hydroxide). MKIs should be administered at least 2 h before, or 4 h after antacid intake, to manage this DDI.[14,15]

Drug transporters and intestinal enzymes

As mentioned previously, MKI absorption is a multifactorial process mediated and affected by passive diffusion, active transport through multiple drug transporters, and intestinal metabolism.[7] The activity of these drug transporters and intestinal enzymes may significantly influence MKI bioavailability.

Drug transporters are located throughout the body, especially in the gut, bile ducts, kidneys and the blood–brain barrier (Figure 2).[39] The US FDA states: 'membrane transporters can have clinically relevant effects on the pharmacokinetics and pharmacodynamics of a drug in various organs and tissues by controlling its absorption, distribution, and elimination. In contrast to drug metabolizing enzymes that are largely expressed in the liver and

Table 1. DDIs regarding gastric acid suppression.

MKI (year of marketing approval)	Acid-suppressive compound	Decrease in C_{max}	Decrease in AUC	Clinical relevance	Recommendations	References
Afatinib (2013)	Not reported yet [a clinical trial is currently ongoing (NTR: 6652)]	NA	NA	Minor	Based on pKa a nonclinically relevant interaction is expected.	EMA;[14] US FDA[15]
Alectinib (2017)	Esomeprazole at least one hour before a regular breakfast for 5 days. Alectinib was administered 30 min after breakfast	16%	22%	Minor	Although the effects are minimal preferably avoid the use of acid-suppressive agents. Otherwise apply separate administration times or consider short-acting antacids.	EMA;[14] US FDA;[15] Morcos and colleagues[16]
Axitinib (2012)	Rabeprazole 20 mg for 5 consecutive days 3 h prior to axitinib intake	42%	5%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA;[15] Rugo and colleagues[17]
Bosutinib (2013)	Lansoprazole 60 mg/day for 2 consecutive days	46%	26%	Minor	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times or consider short-acting antacids.	EMA;[14] US FDA;[15] Abbas and colleagues[18]
Cabozantinib (2016)	Esomeprazole 40 mg delayed release capsule for 6 days 1 h before cabozantinib intake	10%	9%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA;[15] Nguyen and colleagues[19]
Ceritinib (2015)	Esomeprazole 40 mg for 6 consecutive days 1 h before ceritinib intake	79% (healthy subjects) 25% (patients)	76% (healthy subjects) 30% (patients)	Moderate	Avoid the use of acid-suppressive agents. Otherwise separate administration times. Antacids might be used 4 h before or 2 h after ceritinib intake or H_2-antagonists can be used 10 h before or 2 h after ceritinib intake.	EMA;[14] US FDA;[15] Lau and colleagues[20]
Cobimetinib (2015)	Rabeprazole 20 mg for 5 days prior to cobimetinib administration in a fasted and nonfasted state. In the fasted state concomitantly with cobimetinib and 1 h before cobimetinib in the nonfasted state	14% in the nonfasted state	$<$11%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA;[15] Musib and colleagues[21]

Table 1. (Continued)

MKI (year of marketing approval)	Acid-suppressive compound	Decrease in C_{max}	Decrease in AUC	Clinical relevance	Recommendations	References
Crizotinib (2012)	Esomeprazole 40 mg for 5 days concomitant with crizotinib	0%	10%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA[15]
Dabrafenib (2013)	Rabeprazole 40 mg for 4 consecutive days concomitant with dabrafenib	12%	3%	Minor	No interventions needed. Concomitant acid suppression is considered safe.	EMA;[14] US FDA[15]
Dasatinib (2006)	Omeprazole 40 mg for 4 consecutive days with dasatinib	42%	43%	Moderate	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times. H_2-antagonists can be used 2 h after dasatinib intake. Antacids can be used 2 h before or after dasatinib intake.	EMA;[14] US FDA;[15] Eley and colleagues[22]
	Maalox 30 ml concomitantly with dasatinib	58%	55%	Moderate		
	Maalox 30 ml 2 h before dasatinib	26%	NA	Minor		
	Famotidine 40 mg 10 h before dasatinib	63%	61%	Moderate		
Erlotinib (2005)	Omeprazole 40 mg for 7 consecutive days with erlotinib	61%	46%	Moderate	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times. Or H_2-antagonist should be used 2 h after erlotinib intake. Antacids can be used 4 h before or 2 h after erlotinib intake. Furthermore cola may increase erlotinib absorption.	EMA;[14] US FDA;[15] van Leeuwen and colleagues;[23] Kletzl and colleagues[24]
	Ranitidine 300 mg once daily concomitantly with erlotinib	54%	33%	Minor		
	Ranitidine 150 mg twice daily concomitantly with erlotinib	17%	15%	Minor		
Gefitinib (2009)	Ranitidine 450 mg twice daily 1 day before gefitinib intake	71%	47%	Moderate	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times. Antacids may be used 2 h before or after gefitinib intake.	EMA;[14] US FDA;[15] Yokota and colleagues[25]
Ibrutinib (2014)	Omeprazole 40 mg for 5 days in a fasted condition 2 h before ibrutinib intake	63%	nonsignificant difference	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA;[15] de Jong and colleagues[26]
Imatinib (2001)	Omeprazole 40 mg for 5 consecutive days 15 min before imatinib intake	3%	7%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA;[15] Sparano and colleagues;[27] Egorin and colleagues[28]

(Continued)

Table 1. (Continued)

MKI (year of marketing approval)	Acid-suppressive compound	Decrease in C_{max}	Decrease in AUC	Clinical relevance	Recommendations	References
Lapatinib (2008)	Esomeprazole 40 mg for 7 consecutive days in the evening (12 h before lapatinib intake)	NA	26%	Minor	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times. Antacids may be used 2 h before or after lapatinib intake.	EMA;[14] US FDA[15]
Lenvatinib (2015)	H2-blockers, antacids, PPIs not further specified in a PBPK analysis	nonsignificant difference	nonsignificant difference	Minor	No clinical studies, but concomitant use with acid-suppressive therapy is considered safe due to a PBPK analysis.	EMA;[14] US FDA[15]
Nilotinib (2007)	Esomeprazole 40 mg for 5 consecutive days 1 h before nilotinib intake	27%	34%	Minor	Avoid the use of acid-suppressive agents. Otherwise apply separate administration times. Antacids may be used 2 h before or after nilotinib intake or H_2-antagonists can be used 10 h before or 2 h after nilotinib intake.	EMA;[14] US FDA;[15] Yin and colleagues[29–31]
Nintedanib (2015)	No clinical study	NA	NA	Moderate	No clinical studies available, however nintedanib bioavailability decreases rapidly with increasing pH so a gastric acid-suppressive drug is likely to give a DDI.	EMA;[14] US FDA[15]
Osimertinib (2016)	Omeprazole 40 mg in a fasted state for 5 consecutive days	2%	7%	Minor	No interventions needed. Concomitant acid suppression can be used safely.	EMA;[14] US FDA[15]
Pazopanib (2010)	Esomeprazole 40 mg for 5 consecutive days	42%	40%	Minor	Pazopanib should be taken at least 2 h before or 10 h after a dose of an H2-antagonist. Antacids can be used 4 h before or 2 h after pazopanib intake. PPIs should be administered concomitantly with pazopanib in the evening.	EMA;[14] US FDA;[15] Tan and colleagues[32]

Table 1. (Continued)

MKI (year of marketing approval)	Acid-suppressive compound	Decrease in C_{max}	Decrease in AUC	Clinical relevance	Recommendations	References
Ponatinib (2013)	Lansoprazole 60 mg for 2 consecutive days concomitantly with ponatinib	25%	1%	Minor	No interventions needed. Concomitant acid-suppressive therapy is considered safe.	EMA;[14] US FDA;[15] Narasimhan and colleagues[33]
Regorafenib (2013)	Esomeprazole 40 mg for 5 consecutive days 3 h before and concomitantly with regorafenib. A clinical study was recently finished (De Man et al; Clin Pharmacol Ther *in press*.)	NA	NA	Minor	No clinical studies available. However regorafenib is considered to be safe since regorafenib pKa is high.	EMA;[14] US FDA[15]
Ruxolitinib (2012)	No clinical study	NA	NA	Minor	No clinical studies available. Concomitant acid-suppressive therapy is considered safe, since pKa of ruxolitinib is high.	EMA;[14] US FDA[15]
Sorafenib (2006)	Omeprazole 40 mg for 5 consecutive days	no significant difference	no significant difference	Minor	No interventions needed. Concomitant acid-suppressive therapy is considered safe.	EMA;[14] US FDA[15]
Sunitinib (2006)	No clinical study	NA	NA	Minor	Sunitinib shows high solubility and therefore concomitant acid-suppressive therapy is considered safe. However survival seems to be lower in patients using ASA.	EMA;[14] US FDA;[15] Olivier and colleagues[34]
Tivozanib (2017)	No clinical study	NA	NA	Moderate	No clinical studies available. However adverse event rate was higher in PPI users, which suggests higher tivozanib plasma levels due to a DDI.	EMA;[14] US FDA[15]

(Continued)

Table 1. (Continued)

MKI (year of marketing approval)	Acid-suppressive compound	Decrease in C_{max}	Decrease in AUC	Clinical relevance	Recommendations	References
Trametinib (2014)	No clinical study	NA	NA	Minor	Trametinib shows consistent solubility over all pH values. Therefore, concomitant acid-suppressive therapy is considered safe.	EMA;[14] US FDA[15]
Vandetanib (2012)	Omeprazole 40 mg for 5 days concomitantly	15%	6%	Minor	No interventions needed. Concomitant acid-suppressive therapy is considered safe.	EMA;[14] US FDA;[15] Johansson and colleagues[35]
	150 mg ranitidine for 5 days concomitantly with vandetanib	8%	1%	Minor		
Vemurafenib (2012)	No clinical study	NA	NA	Minor	No interventions needed. Concomitant acid-suppressive therapy is considered safe.	EMA;[14] US FDA[15]

Clinical relevance is scored by means of the US FDA Clinical Drug Interaction Studies, Study Design, Data Analysis, and Clinical Implications Guidance for Industry as a guideline as Major (AUC increase ⩾80%), Moderate (AUC increase ⩾50–<80%), Minor (AUC increase ⩾20–<50%) and by taking into account the performed study and the available evidence regarding pKa and the available assessment report.[10,14,15]

AUC, area under the curve; DDI, drug–drug interaction; EMA, European Medicines Agency; MKI, multikinase inhibitor; NA, not applicable/unknown; PBPK, physiologically based pharmacokinetic model; PPI, proton pump inhibitor; US FDA, United States Food and Drug Administration.

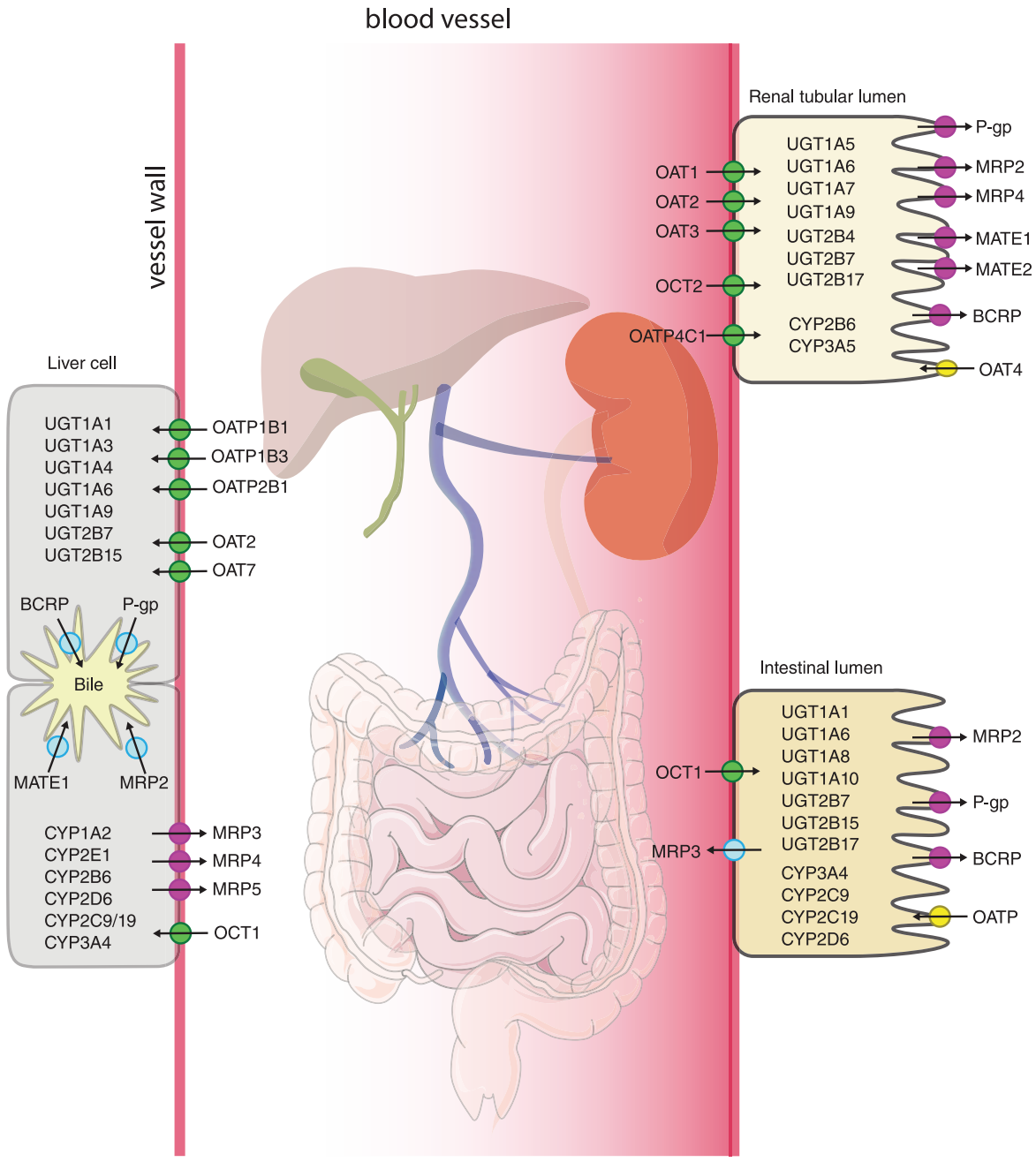

Figure 2. Distribution of drug transporters and metabolizing enzymes: A complete overview of all the drug transporters and metabolizing phase I and phase II enzymes are presented in this figure for the main organs involved in the pharmacokinetics of drugs.
BCRP, breast cancer resistance protein (ABCG2); CYP, cytochrome P450 iso-enzyme, MATE, multi-antimicrobial extrusion protein; MRP, multidrug resistance associated protein; OAT, organic anion transporters; OATP, organic anion transporting peptides; OCT, organic cation transporters; P-gp, P-glycoprotein (ABCB1); UGT, UDP-glucuronosyltransferase.

small intestines'.[10] Therefore, the effect of a DDI considering drug transporters may be of greater clinical relevance then is assumed so far.

Furthermore, efflux drug transporters like P-glycoprotein, or P-gp (ATP-binding cassette subfamily B member 1, ABCB1) and also breast cancer resistance protein (BCRP; ATP-binding cassette subfamily G member 2, ABCG2) may play a crucial role in drug absorption and enterohepatic recirculation. Enterohepatic recirculation is the process in which foreign chemicals are absorbed

into the portal blood stream and metabolized by hepatocytes, secreted into the bile and eventually are reabsorbed after secretion of bile in the gut lumen.[40] In this multi-step process drug transporters like P-gp and BCRP play a significant role. Other drug efflux transporters that may influence MKI bioavailability are the multidrug resistance protein subfamily (ATP-binding cassette subfamily C member 1 to 12, ABCC1 to 12, like MRP1) and the multi-antimicrobial extrusion protein (MATE), while several uptake transporters may be involved as well [e.g. organic anion transporting peptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs), see Figure 2].

Many drugs are known P-gp inhibitors (e.g. verapamil) or act as a strong P-gp-inducer (e.g. rifampicin). Drugs like cyclosporine, an inhibitor of several OATPs (e.g. OATP1B1 and BCRP) and cimetidine (OCT2 inhibitor) may influence other drug transporters as well. [41] For example, nintedanib showed a decrease in both area under the curve (AUC) and maximum concentration (C_{max}) when co-administered with rifampicin. Since nintedanib is almost exclusively metabolized by phase II enzymes, this effect on AUC and C_{max} is most likely due to P-gp induction.[42] In general the use of strong P-gp or BCRP inhibitors or inducers is discouraged when MKIs are substrates for these transporters. Furthermore, many MKIs show inhibition of several drug transporters by themselves (Table 2).[14,15,18,21,35,41,43–59] When a MKI acts like an inhibitor of these transporters and is co-administered with drug transporter substrates with a narrow therapeutic window (e.g. digoxin), close monitoring of side effects (e.g. severe arrhythmia for digoxin) is warranted. For some MKIs the clinical relevance of DDIs regarding drug transporters is negligible and the combination with inhibitory or inducing compounds is considered to be well tolerated (e.g. bosutinib).[14,15]

In contrast with the above mentioned unwanted adverse effects, mostly found in preclinical studies, DDIs concerning drug transporters and MKIs may also be used in a beneficial way. For example, MKIs may potentially increase chemotherapy concentrations through P-gp or BCRP inhibition (e.g. increased paclitaxel plasma concentration resulting from P-gp inhibition by nilotinib or increased nilotinib concentrations as a result of P-gp inhibition by imatinib).[60,61]

In conclusion, we found only a limited number of clinical studies, which investigated the effects of inhibition or induction of drug transporters by MKIs, since this is a relatively novel field of DDI research. Combinations between strong drug transporter inhibitory or inducing compounds should be avoided for most MKIs as mentioned in Table 2.

Intestinal metabolism

Another important factor in drug absorption is intestinal metabolism. Many MKIs are metabolized in the gut wall through intestinal CYP3A4, which is often in close proximity of drug transporters, such as P-gp. When a MKI is given concomitantly with an intestinal CYP3A4 inducer (e.g. rifampicin) or inhibitor (e.g. grapefruit juice) this may significantly change MKI bioavailability.[62] However, in contrast, Van Erp and colleagues failed to show a significant increase in sunitinib exposure, when co-administered with grapefruit juice.[63] Moreover, since many MKIs undergo extensive first-pass metabolism and are thus dependent of both intestinal and hepatic metabolism, it is difficult to determine whether intestinal metabolism or hepatic metabolism is the main contributor to an altered drug bioavailability.

Metabolism

In the liver, MKIs are predominately metabolized by CYP enzymes into either active or inactive metabolites. For some MKIs, like nintedanib, phase II metabolism through UDP-glycosyltransferases (UGTs), glutathione S-transferases and sulfotransferases (SULTs) is dominant in their metabolism.[6,64,65] Inhibition or induction of these phase I and II enzymes by co-administered medication may lead to either (severe) toxicity or loss of effective MKI therapy, respectively.

As DDIs with strong CYP3A4 inhibitors and inducers (e.g. ketoconazole and rifampicin, respectively) play a significant role in MKI therapy, they are usually well described and clear recommendations for the management of these DDIs are presented in the assessment report. There are many (strong) inducers or inhibitors of CYP enzymes for which a complete overview can be found at the FDA and EMA websites.[41,66] Moreover, some MKIs (e.g. imatinib, pazopanib) also displayed inhibitory or inducing activity by themselves.[67–70] The general advice is to avoid concomitant administration with strong inhibitors or inducers of CYP enzymes. If this is not possible, a MKI dose

Table 2. DDIs with drug transporters.

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Afatinib	P-gp, BCRP	*in vitro*: P-gp, BCRP	Ritonavir: 38% increase Rifampicin: 22% decrease	Ritonavir: 48% increase Rifampicin: 34% decrease	For strong P-gp and BCRP inhibitors (e.g. ritonavir, cyclosporine); use staggered dosing, preferably 6 h or 12 h apart from afatinib. When afatinib is administered with a strong P-gp inducer (e.g. rifampicin) increase the afatinib dose with 10 mg with close monitoring of side effects. For substrates of P-gp and BCRP close monitoring of side effects is recommended.	Moderate	EMA;[14] US FDA;[15] Wind and colleagues[43]
Alectinib	M4 is a P-gp substrate	*in vitro*: P-gp, BCRP	NA	NA	When alectinib is co-administered with P-gp or BCRP substrates appropriate monitoring of side effects of these substrates is recommended.	Minor	EMA;[14] US FDA;[15] Morcos and colleagues[44]
Axitinib	P-gp, BCRP	*in vitro*: P-gp, BCRP	NA	NA	appropriate monitoring of side effects is recommended when axitinib is used with P-gp and BCRP substrates or inhibitors and inducers.	Minor, since there is only *in vitro* evidence and axitinib is only a weak P-gp and BCRP substrate	EMA;[14] US FDA[15]
Bosutinib	P-gp	*in vitro*: P-gp, BCRP, OCT1 dabigatran (P-gp substrate): no effect on dabigatran pharmacokinetics	NA	NA	Clinical relevant interactions with drug transporters are not likely to appear.	Minor	EMA;[14] US FDA;[15] Abbas and colleagues;[18] Hsyu and colleagues[45]
Cabozantinib	MRP2	*in vitro*: P-gp, BCRP, MATE1, MATE2	NA	NA	Appropriate monitoring is recommended when using substrates of P-gp of BCRP. Interactions with MATE1-2 in clinically relevant concentrations are unlikely. If necessary, a 20 mg dose alteration may be applied. Close monitoring of side effects is warranted when administered with strong MRP2 inhibitors (e.g. cyclosporine).	Moderate	EMA;[14] US FDA[15]

(Continued)

Table 2. (Continued)

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Ceritinib	P-gp	P-gp, BCRP	NA	NA	Concomitant administration with strong inducers or inhibitors of P-gp must be avoided since plasma concentration of ceritinib might be altered. Close monitoring of side effects is warranted when administered with P-gp or BCRP substrates. However CYP DDIs are of greater influence.	Minor, since interactions regarding CYP enzymes are of greater clinical importance	EMA;[14] US FDA[15]
Cobimetinib	P-gp	*in vitro*: BCRP, OATP1B1, OATP1B3, OCT1	NA	NA	Concomitant administration with strong P-gp inducers or inhibitors must be avoided. Appropriate monitoring is recommended when using BCRP, OATP1B1, OATP1B3, OCT1 substrates.	Moderate	EMA;[14] US FDA;[15] Musib and colleagues[21]
Crizotinib	P-gp	*in vitro*: P-gp, OCT1, OCT2	NA	NA	Appropriate monitoring of side effects is recommended when using concomitant P-gp substrates, inhibitors and inducers. Furthermore, close monitoring is recommended when using P-gp, OCT1, OCT2 substrates.	Minor, since CYP interactions are of greater clinical importance	EMA;[14] US FDA[15]
Dabrafenib	P-gp, BCRP	*in vitro*: OATP1B1, OATP1B3, BCRP	Rosuvastatin: 160% increase	Rosuvastatin: 7% increase	Dabrafenib is not likely to have a clinically relevant interaction with OATP1B1, OATP1B3 and BCRP. Concomitant use with substrates of these transporters is considered safe. The influence of P-gp and BCRP inhibitors or inducers is considered to be small since the bioavailability of dabrafenib is high (95%), therefore only limited pharmacokinetic effects can be expected.	Minor	EMA;[14] US FDA[15]
Dasatinib	P-gp, BCRP	NA	NA	NA	Concomitant administration with strong inducers or inhibitors of P-gp and BCRP must be avoided or side effects must be monitored closely when administered with strong inhibitors.	Minor	EMA;[14] US FDA;[15] Haouala and colleagues[46]

Table 2. (Continued)

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Erlotinib	P-gp, BCRP	*in vitro*: OCT2, OAT3	NA	NA	Concomitant administration with strong inducers or inhibitors of P-gp or BCRP must be avoided since an altered plasma concentration is possible. Administration with OCT2 and OAT3 substrates should be avoided.	Moderate	EMA;[14] US FDA;[15] Marchetti and colleagues;[47] Sprowl and colleagues; Elmeliegy and colleagues[49]
Gefitinib	P-gp, BCRP	*in vitro*: BCRP, P-gp	NA	*In vitro* Irinotecan: AUC irinotecan 63% increase	Concomitant administration with P-gp and BCRP substrates should be avoided. BCRP inhibition is 10-fold stronger than P-gp inhibition. So especially be careful when gefitinib is combined with BCRP substrates. Avoid the use of strong BCRP or P-gp inhibitors or inducers since gefitinib plasma concentration may be altered.	Moderate	EMA;[14] US FDA;[15] Stewart and colleagues[50]
Ibrutinib	NA	*in vitro*: P-gp, BCRP	NA	NA	When P-gp or BCRP substrates are used, they should be taken at least 6 h before or after ibrutinib intake. Inhibitors or inducers of transporters are not likely to result in clinically meaningful changes in ibrutinib pharmacokinetics and can be used concomitantly.	Minor	EMA;[14] US FDA;[15] de Jong and colleagues[51]
Imatinib	P-gp, BCRP	*in vitro*: BCRP	NA	NA	A clinical relevant interaction with P-gp or BCRP inhibitors or inducers may be possible. Close monitoring of substrate specific side effects is advised when used concomitantly with BCRP substrates. Although the interaction potential is considered to be low.	Minor	EMA;[14] US FDA;[15] Eechoute and colleagues[52]
Lapatinib	P-gp, BCRP	*in vitro*: P-gp, BCRP, OATP1B1	Digoxin (P-gp substrate): 100% increase (digoxin)	Digoxin (P-gp substrate): 60–80% increase (digoxin)	Lapatinib is highly susceptible for interactions regarding drug transporters. When using P-gp, BCRP, OATP1B1 substrates close monitoring of side effects is recommended. The use of strong P-gp and BCRP inhibitors or inducers should be avoided.	**Major**	EMA;[14] US FDA;[15] Koch and colleagues[53]

(Continued)

Table 2. (Continued)

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Lenvatinib	P-gp, BCRP, MDR1	*in vitro*: P-gp, BCRP, OATP1B3	Ketoconazole: 19% increase single-dose rifampicin: 33% increase	Ketoconazole: 15% increase single-dose rifampicin: 31% increase	Clinical relevant interactions with strong inhibitors or inducers of P-gp, BCRP are not likely to appear, but close monitoring for lenvatinib specific side effects is recommended. Concomitant administration with P-gp, BCRP and OATP1B3 substrates should be avoided.	Minor	EMA;[14] US FDA;[15] Shumaker and colleagues [54,55]
Nilotinib	P-gp, BCRP	*in vitro*: P-gp, BCRP	NA	Imatinib (CYP3A4/P-gp inhibitor): nilotinib AUC increased with 18–40%	Concomitant administration with strong P-gp or BCRP inducers or inhibitors must be avoided since an altered plasma concentration is possible otherwise side effects should be monitored closely.	Minor	EMA;[14] US FDA;[15] Lemos and colleagues[56]
Nintedanib	P-gp	*in vitro*: P-gp, OCT1, BCRP	Ketoconazole: 83% increase Rifampicin: 60% decrease	Ketoconazole: 61% increase Rifampicin: 50% decrease	when administered with strong P-gp inhibitors a 100 mg step-wise dose reduction must be considered. The duration of therapy with strong inducers must be minimized since inadequate plasma levels of nintedanib might occur. Concomitant administration with P-gp, BCRP and OCT1 substrates should be avoided.	**Major**	EMA;[14] US FDA[15]
Osimertinib	P-gp, BCRP	*in vitro*: P-gp, BCRP	Rosuvastatin (BCRP substrate): 72% increase	Rosuvastatin (BCRP substrate): 35% increase	Concomitant administration with strong P-gp and BCRP inducers or inhibitors must be avoided since an altered plasma concentration is likely. When co-administered with BCRP or P-gp substrates close monitoring of side effects is recommended.	Minor	EMA;[14] US FDA[15]
Pazopanib	P-gp, BCRP	*in vitro*: OATP1B1, P-gp, BCRP	Lapatinib (P-gp and BCRP inhibitor) 60% Increase	Lapatinib (P-gp and BCRP inhibitor): 50% increase	Co-administration with strong P-gp or BCRP inhibitors must be avoided. Close monitoring of side effects is advised when used concomitantly with P-gp or BCRP substrates.	Moderate	EMA;[14] US FDA[15]

Table 2. (Continued)

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Ponatinib	P-gp, BCRP	*in vitro*: P-gp, BCRP	NA	NA	Appropriate monitoring is recommended when co-administered with P-gp or BCRP substrates. Also, the use of strong inhibitors or inducers of P-gp, BCRP must be avoided, although DDI potential is considered to be low since ponatinib is only a weak substrate for P-gp and BCRP.	Minor	EMA;[14] US FDA[15]
Regorafenib	P-gp, BCRP	*in vitro*: BCRP regorafenib has no effect on digoxin AUC	Rosuvastatin (BCRP substrate): 360% increase	Rosuvastatin (BCRP substrate): 280% increase	BCRP substrates should be used with caution. When administered with strong inhibitors or inducers of P-gp and BCRP close observation of side effects is warranted.	**Major**	EMA;[14] US FDA[15]
Ruxolitinib	NA	*in vitro*: P-gp, BCRP	NA	NA	When ruxolitinib is administered with P-gp or BCRP substrates close monitoring of side effects is advised for these substrates. DDI potential can be minimized if time between administration is kept apart as long as possible.	Minor	EMA;[14] US FDA[15]
Sorafenib	P-gp, OATP1B1, OATP1B3, MRP2-3	P-gp	NA	NA	Concomitant administration with strong inhibitors or inducers of P-gp, OATP1B1, OATP1B3 and MRP2-3 should be avoided. Administration with P-gp substrates should be done with caution.	Moderate	EMA;[14] US FDA;[15] Bins and colleagues[57]
Sunitinib	P-gp	*in vitro*: P-gp, BCRP co-administration with gefitinib (BCRP inhibitor) did not result in significant AUC changes of sunitinib	NA	NA	Appropriate monitoring is recommended when co-administered with P-gp or BCRP substrates. Also, the use of strong inhibitors or inducers of P-gp must be avoided.	Minor	EMA;[14] US FDA[15]
Tivozanib	NA	*in vitro*: BCRP	NA	NA	Co-administration with BCRP substrates must be avoided or side effects must be monitored closely.	Minor	EMA;[14] US FDA[15]

(Continued)

Table 2. (Continued)

MKI	Substrate	Inhibits	C_{max}	AUC	Clinical implications	Interaction potential	References
Trametinib	P-gp	*in vitro*: P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT2, and MATE1	NA	NA	Co-administration of strong inhibitors or inducers of P-gp must be avoided. When P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2 and MATE1 substrates are used, staggered dosing must be applied (at least 2 h apart) to minimize DDI risk. However, based on the low dose and low clinical systemic exposure relative to the *in vitro* inhibition or induction potential this is not expected to be of *in vivo* significance.	Minor	EMA;[14] US FDA[15]
Vandetanib	NA	*in vitro*: P-gp, BCRP, OCT2	Metformin (OCT-2 substrate) increased with 50% Digoxin (P-gp substrate) increased with 29%	Metformin (OCT-2 substrate) increased with 74% Digoxin (P-gp substrate) increased with 23%	Co-administration with P-gp, BCRP, OCT2 substrates must be avoided and side effects must be monitored closely. Concomitant intake with strong inhibitors or inducers of drug transporters is safe.	Moderate	EMA;[14] US FDA;[15] Johansson and colleagues[35]
Vemurafenib	P-gp, BCRP	*in vitro*: P-gp, BCRP	Digoxin (P-gp substrate) increased 50%	Digoxin (P-gp substrate) increased 80%	Concomitant administration with strong inhibitors or inducers of P-gp and BCRP should be avoided. Appropriate monitoring is recommended when co-administered with P-gp or BCRP substrates.	**Major**	EMA;[14] US FDA;[15] Zhang and colleagues[59]

Clinical relevance is scored by means of the US FDA Clinical Drug Interaction Studies, Study Design, Data Analysis, and Clinical Implications Guidance for Industry as a guideline as major (AUC increase ⩾80%), moderate (AUC increase ⩾50 to <80%), minor (AUC increase ⩾20 to <50%) taken into account the available evidence for both change in AUC of MKI and change in AUC for transporter substrates, since there is no separate scoring system for drug transporter interactions. If there was no clinical evidence, clinical relevance was estimated on the basis of available evidence regarding inhibitory concentrations and the assessment report. Interaction potential was then scored as minor or at most moderate.
Strong drug transporter inhibitors: *P-gp*: amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir and ritonavir, verapamil. *BCRP*: curcumin, cyclosporine, eltrombopag *OATP1B1/OATP1B3*: atazanavir, ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir, rifampin (single dose), simeprevir *OAT1/OAT3*: p-aminohippuric acid (PAH), probenecid, teriflunomide, *MATE1/MATE2-K*: cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib strong drug transporter inducers: *P-gp*: rifampicin, carbamazepine, phenytoin, St. John's wort, ritonavir.[10,41,58]
AUC, area under the curve; BCRP, breast cancer resistance protein (ABCG2); DDI, drug–drug interaction; EMA, European Medicines Agency; MATE; multi-antimicrobial extrusion protein; MKI, multikinase inhibitor; MRP, multidrug resistance associated protein; NA, not applicable or only preclinical data available; OAT, organic anion transporters; OATP, organic anion transporting peptides; OCT, organic cation transporters; P-gp, P-glycoprotein (ABCB1); US FDA, United States Food and Drug Administration.

adjustment, based on the advice given in the assessment report is recommended. For strong inducers a gradual dose escalation of the prescribed dose is advised with close monitoring of MKI-specific side effects. For an overview of clinically relevant DDIs and for practical recommendations see Table 3.[14,15,41,43,44,67-69,71–93]

Interactions with novel MKIs

In the last decade there has been a significant increase in the development of and treatment with MKIs resulting in more than a doubling of registered MKIs in the past 5 years. Earlier, we described the DDIs with MKIs which were approved before 1 August 2013.[6] Here, we give an extensive overview of the DDI potential and management of the novel MKIs, which have been approved after August 2013. A complete overview including all (new and older) MKIs is presented in Tables 1–3.

Afatinib. Afatinib is used in the treatment of non-small cell lung cancer (NSCLC). It is a substrate of P-gp and BCRP and is mainly metabolized through enzyme-catalyzed Michael adduct formation (phase II) and only in a minor extent to phase I enzymes like CYP3A4 and FMO (2%).[14,15] Concomitant administration with ritonavir (a P-gp inhibitor) showed a 48% increase in AUC and 39% increase in $C_{max.}$[43] Treatment with a potent P-gp inducer (rifampicin) prior to single-dose afatinib showed a moderate effect on both afatinib AUC and C_{max} (34% and 22% decrease respectively).[43] When afatinib is administered with strong P-gp and BCRP inhibitors, staggered dosing may be used, preferably 6 h or 12 h apart from afatinib intake. When afatinib is administered with strong P-gp inducers the dose may be increased with 10 mg with close monitoring of side effects. Administration with strong CYP inducers or inhibitors is considered safe, since no CYP enzymes are involved in afatinib metabolism. Furthermore *in vitro* studies showed afatinib itself to be an inhibitor of P-gp and BCRP, so close monitoring of side effects when administered with substrates for these transporters with a narrow therapeutic window is recommended.[14,15]

Alectinib. The anaplastic lymphoma kinase (ALK) inhibitor alectinib is used in the treatment of metastatic lung cancer. Alectinib as well as its M4 metabolite are considered equally active. Alectinib is primary metabolized by CYP3A4.[14,15] Co-administration with the strong CYP3A4 inhibitor posaconazole resulted in a 75% increase of AUC, while co-administration with rifampicin led to a 73% decrease in alectinib AUC.[44] Since alectinib and M4 are equally active, a dose modification is not necessary (unless patients experience a significant increase in toxicity) when alectinib is administered with strong inhibitors or inducers of CYP3A4. Since alectinib is a P-gp and BCRP inhibitor, close monitoring of side effects of these substrates is recommended, especially for drugs with a narrow therapeutic window (e.g. digoxin).

Bosutinib. Bosutinib is used in the treatment of chronic myeloid leukemia (CML). Although bosutinib is a P-gp substrate and inhibitor, DDIs are not likely to appear, since clinical studies demonstrated no significant effect on dabigatran (P-gp substrate) or bosutinib (when administered with the P-gp inhibitor lansoprazole) pharmacokinetics.[18,45] Therefore no bosutinib dose reductions are necessary, when administered with strong P-gp inducers or inhibitors. Bosutinib is mainly metabolized through CYP3A4 and co-administration with the strong inhibitor ketoconazole resulted in 420% increase in C_{max} and 760% increase in AUC.[74] Administration with rifampicin showed a significant 86% reduction in C_{max} and a 92% decrease in AUC of bosutinib. Administration with the moderate inhibitor aprepitant also showed an increase in AUC and $C_{max.}$[73] In conclusion; strong inhibitors or inducers of CYP3A4 must be avoided or a gradual 20% dose reduction should be applied, when co-administered with strong inhibitors of CYP3A4. Increasing the bosutinib dose is not useful, when co-administered with strong CYP3A4 inducers, since a maximal tolerated bosutinib dose of 600 mg is often not sufficient to compensate for the relatively large loss of exposure.[14,15]

Cabozantinib. Cabozantinib is used in the treatment of medullary thyroid carcinoma and renal cell carcinoma (RCC). Since cabozantinib is a P-gp and BCRP inhibitor, close monitoring of side effects of substrates with a narrow therapeutic window is recommended when co-administered with cabozantinib.[14,15] A study with ketoconazole and rifampicin showed a significant change in AUC (38% increase and 77% decrease, respectively).[75] There was no significant effect of cabozantinib on rosiglitazone (a CYP2C8 substrate) plasma pharmacokinetics, indicating no inhibitory effect on CYP2C8 in contrast to the *in vitro* data.[75] The product label recommends minimizing the risk of a

Table 3. DDIs regarding drug metabolism.

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Afatinib	mainly due to nonenzyme-catalyzed Michael adduct formation	FMO3, CYP3A4	NA	NA	ritonavir		38 % increase	48 % increase	No DDI is expected, combination with CYP inducers or inhibitors is considered safe. The effect is most likely through P-gp induction and inhibition.	Minor	EMA;[14] US FDA;[15] Wind and colleagues[43]
						rifampicin	22 % decrease	34% decrease			
Alectinib	CYP3A4	CYP2C8, CYP3A5	There was no influence on midazolam (CYP3A4 substrate) pharmacokinetics	CYP1A2, CYP2B6, CYP3A4 (*in vitro*)	Posaconazole		18% increase	75% increase	Since alectinib metabolites are equally effective as alectinib strong inhibitors or inducers of CYP3A4 can be safely combined with close monitoring of side effects from alectinib.	Minor (since alectinib metabolites are equally active)	EMA;[14] US FDA;[15] Morcos and colleagues[44]
						rifampicin	51% decrease	73% decrease			
Axitinib	CYP3A4	CYP3A5, CYP1A2, CYP2C19, UGT1A1	UGT1A4, UGT1A7, UGT1A9, CYP1A2	NA	ketoconazole		50% increase	106% increase	50% dose reduction of axitinib is recommended when concomitantly used with strong inhibitors of CYP3A4 and slow dose escalation is advised for strong inducers of CYP3A4. Smoking is not allowed since it might alter CYP1A2 metabolism.	Moderate	EMA;[14] US FDA;[15] Pithavala and colleagues[71,72]
						rifampicin	71% decrease	79% decrease			
Bosutinib	CYP3A4	Mono-oxygenase enzymes (FMO)	NA	NA	ketoconazole aprepitant (moderate CYP3A4 inhibitor)		420% increase 50% increase	760% increase 100% increase	Avoid strong and moderate CYP3A4 inhibitors or inducers. Otherwise stop bosutinib treatment or reduce bosutinib dose by 20%. Dose escalation is often not useful since adequate plasma levels are not reached with a maximum dose of 600 mg qd.	**Major**	EMA;[14] US FDA;[15] Hsyu and colleagues;[73] Abbas and colleagues[74]
						rifampicin	86% decrease	92% decrease			
Cabozantinib	CYP3A4	CYP2C9	CYP2C9, CYP3A, CYP2C19 (*in vitro*) No significant effect on Rosiglitazone AUC (CYP2C8 substrate)	NA	ketoconazole		no significant difference	38% increase	(Chronic) co-administration of strong inhibitors and inducers of CYP3A4 must be avoided. If necessary, a 20 mg dose alteration may be applied. For CYP2C9, CYP2C19 or CYP3A4 substrates with a narrow therapeutic window close monitoring of side effects is recommended, however the inhibitory and inducing potential of cabozantinib is likely to be low.	Moderate	EMA;[14] US FDA;[15] Nguyen and colleagues[75]
						rifampicin	no significant difference	77% decrease			

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Ceritinib	CYP3A4	NA	CYP3A4, CYP2C9, CYP2A6, CYP2E1 (*in vitro*)	CYP3A4	ketoconazole		20% increase	190% increase	A 30% dose reduction may be applied when ceritinib is administered with strong inhibitors of CYP3A4. Concomitant use of strong inducers should be avoided. When administered with CYP2C9, CYP2A6, CYP2E1 or CYP3A4 substrates close monitoring of side effects is recommended.	Moderate	EMA;[14] US FDA[15]
						rifampicin	44% decrease	70% decrease			
Cobimetinib	CYP3A4	CYP2C19, CYP2D6, UGT2B7	Dextromethorphan (CYP2D6 substrate) and midazolam exposure was not altered by cobimetinib.	CYP1A2 (*in vitro*)	itraconazole		220% increase	570% increase	Avoid the (chronic) use of strong CYP3A4 inhibitors or inducers (especially treatment with strong inhibitors). If treatment is necessary monitoring of side effects must be applied and the use must be limited. Also, a 20 mg dose adjustment may be made. Concomitant administration with CYP1A2 substrates must be avoided or side effects must be monitored closely.	**Major**	EMA;[14] US FDA;[15] Budha and colleagues[76]
						rifampicin (PBPK model)	63% decrease	83% decrease			
Crizotinib	CYP3A4	CYP3A5, CYP2C8, CYP2C19, CYP2D6	CYP3A4, CYP2B6, UGT1A1, UGT2B7 Midazolam AUC increased with 270%	UGT1A1, CYP2B6, CYP2C8, CYP2C9	ketoconazole		40% increase	220% increase	Avoid the (chronic) use of strong CYP3A4 inhibitors or inducers. If treatment is necessary monitoring of side effects is recommended. When administered with CYP3A4, UGT1A1, UGT2B7, CYP2C8, CYP2C9 or CYP2B6 substrates close monitoring is recommended.	**Major**	EMA;[14] US FDA;[15] Xu and colleagues[77]
						rifampicin	79% decrease	84% decrease			
Dabrafenib	CYP2C8	CYP3A4	CYP1A2, CYP2D6 R-warfarin (CYP2C19 substrate) AUC decreased with 33% and C_{max} increased with 19% S-warfarin (CYP2C9 substrate) AUC decreased with 37% and C_{max} increased with 17%	CYP3A4, CYP2B6 midazolam (a CYP3A4 substrate) AUC and C_{max} decreased with 47% and 65% respectively	ketoconazole gemfibrozil		33% increase no significant difference	71% increase 47% increase	Avoid the (chronic) use of strong CYP3A4 and CYP2C8 inhibitors or inducers. If there is a hard indication for the use of strong inhibitors or inducers, the duration of use must be limited. When used with CYP3A4, CYP1A2, CYP2B6, CYP2C9 and CYP2C19 substrates side effects must be monitored closely, especially in the first 3 days of use.	Minor	EMA;[14] US FDA;[15] Suttle and colleagues[78]
						rifampicin	27% decrease	34% decrease			

(Continued)

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Dasatinib	CYP3A4	FMO, UGT	CYP2C8, CYP3A4 simvastatin (CYP3A4 substrate) AUC and C_{max} increased with 20% and 37% respectively.	NA	Ketoconazole		384% increase	256% increase	Avoid strong CYP3A4 inducers or inhibitors. When administered with strong inhibitors dasatinib dose must be reduced with 20–40 mg. When administered with strong inducers a dose escalation must be applied with close monitoring of side effects. When administered with CYP2C8 or CYP3A4 substrates close monitoring of side effects is recommended.	**Major**	EMA;[14] US FDA;[15] Johnson and colleagues[79]
						rifampicin	81% decrease	82% decrease			
Erlotinib	CYP3A4	CYP1A2, CYP1A1, CYP1B1, CYP3A5	CYP1A1, CYP3A4, CYP2C8 and UGT1A1 Midazolam AUC decreased with 24% Paclitaxel (CYP2C8) AUC was unchanged	NA	Ketoconazole Ciprofloxacin (CYP1A2 inhibitor)		69% increase No significant difference	86% increase 39% increase	When strong CYP3A4, CYP1A2 inducers are used dose increase up to 300 mg is advised with monitoring of side effects. For strong inhibitors a 50 mg dose reduction is recommended. Use of CYP1A2 inducers or inhibitors (e.g. smoking) is discouraged. When administered with CYP3A4, CYP1A1, and UGT1A1 substrates close monitoring of side effects is recommended.	Moderate	EMA;[14] US FDA;[15] Hamilton and colleagues[80]
						rifampicin	29% decrease	69% decrease			
Gefitinib	CYP3A4	CYP3A5, CYP2C19 CYP2D6	CYP2D6 and CYP2C19 Metoprolol (a CYP2D6 substrate) AUC increased with 35%	NA	itraconazole		61% increase	78% increase	Dose reduction is not necessary, when combined with strong CYP3A4 inhibitors, since gefitinib has a good tolerability profile. The use of strong CYP3A4 inducers needs to be avoided. When combined with CYP2D6 or CYP2C19 substrates close monitoring of side effects is recommended.	**Major**	EMA;[14] US FDA;[15] Swaisland and colleagues[81]
						rifampicin	65% decrease	83% decrease			
Ibrutinib	CYP3A4	CYP2D6	CYP3A4	CYP2B6	ketoconazole grapefruit juice erythromycin voriconazole		2800% increase 250% increase 240% increase 570% increase	2300% increase 120% increase 200% increase 470% increase	If the use of strong CYP3A4 inhibitors is necessary reduce ibrutinib dose to 140 mg or temporarily (<7 days) stop ibrutinib therapy. For moderate inhibitors reduce ibrutinib dose to 280 mg. Minimize the time of use for strong inducers of CYP3A4. Strong inhibitors or inducers of CYP2D6 must be used with caution.	**Major**	EMA;[14] US FDA;[15] de Jong and colleagues[82]
						Rifampicin	92% decrease	90% decrease			

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Imatinib	CYP3A4	CYP3A5, CYP1A2, CYP2D6, CYP2C9, CYP2C19	CYP2C9 Cyclosporin (a CYP3A4/CYP2C8 substrate) concentration raised with 26% during imatinib therapy metoprolol (CYP2D6 substrate) AUC increased with 23% simvastatin (CYP3A4 substrate) AUC increased with 250%	NA	Ketoconazole		26% increase	40% increase	No intervention is needed for strong CYP3A4 inhibitors but monitoring for toxic effects is recommended and duration of strong CYP3A4 inhibitor compounds needs to be minimized. For CYP3A4 inducers a 50% imatinib dose increase may be applied. Also, close monitoring is recommended for concomitant use of CYP3A4, CYP2C9 and CYP2B6 substrates with narrow therapeutic windows.	Moderate	EMA;[14] US FDA;[15] Wang and colleagues;[67] O'Brien and colleagues; Atiq and colleagues[69]
						rifampicin	54% decrease	74% decrease			
Lapatinib	CYP3A4	CYP3A5, CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19	CYP3A4, CYP2C8 Midazolam (CYP3A4 substrate) AUC increased with 45% Paclitaxel (CYP2C8 substrate) AUC increased with 37% concomitant with pazopanib	NA	ketoconazole		114% increase	257% increase	For strong inhibitors lapatinib dose must be lowered to 500 mg. For strong inducers a gradual increase of lapatinib dose must be administered with close monitoring of side effects. When administered with CYP3A4 or CYP2C8 substrates close monitoring of side effects is recommended.	Moderate	EMA;[14] US FDA;[15] Tan and colleagues[83] Koch and colleagues[84]
						carbamazepine	59% decrease	72% decrease			
Lenvatinib	Oxidase by aldehyde oxydase and conjugation by glutathione	CYP3A4	NA	NA	ketoconazole		19% increase	15% increase	Lenvatinib administration with CYP3A4 inducers or inhibitors is considered safe.	Minor	EMA;[14] US FDA[15]
						rifampicin	no significant difference	18% decrease			
Nilotinib	CYP3A4	CYP2C8, CYP1A1, CYP1A2, CYP1B1	CYP2D6, CYP2C9, CYP3A4, CYP2C8, UGT1A1 (*in vitro*) Midazolam AUC increased 160% and C_{max} 100% Warfarin (CYP2C9 substrate) AUC did nog change	CYP2B6, CYP2C8, CYP2C9 (*in vitro*)	ketoconazole		84% increase	201% increase	For strong CYP3A4 inhibitors nilotinib dose must be lowered to 400 mg once daily. For strong inducers nilotinib dose must be gradually increased depending on toxic side effects. When administered with CYP2D6, CYP2C8 or CYP3A4, CYP2C9, UGT1A1 substrates close monitoring of side effects is recommended.	**Major**	EMA;[14] US FDA;[15] Zhang and colleagues[85]
						rifampicin	64% decrease	80% decrease			

(Continued)

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Nintedanib	Hydrolysis due to esterases	UGT1A1, UGT1A7, UGT1A8, UGT1A10, CYP's (5%)	NA	NA	ketoconazole		83% increase	61% increase	Nintedanib co-administration with strong CYP inducers or inhibitors is considered safe since only a small part is metabolized by CYP enzymes and the interaction is more likely through P-gp inhibition or induction.	Minor	EMA;[14] US FDA[15]
						rifampicin	60% decrease	50% decrease			
Osimertinib	CYP3A4	CYP3A5, CYP1A2, CYP2A6, CYP2C9, CYP2E1	CYP1A2, CYP2C8, UGT1A1(*in vitro*) CYP3A4, CYP3A5 Simvastatin AUC and C_{max} decreased with 9% and 23% respectively	CYP3A4, CYP1A2	itraconazole		20% decrease	24% increase	Administration with strong inhibitors of CYP3A4 is considered safe. Strong inducers of CYP3A4 must be used with caution and the duration must be minimized. When administered with CYP3A4/3A5, CYP1A2, CYP2C8 and UGT1A1 substrates close monitoring of side effects is recommended.	Moderate	EMA;[14] US FDA;[15] Vishwanathan and colleagues;[86] Harvey and colleagues[87]
						Rifampicin	73% decrease	78% decrease			
Pazopanib	CYP3A4	CYP1A2, CYP2C8	*in vitro*: CYP3A4, CYP2B6, CYP2C8, CYP2D6, CYP2E1, UGT1A1 midazolam AUC and C_{max} increased both with 30% respectively dextromethorphan (CYP2D6 substrate) AUC and C_{max} increased with 33% an 64% respectively paclitaxel (a CYP2C8 substrate) AUC and C_{max} increased with 26% and 31% respectively Caffeine (CYP1A2 substrate), Warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) AUC did not change	NA	ketoconazole		45% increase	66% increase	When a strong CYP3A4 inhibitor is administered a 50% pazopanib dose reduction may be applied for strong inducers duration of therapy must be limited. Close observations for CYP2C8, CYP2D6, CYP2E1, UGT1A1 and CYP3A4 substrates with narrow therapeutic windows must be applied when co-administered with pazopanib.	Minor	EMA;[14] US FDA;[15] Tan and colleagues[83]
						Phenytoin or carbamazepine	50% decrease	30% decrease			

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Ponatinib	CYP3A4	CYP2D6, CYP2C8, CYP3A5	NA	NA	ketoconazole		47% increase	78% increase	When administered with strong CYP3A4 inhibitors a dose reduction to 30 mg may be administered. The co-administration of strong inducers should be avoided or therapy duration should be minimized.	Moderate	EMA;[14] US FDA;[15] Narasimhan and colleagues[88,89]
						Rifampicin	42% decrease	62% decrease			
Regorafenib	CYP3A4	UGT1A9	*in vitro*: UGT1A1, UGT1A9, CYP2C8, CYP2B6, CYP2C9, CYP2C19, CYP3A4 Irinotecan metabolite (SN-38) (substrate of UGT1A1) AUC increased with 44%	NA	ketoconazole		40% increase	33% increase	Co-administration with strong inhibitors or inducers of CYP3A4 and UGT1A9 should be avoided. Influence on regorafenib plasma levels is relatively small. Regorafenib dose must be gradually increased when administered with strong CYP3A4 inhibitors and close monitoring of side effect with a 40mg dose escalation may be applied when administered with strong CYP3A4 inducers and the use must be minimized. Toxicity must be monitored for UGT1A1, UGT1A9, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 substrates; however, pharmacokinetic data did not result in clinically meaningful interactions.	Moderate	EMA;[14] US FDA[15]
						Rifampicin	20% decrease	50% decrease			
Ruxolitinib	CYP3A4	CYP2C9	Intestinal CYP3A4	NA	ketoconazole erythromycin		33% increase 8% increase	91% increase 27% increase	When administered with strong inhibitors of CYP3A4 and CYP2C9 a 50% dose reduction may be applied if there is relevant toxicity. For moderate inhibitors a dose reduction is not necessary. For strong CYP3A4 and CYP2C9 inducers the use must be minimized.	Moderate	EMA;[14] US FDA;[15] Shi and colleagues[90]
						Rifampicin	52% decrease	71% decrease			

(Continued)

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Sorafenib	CYP3A4	UGT1A9	UGT1A9, UGT1A1 Administration with cyclophosphamide (a CYP2B6 substrate), warfarin, midazolam, dextromethorphan, omeprazole or paclitaxel did not result in any significant changes in AUC of these substrates.	NA	ketoconazole		26% increase	11% increase	Sorafenib administration with strong inhibitors or inducers of CYP3A4 is considered safe. For UGT1A1 and UGT1A9 substrate specific side effects should be closely monitored. The use of strong UGT1A9 inhibitors or inducers should be avoided.	Minor	EMA;[14] US FDA[15]
						Rifampicin	no significant difference	37% reduction			
Sunitinib	CYP3A4	CYP1A2	NA	NA	ketoconazole		49% increase	51% increase	Dose reduction is advised when co-administered with strong CYP3A4 inhibitors to a minimum of 37.5 mg for GIST and metastatic renal cell carcinoma or 25 mg for neuro-endocrine tumors based on monitoring of tolerability. For strong CYP3A4 inducers an increase in 12.5 mg increments may be applied with monitoring of tolerability.	Minor	EMA;[14] US FDA[15]
						Rifampicin	23% decrease	46% decrease			
Tivozanib	CYP3A4	UGT1A, CYP1A1	CYP2B6, CYP2C8	NA	Ketoconazole		3% decrease	5% increase	Administration with strong inhibitors of CYP3A4 is considered safe. The use of strong CYP3A4 inducers must be minimized. Also, close monitoring of side effects is recommended when administered with CYP2B6 or CYP2C8 substrates.	Moderate	EMA;[14] US FDA;[15] Cotreau and colleagues[91]
						Rifampicin	9% increase	52% decrease			

Table 3. (Continued)

MKI	Major CYP	Minor CYPs and others	Inhibitory activity	Inducing activity	Inhibitory compound	Inducing compound	Change in C_{max}	Change in AUC	Clinical recommendations	Clinical relevance	References
Trametinib	Deacetylation and glucuronidation	CYP3A4	CYP2C8, CYP2C9, CYP2C19 (*in vitro*)	CYP3A4 (*in vitro*)	No studies available		NA	NA	Administration with strong inhibitors or inducers of CYP enzymes is considered safe since primary metabolism is not due to metabolism. DDI potential is likely to be low.	Minor	EMA;[14] US FDA[15]
						no studies available	NA	NA			
Vandetanib	CYP3A4	FMO1, FMO3	CYP2D6	CYP1A2, CYP2C9, CYP3A4 Midazolam AUC did not change	Itraconazole		4% decrease	9% increase	Administration with strong inhibitors of CYP3A4 is considered safe. Concomitant administration with strong inducers must be avoided or dose may be gradually increased. When administered with substrates for CYP2D6, CYP1A2, CYP2C9 and CYP3A4 close monitoring of side effects is recommended.	Minor	EMA;[14] US FDA;[15] Martin and colleagues[92]
						rifampicin	3% increase	40% decrease			
Vemurafenib	CYP3A4	UGT	*in vitro*: CYP1A2, CYP2C8, CYP2C9 150% increase in caffeine (CYP1A2 substrate) exposure was seen Warfarin (CYP2C9 substrate) exposure increased with 18%	CYP3A4, CYP2B6 Midazolam AUC decreased with 32%	no completed clinical study		NA	NA	The influence of CYP3A4 or UGT inhibitors or inducers is considered minimal. When administered with CYP1A2, CYP2C8, CYP2C9, CYP3A4 or CYP2B6 substrates close monitoring of side effects is recommended.	Minor	EMA;[14] US FDA[15]
						rifampicin	unknown	40% decrease			

Clinical relevance is scored by means of the US FDA Clinical Drug Interaction Studies, Study Design, Data Analysis, and Clinical Implications Guidance for Industry, for inducers as major (AUC decrease ⩾80%), moderate (AUC decrease ⩾50 to 80%), minor (AUC decrease ⩾20 to <50%) or unknown and for inhibitors as major (AUC increase ⩾400%), moderate (AUC increase ⩾100 to 400%), minor (AUC increase ⩾25 to <100%) or unknown as on the basis of the available evidence regarding inhibitory concentrations and the assessment report. Clinical relevance was scored on the basis of the highest score. Major CYP inhibitors: *CYP1A2*: Ciprofloxacin, enoxacin, fluvoxamine, zafirlukast *CYP2C8*: clopidogrel, gemfibrozil *CYP2C9*: fluconazole *CYP2C19*: fluconazole, fluoxetine, fluvoxamine, ticlopidine *CYP2D6*: bupropion, fluoxetine, paroxetine, quinidine, terbinafine, cinacalcet *CYP3A4*: boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, itraconazole, ketoconazole Major CYP inducers: *CYP2B6*: carbamazepine *CYP2C9*: carbamazepine, enzalutamide *CYP2C19*: enzalutamide, rifampicin, ritonavir *CYP3A4*: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort.[10,41,58,93]

AUC, area under the curve; CYP, cytochrome P450 iso-enzyme; DDI, drug–drug interaction; EMA, European Medicines Agency; FMO, flavin-containing monooxygenase; GIST, gastrointestinal stromal tumor; MKI, multikinase inhibitor; NA, not applicable/not available; PBPK, physiologically based pharmacokinetic; UGT, UDP-glucuronosyltransferase; US FDA, United States Food and Drug Administration.

DDI by avoiding co-administration with strong inducers or inhibitors of CYP3A4. If necessary, a dose adjustment (decrease or increase) of 20 mg following a step-by-step approach may be warranted.

Ceritinib. Ceritinib is used in the treatment of ALK-positive NSCLC. Ceritinib is a substrate and inhibitor for P-gp. Furthermore, ceritinib is mainly metabolized by CYP3A4. Treatment with ketoconazole resulted in 190% and 20% increase in ceritinib AUC and C_{max}, respectively.[14,15] Co-administration with rifampicin showed a 70% and 44% decrease in AUC and C_{max}, respectively.[14,15] If concomitant administration with strong inhibitors of CYP3A4 is unavoidable a dose reduction by one third of the initial dose is necessary (rounded to units of 150 mg). For strong CYP3A4 inducers gradual dose escalation is possible with close monitoring of MKI-specific side effects.

Cobimetinib. Cobimetinib is a BRAF inhibitor used in the treatment of melanoma. It is a substrate for P-gp and inhibits BCRP, OATP1B1, OATP1B3, and OCT1.[14,15] Therefore, close monitoring of side effects is warranted when cobimetinib is administered with BCRP (e.g. rosuvastatin), OATP1B1, OATP1B3 (e.g. atorvastatin) or OCT1 substrates (metformin) with a narrow therapeutic window. Cobimetinib is primarily metabolized by CYP3A4 and UGT2B7. When co-administered with itraconazole 570% and 220% increase in AUC and C_{max} was seen, respectively.[14,15] A physiologically based pharmacokinetic (PBPK) model demonstrated rifampicin to decrease cobimetinib AUC by 83% and C_{max} by 63%.[76] So, the co-administration with strong inhibitors or inducers of CYP3A4 and P-gp must be avoided. However, rabeprazole (a P-gp inhibitor) showed no effects on the pharmacokinetics of cobimetinib.[21] If concomitant use of cobimetinib and strong CYP3A4 inhibitors is unavoidable, the cobimetinib dose should be decreased with 20 mg (33%) following a step-by-step approach. Furthermore, since cobimetinib is a CYP1A2 inhibitor, concomitant use with CYP1A2 substrates (e.g. haloperidol) may lead to altered plasma concentrations of these substrates.[14,15]

Dabrafenib. Dabrafenib is a BRAF inhibitor used in the treatment of advanced melanoma and NSCLC. Dabrafenib was shown to be a substrate for P-gp and BCRP. Since the bioavailability of dabrafenib is high (95%), only limited pharmacokinetic effects can be expected with inhibitors and inducers of these drug transporters. Dabrafenib is metabolized by both CYP3A4 (24%) and CYP2C8 (67%). Administration of dabrafenib with ketoconazole, gemfibrozil (a CYP2C8 inhibitor), and rifampicin showed significant changes in AUC, however these effects were mostly relatively small.[14,15] Furthermore, dabrafenib is known to auto-induce CYP3A4 mediated metabolism.[14,15] In conclusion, concomitant administration with strong CYP3A4 and CYP2C8 inhibitors or inducers must be avoided. Furthermore, a study with warfarin showed a 37% and 33% decrease in AUC and an 18% and 19% decrease in C_{max} for S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4/CYP1A2 substrate), respectively.[78] Therefore, dabrafenib is characterized as a moderate CYP3A4 inducer and a weak CYP2C9 inducer and as a result concomitant use of substrates for these enzymes must be avoided.[78]

Ibrutinib. Ibrutinib is used as treatment for chronic lymphatic leukemia (CLL) and mantle cell lymphoma. Ibrutinib is an inhibitor of P-gp and BCRP.[14,15] Ibrutinib is mainly metabolized by CYP3A4. Ketoconazole gave 2800% and 2300% increase in C_{max} and AUC respectively.[14,15,51] Furthermore concomitant administration with rifampicin showed 92% and 90% decrease in C_{max} and AUC respectively.[14,15] Administration with a moderate inhibitor of CYP3A4 (e.g. erythromycin) led to 240% and 200% increase in C_{max} and AUC respectively.[14,15,82] Overall concomitant administration with strong CYP3A4 inhibitors or inducers must be avoided. If ibrutinib is administered with moderate and strong CYP3A4 inhibitors the ibrutinib dose should be reduced to 280 mg and 140 mg respectively. When ibrutinib is administered with substrates of P-gp and BCRP monitoring of side effects of these substrates is warranted. When toxicity appears the dose of these substrates may be decreased.

Lenvatinib. Lenvatinib is used in the treatment of RCC and advanced thyroid carcinoma. It was shown to be a MDR1 substrate, a P-gp and BCRP substrate and inhibitor and an OATP1B3 inhibitor *in vitro*.[14,15] When lenvatinib is administered with ketoconazole or rifampicin, only marginal changes in AUC and C_{max} were observed.[54,55] Since lenvatinib is mainly metabolized through several phase II mechanisms (e.g. aldehyde oxidase and glutathione conjugation) into less active metabolites and only for a small part by CYP3A4, these changes were most likely due to an

interaction with P-gp.[14,15] Lenvatinib has an overall low DDI potential and dose modifications are currently not considered necessary.

Nintedanib. Nintedanib is used in the treatment of NSCLC. It is a substrate and weak inhibitor of P-gp.[14,15,94] When nintedanib is administered with a strong P-gp inhibitor, a 100 mg (25%) step-wise daily dose reduction must be considered with close monitoring of side effects. Use of strong P-gp inducers must be avoided, since nintedanib plasma concentrations may decrease. Nintedanib is mainly metabolized due to hydrolysis by esterases and glucuronidated by UGT with only a minor involvement of CYP enzymes (CYP3A4; 5%).[14,15] Administration with ketoconazole resulted in 61% and 83% increase in AUC and C_{max} respectively and administration with rifampicin demonstrated a decrease in AUC of 50% and 60% of C_{max} respectively.[42] These differences were probably due to a DDI with P-gp. Therefore, concomitant administration with strong inhibitors or inducers of CYP3A4 is considered safe.

Osimertinib. Osimertinib is used in the treatment of NSCLC.[14,15] Osimertinib is a substrate and inhibitor for P-gp and BCRP.[14,15] A study with rosuvastatin (a sensitive BCRP substrate) showed an increase in AUC and C_{max} of 35% and 72% of rosuvastatin respectively.[87] Osimertinib is mainly metabolized by CYP3A4 and CYP3A5, but only rifampicin resulted in a significant change in both AUC and C_{max} in contrast to itraconazole.[86] A study with simvastatin (a CYP3A4 substrate) resulted in a slight decrease in AUC and C_{max} of simvastatin of 9% and 23%, but these changes are not considered to be of clinical significance.[87] In conclusion only strong CYP3A4 inducers must be used with caution and close monitoring of side effects of osimertinib is warranted.

Ponatinib. Ponatinib is used in the treatment of CML and Acute lymphatic leukemia (ALL). Ponatinib is a substrate and inhibitor of P-gp and BCRP.[14,15] Therefore, concomitant use of ponatinib with strong inhibitors or inducers of these transporters should be avoided. Ponatinib is mainly metabolized into nonactive metabolites by CYP3A4 and to a lesser extent by CYP2D6, CYP2C8 and CYP3A5.[14,15] A study with concomitant ketoconazole administration showed an increase in C_{max} of 47% and 78% in AUC of ponatinib.[88] Multiple dosing of rifampicin demonstrated a decrease in AUC and C_{max} of 42% and 62% respectively.[89] As a consequence, concomitant administration with inhibitors of CYP3A4 and P-gp should be avoided or a dose reduction to 30 mg should be applied when administered concomitantly. Moreover, the use of strong CYP3A4 or P-gp inducers must be avoided or duration must be minimized, since ponatinib exposure may change.

Tivozanib. Tivozanib is used in the treatment of RCC. Tivozanib is an inhibitor of BCRP and is metabolized by multiple liver enzymes, including CYP3A4, CYP1A1 and several UGT1A enzymes (e.g. UGT1A1, UGT1A3 and UGT1A7).[14,15] A study with rifampicin showed a 52% decrease in tivozanib AUC. Therefore, the administration with strong CYP3A4 inducers should be avoided. A dose escalation is not necessary since the effect on tivozanib exposure is relatively small. Ketoconazole did not result in significant changes in tivozanib exposure.[14,15,91] Administration with strong CYP3A4 inhibitors is therefore considered safe. Furthermore, the concomitant administration with strong UGT inhibitors or inducers (e.g. probenecid or ibuprofen) should be avoided since tivozanib plasma concentrations potentially may change.

Trametinib. Trametinib is used in the treatment of melanoma and NSCLC. It is a known inhibitor of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OAT2B1, OCT2 and MATE1 and a substrate for P-gp.[14,15] As a result, the use of strong inhibitors or inducers of P-gp (e.g. ketoconazole) must be avoided. Trametinib is metabolized through deacetylation, oxidation and glucuronidation pathways.[14,15] No drug interaction studies are available to date, however since trametinib is not dependent on CYP isoenzymes, no DDIs with CYPs are to be expected.

DDI studies with longer available MKIs

In recent years several new studies have been published that investigated DDIs with longer available MKIs. Most of these studies are listed in Tables 1–3. There are only a few clinical DDI studies concerning drug transporters, since most studies mainly focus on CYP interactions. A phase I study investigated the combination of gefitinib and irinotecan and found an increase in SN-38 (the active irinotecan metabolite) and irinotecan plasma exposure, attributed to an enhanced BCRP activity in the gut.[50] Moreover, in patients using sorafenib with rifampicin, the concentration of the metabolite sorafenib-glucuronide increased, suggesting inhibition of

OATP1B1 by rifampicin and confirms sorafenib as an OATP1B1 substrate.[57]

Several new studies investigated possible DDIs regarding drug metabolism. For a complete overview see Table 3. For example: imatinib co-administration caused a 26% increase in cyclosporine (CYP3A4 and CYP2C8 substrate) plasma levels, explained by CYP3A4 inhibition by imatinib.[69] In addition, lapatinib and pazopanib demonstrated an increase of 23% and 26% in paclitaxel AUC respectively, suggesting inhibition of CYP2C8 by these MKIs.[83,95] Furthermore, regorafenib significantly increased the exposure to irinotecan and its active metabolite SN-38 due to UGT1A1 inhibition.[96,97]

Although most MKIs are metabolized through CYP enzymes it becomes more apparent that MKI metabolism is multifactorial and the inhibition and induction of other pathways (such as drug transporters) may also significantly influence MKI exposure. More research is needed to fully assess the DDI potential of these new pathways and their clinical relevance.

Discussion

Many MKIs have a narrow therapeutic window, with a clear relation between exposure and response on one hand and toxicity on the other.[98] For example, sunitinib and pazopanib show increasing severe toxicity with raising plasma concentration, leading to dose reductions and discontinuation of treatment in many patients.[99,100] Meanwhile, a threshold for efficacy for these drugs is seen.[98–100] Therefore, it is important to provide the right dose for the individual patient, in order to optimize treatment efficacy and minimize toxicity. To accomplish this, there is a shifting paradigm towards personalized dosing in oncology practice.[5] Along with other factors, DDIs are key factors influencing MKI exposure and subsequent clinical outcome. In addition, cancer patients are at greater risk for DDIs.[7] Therefore, a structured medication review for clinically relevant DDIs should take place on a regular basis.

To create a solid base for medication review, more DDI studies are strongly needed and results should be weighed on their clinical relevance. Specific and practical guidelines must be developed to guide clinicians and pharmacists in the management of DDIs in clinical practice. A practical way to reach this goal is by establishing clinical expert groups for consensus-based evaluation of clinical significance and management of the DDIs.[101]

ASAs may strongly decrease MKI bioavailability. Since there is no clear general consensus on the management of this DDI we presented a practical advice for all ASAs. However, another problem is that there is no standard design for clinical DDI research with ASAs. Ideally, drug exposure should be compared in a crossover design between MKI monotherapy and during co-administration of the strongest ASA [e.g. the PPI esomeprazole (40 mg)] 3 h prior to MKI administration, since maximum intragastric pH elevating effect of this PPI is reached after this time period.[38] In that case, when no effects are seen, a DDI between MKIs and PPIs can be ruled out. When a significant DDI with H_2-antagonists and antacids is expected, a corresponding treatment arm may be added. A more standardized study design of these ASA-DDI studies may provide a solid basis for practical management of this DDI, since study results could more easily be interpreted and compared between different MKIs.

Drug transporters are located throughout the body and thus potentially influence pharmacokinetics on multiple levels.[39] To date, insufficient attention has been given to the clinical relevance of these DDIs concerning drug transporters. Unfortunately, there is a lack of clinical studies investigating this type of DDI. Furthermore, many registration studies use ketoconazole or rifampicin as an inhibitor or inducer of CYP3A4, but these drugs are also strong inhibitors or inducers of P-gp. As a result, the P-gp effect may be underestimated or overestimated in the assessment reports. More research is needed to fully assess the DDI potential concerning drug transporters.

In contrast, DDIs with drug transporters may also be used for beneficial purposes. For instance, inhibition of certain drug transporters (e.g. P-gp) in the blood–brain barrier might theoretically lead to altered blood–brain barrier penetration, which may result in better brain (metastasis) penetration of a MKI, for example, osimertinib.[102] In addition, Zimmerman and colleagues demonstrated a protective effect on hand-foot skin reaction in mice, a frequently seen side effect of sorafenib, when sorafenib was concomitantly taken with the OAT6 inhibitor probenecid.[103]

Furthermore erlotinib may reduce cisplatin toxicity (e.g. nephrotoxicity and ototoxicity) through OCT2 inhibition.[48] Such potentially useful applications of DDIs between MKIs and drug transporters need to be further explored, and may in the future result in more effective MKI therapy.

In current DDI research there is a trend towards a model-based DDI prediction, like the PBPK-models.[104,105] PBPK-models are multi-compartmental (often represented as single organs or tissues) models which use (*in vitro*) pharmacokinetic data and human physiologically-dependent system parameters to predict DDIs with a mathematical model.[106] A disadvantage of PBPK modeling is the lack of sufficient *in vivo* data that adds to the uncertainty in the predictions of the PBPK model. Also, the lack of knowledge regarding multifactorial physiologic changes in, for instance, enzyme and transporter expression and activity might be a possible confounding factor. Despite the evident benefits of PBPK modeling in current DDI research, confirmatory evidence from clinical trials in humans is needed to assess a good predicting model.[105]

Another novel approach in oncology in managing DDIs is therapeutic drug monitoring (TDM). For many MKIs there is a clear relationship between exposure, toxicity and treatment efficacy (e.g. imatinib, pazopanib and sunitinib).[98,100,107] For some MKIs TDM could be an alternative way to manage DDIs in MKI therapy, where dose adjustments can be made if plasma levels are outside the therapeutic range. Furthermore, TDM has the advantage of monitoring MKI treatment, continuously over a longer time period which may result in better therapy efficacy. However, further research is needed to confirm the clinical relevance of TDM as a tool in DDI management.

In conclusion, most MKIs are highly prone to cause DDIs. Drugs that elevate intragastric pH, strong inhibitors or inducers of CYP enzymes and drug transporters can result in clinically relevant changes in MKI exposure. For many DDIs the only evidence for a potential DDI comes from *in vitro* data or is predicted based on PBPK modeling. Without clinical data it is difficult to determine the exact clinical relevance of these possible DDIs. In this review, we present practical recommendations for management of MKI interactions in clinical practice. Acknowledging these DDIs by clinicians may eventually result in a more personalized and effective treatment with MKIs.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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