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.\(^2\) \(^3\) \(^4\) 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...
Therapeutic Advances in Medical Oncology 11

(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. 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.

DDIs can be classified as pharmacodynamic or pharmacokinetic. 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.

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.

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). 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, H₂-antagonists and antacids) must be assessed on an individual basis. A complete overview can be found in Table 1.

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. The general consensus is, if possible, to avoid the combination between MKIs and ASAs. 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 must be assessed on an individual basis. A complete overview can be found in Table 1.

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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
| MKI (year of marketing approval) | Acid-suppressive compound | Decrease in $C_{\text{max}}$ | 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; US FDA |
| 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; US FDA; Morcos and colleagues |
| 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; US FDA; Rugo and colleagues |
| 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; US FDA; Abbas and colleagues |
| 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; US FDA; Nguyen and colleagues |
| 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; US FDA; Lau and colleagues |
| 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; US FDA; Musib and colleagues |
| MKI (year of marketing approval) | Acid-suppressive compound | Decrease in $C_{\text{max}}$ | 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; US FDA |
| 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; US FDA |
| Dasatinib (2006)                 | Omeprazole 40 mg for 4 consecutive days with dasatinib Maalox 30 ml concomitantly with dasatinib Maalox 30 ml 2 h before dasatinib Famotidine 40 mg 10 h before 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; US FDA; Eley and colleagues |
| Erlotinib (2005)                | Omeprazole 40 mg for 7 consecutive days with erlotinib Ranitidine 300 mg once daily concomitantly with erlotinib Ranitidine 150 mg twice daily concomitantly 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; US FDA; van Leeuwen and colleagues; Kletzl and colleagues |
| 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; US FDA; Yokota and colleagues |
| 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; US FDA; de Jong and colleagues |
| 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; US FDA; Sparano and colleagues; Egorin and colleagues |
| MKI (year of marketing approval) | Acid-suppressive compound | Decrease in $C_{\text{max}}$ | 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; US FDA |
| 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; US FDA |
| 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 H2-antagonists can be used 10 h before or 2 h after nilotinib intake. | EMA; US FDA; Yin and colleagues |
| 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; US FDA |
| 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; US FDA |
| 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; US FDA; Tan and colleagues |
| MKI (year of marketing approval) | Acid-suppressive compound | Decrease in $C_{\text{max}}$ | 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; US FDA; Narasimhan and colleagues |
| 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; US FDA15 |
| 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; US FDA15 |
| 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; US FDA15 |
| 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; US FDA; Olivier and colleagues |
| 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; US FDA15 |
## Table 1. (Continued)

| MKI (year of marketing approval) | Acid-suppressive compound | Decrease in $C_{\text{max}}$ | 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; US FDA |
| Vandetanib (2012)                | Omeprazole 40 mg for 5 days concomitantly 150 mg ranitidine for 5 days concomitantly with vandetanib | 15%                           | 6%              | Minor           | No interventions needed. Concomitant acid-suppressive therapy is considered safe. | EMA; US FDA; Johansson and colleagues |
| Vemurafenib (2012)               | No clinical study        | NA                            | NA              | Minor           | No interventions needed. Concomitant acid-suppressive therapy is considered safe. | EMA; US FDA |

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 $\geq$80%), Moderate (AUC increase $\geq$50–<80%), Minor (AUC increase $\geq$20–<50%) and by taking into account the performed study and the available evidence regarding pKa and the available assessment report. 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.
Therefore, the effect of a DDI considering drug transporters may be of greater clinical relevance than 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. 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. For example, nintedanib showed a decrease in both area under the curve (AUC) and maximum concentration (Cmax) when co-administered with rifampicin. Since nintedanib is almost exclusively metabolized by phase II enzymes, this effect on AUC and Cmax is most likely due to P-gp induction. 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).

In intestinal metabolism, 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. 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. Moreover, some MKIs (e.g. imatinib, pazopanib) also displayed inhibitory or inducing activity by themselves. The general advice is to avoid coadministered medication 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 | $C_{\text{max}}$               | AUC               | Clinical implications                                                                 | Interaction potential | References                  |
|---------|-----------|----------|-------------------------------|-------------------|--------------------------------------------------------------------------------------------|-----------------------|----------------------------|
| Afatinib| P-gp, BCRP| in vitro| Ritonavir: 38% increase       | Ritonavir: 48%    | 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 colleagues43 |
|         |           |          | Rifampicin: 22% decrease      | increase          |                                                                                             |                       |                            |
| Alectinib| M4 is a P-gp substrate | in vitro| P-gp, BCRP                      | 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 colleagues44 |
|         |           |          |                               | NA                |                                                                                             |                       |                            |
| Axitinib| P-gp, BCRP| in vitro| P-gp, BCRP                      | NA                | appropriate monitoring of side effects is recommended when axitinib is used with P-gp and BCRP substrates or inhibitors and inducers. | Minor                | EMA;14 US FDA15            |
|         |           |          |                               | NA                |                                                                                             |                       |                            |
| Bosutinib| P-gp      | in vitro| P-gp, BCRP, OCT1               | NA                | Clinical relevant interactions with drug transporters are not likely to appear.               | Minor                | EMA;14 US FDA;15 Abbas and colleagues;18 Hsyu and colleagues45 |
|         |           |          | dabigatran (P-gp substrate): no effect | dabigatran pharmacokinetics |                                                                                             |                       |                            |
| Cabozantinib| MRP2     | in vitro| P-gp, BCRP, MATE1, MATE2 | 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 FDA15            |
|         |           |          |                               | NA                |                                                                                             |                       |                            |

(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; US FDA |  |
| 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; US FDA; Musib and colleagues |  |
| 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; US FDA |  |
| 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; US FDA |  |
| 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; US FDA; Haouala and colleagues |  |
### Table 2. (Continued)

| MKI | Substrate | Inhibits | C<sub>max</sub> | 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;<sup>14</sup> US FDA;<sup>15</sup> Marchetti and colleagues;<sup>47</sup> Sprowl and colleagues;<sup>49</sup> Elmeliegy and colleagues<sup>50</sup> |
| 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;<sup>14</sup> US FDA;<sup>15</sup> Stewart and colleagues<sup>50</sup> |
| 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;<sup>14</sup> US FDA;<sup>15</sup> de Jong and colleagues<sup>51</sup> |
| 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;<sup>14</sup> US FDA;<sup>15</sup> Eechoute and colleagues<sup>52</sup> |
| Lapatinib | P-gp, BCRP, OATP1B1 | in vitro: P-gp, BCRP, 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;<sup>14</sup> US FDA;<sup>15</sup> Koch and colleagues<sup>53</sup> |
| MKI         | Substrate | Inhibits                  | $C_{\text{max}}$ | 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 colleagues56 |
| 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 100mg 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 FDA15 |
| 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 FDA15 |
| 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 FDA15 |
### Table 2. (Continued)

| MKI | Substrate | Inhibits | C<sub>max</sub> | 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; FDA<sup>14</sup> US FDA<sup>15</sup> |
| 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; FDA<sup>14</sup> US FDA<sup>15</sup> |
| 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; FDA<sup>14</sup> US FDA<sup>15</sup> |
| 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; FDA;<sup>1</sup> Bins and colleagues<sup>57</sup> |
| 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; FDA<sup>14</sup> US FDA<sup>15</sup> |
| Tivozanib | NA | *in vitro*: BCRP | NA | NA | Co-administration with BCRP substrates must be avoided or side effects must be monitored closely. | Minor | EMA; FDA<sup>14</sup> US FDA<sup>15</sup> |

*(Continued)*
MKI Substrate Inhibits C\textsubscript{max} AUC Clinical implications Interaction potential References

Trametinib P-gp \textit{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 \textit{in vitro} inhibition or induction potential this is not expected to be of \textit{in vivo} significance. Minor EMA\textsuperscript{14} US FDA\textsuperscript{15}

Vandetanib NA \textit{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\textsuperscript{14} US FDA\textsuperscript{15} Johansson and colleagues\textsuperscript{35}

Vemurafenib P-gp, BCRP \textit{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\textsuperscript{14} US FDA\textsuperscript{15} Zhang and colleagues\textsuperscript{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 $\geq 80\%$), moderate (AUC increase $\geq 50$ to $< 80\%$), minor (AUC increase $\geq 20$ 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, quinine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir and ritonavir, verapamil. BCRP: curcumin, cyclosporine, eltrombopag OATP1B1/OATP1B3: atazanavir, ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir, rifampin [single dose], simprevir 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, phenytion, St. John’s wort, ritonavir.\textsuperscript{10,41,58}

AUC, area under the curve; BCRP, breast cancer resistance protein (ABCG2); DDI, drug–drug interaction; EMA, European Medicines Agency; MATE, multi-an 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 Cmax.43 Treatment with a potent P-gp inducer (rifampicin) prior to single-dose afatinib showed a moderate effect on both afatinib AUC and Cmax (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 Cmax and 760% increase in AUC.74 Administration with rifampicin showed a significant 86% reduction in Cmax and a 92% decrease in AUC of bosutinib. Administration with the moderate inhibitor aprepitant also showed an increase in AUC and Cmax.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 $C_{\text{max}}$ | Change in AUC | Clinical recommendations | Clinical relevance | References |
|-------|-------------|-----------------------|---------------------|-------------------|---------------------|-------------------|--------------------------|----------------|--------------------------|-----------------|------------|
| Afatinib | mainly due to non-enzyme-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; US FDA; Wind and colleagues |
| Alectinib | CYP3A4 | CYP2C8, CYP3A5 | There was no influence on midazolam (CYP3A4 substrate) pharmacokinetics | CYP1A2, CYP2B6, CYP3A4 | Posaconazole | 18% increase | 79% 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 | EMA; US FDA; Morcos and colleagues |
| Axitinib | CYP3A4 | CYP3A5, CYP1A2, CYP2C19, UGT1A1 | UGT1A6, UGT1A7, UGT1A9, CYP1A2 | NA | ketoconazole | 50% increase | 104% 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; US FDA; Pithavala and colleagues |
| Bosutinib | CYP3A4 | Mono-oxygenase enzymes (FMO) | NA | NA | ketoconazole, aprepitant (moderate CYP3A4 inhibitor) | 420% increase | 760% 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; US FDA; Hsyu and colleagues; Abbas and colleagues |
| Cabozantinib | CYP3A4 | CYP2C9 | CYP2C9, CYP3A, CYP2C19 (in vitro) | NA | ketoconazole | no significant difference | no significant difference | (Chronic) co-administration of strong inhibitors and inducers of CYP3A4 must be avoided. If necessary, a 20mg 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; US FDA; Nguyen and colleagues |
| MKI | Major CYP | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in C<sub>max</sub> | 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 FDA15 |
| 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. 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 colleagues76 |
| Crizotinib | CYP3A4 | CYP3A5, CYP2B1, CYP2C9, 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 colleagues77 |
| Dabrafenib | CYP2C8 | CYP3A4 | CYP1A2, CYP2D6 | R-warfarin (CYP2C19 substrate) AUC decreased with 33% and C<sub>max</sub> increased with 19% | S-warfarin (CYP2C9 substrate) AUC increased with 37% and C<sub>max</sub> increased with 17% | ketoconazole gemfibrozil | 33% increase no significant difference | 71% increase 47% increase | Avoid the (chronic) use of strong CYP3A4 and CYP2C9 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 colleagues76 |

Table 3. (Continued)
### Table 3. (Continued)

| MKI | Major CYP | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in $C_{\text{max}}$ | Change in AUC | Clinical recommendations | Clinical relevance | References |
|-----|------------|-----------------------|---------------------|------------------|---------------------|------------------|-----------------------------|----------------|--------------------------|------------------|------------|
| **Dasatinib** | CYP3A4 | FM0, UGT | CYP2C8, CYP3A4 | simvastatin (CYP3A4 substrate) AUC increased with 20% and 37% respectively. | 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 colleagues9 |
| **Erlotinib** | CYP3A4 | CYP1A2, CYP1A1, CYP1B1, CYP3A5 | CYP1A1, CYP3A4, CYP2C8 and UGT1A1 | Midazolam AUC decreased with 24% Paclitaxel (CYP2C8) AUC was unchanged | 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 colleagues10 |
| **Gefitinib** | CYP3A4 | CYP3A5, CYP2C19 | CYP2D6 | Metoprolol (a CYP2D6 substrate) AUC increased with 35% | Ketoconazole | | 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 colleagues81 |
| **Ibrutinib** | CYP3A4 | CYP2D6 | CYP3A4 | CYP2B6 | Ketoconazole grapefruit juice erythromycin voriconazole | 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 colleagues82 |

**References:**
14. EMA; 15. US FDA; 81. Swaisland and colleagues; 82. de Jong and colleagues.
**Table 3. (Continued)**

| MKI     | Major CYP        | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in C<sub>max</sub> | Change in AUC | Clinical recommendations | Clinical relevance | References |
|---------|------------------|-----------------------|---------------------|------------------|---------------------|------------------|-------------------------|----------------|--------------------------|------------------|------------|
| Imatinib | CYP3A4           | CYP3A5, CYP1A2, CYP2D6, CYP2C9, CYP2C19 | CYP2C9, CYP3A4/CYP2B8 substrate | Concentration raised with 26% during imatinib therapy, midazolam (CYP3A4 substrate) AUC increased with 3%; simvastatin (CYP3A4 substrate) AUC increased with 26% | Ketoconazole | 26% increase | 40% increase | No intervention is needed for strong CYP3A4 inhibitors but monitoring for side 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; US FDA; Wang and colleagues; O'Brien and colleagues; Atiq and colleagues |
| Lapatinib | CYP3A4           | CYP3A4, CYP3A5, CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19 | | Midazolam (CYP3A4 substrate) AUC increased with 5%; paclitaxel (CYP2C8 substrate) AUC increased with 37% concomitant with pazopanib | 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; US FDA; Tan and colleagues; Koch and colleagues |
| Lenvatinib | Oxidase by aldehyde oxidase and conjugation by glutathione | CYP3A4 | | | Ketoconazole | 19% increase | 15% increase | Lenvatinib administration with CYP3A4 inducers or inhibitors is considered safe. | Minor | EMA; US FDA |
| Nilotinib | CYP3A4           | CYP2C8, CYP1A1, CYP1A2, CYP1B1 | CYP2D6, CYP2C9, CYP3A4, CYP2C8, UGT1A1 (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; US FDA; Zhang and colleagues |

(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, UGT1A2, UGT1A8, UGT1A10, CYP's (5%) | NA | NA | ketoconazole | rifampicin | 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; US FDA; Tan and colleagues |
| Osimertinib | CYP3A4 | CYP3A5, CYP1A2, CYP2A6, CYP2C9, CYP2E1 | CYP1A2, CYP2C8, UGT1A1 (in vitro) | CYP3A4, CYP1A2 | simvastatin | 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/CYP3A5, CYP1A2, CYP2C8 and UGT1A1 substrates close monitoring of side effects is recommended. | Moderate | EMA; US FDA; Vishwanathan and colleagues; Harvey and colleagues |
| Pazopanib | CYP3A4 | CYP1A2, CYP2C8 | in vitro: CYP3A4, CYP2B6, CYP2C8, CYP2D6, CYP2E1, UGT1A1 | midazolam | ketoconazole | rifampicin | 73% decrease | 78% decrease | 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 CYP2D6, CYP2E1, UGT1A1 and CYP3A4 substrates with narrow therapeutic windows must be applied when co-administered with pazopanib. | Minor | EMA; US FDA; Tan and colleagues |
| MKI | Major CYP | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in $C_{\text{max}}$ | 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; US FDA; Narasimhan and colleagues |
| Regorafenib | CYP3A4 | UGT1A9 | in vitro: UGT1A1, UGT1A9, CYP2C8, CYP2B6, CYP2C9, CYP2C19, CYP3A4 | Irinotecan metabolite (SN-38) (substrate of UGT1A1) | 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 40 mg 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; US FDA |
| Ruxolitinib | CYP3A4 | CYP2C9 | Intestinal CYP3A4 | NA | ketoconazole | 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; US FDA; Shi and colleagues |

(Continued)
| MKI | Major CYP | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in C<sub>max</sub> | 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. | ketoconazole | 26% increase | 11% increase | Sorafenib administration with strong inhibitors or inducers of CYP3A4 is considered safe. For UGT1A1 and UGT1A9 substrates specific side effects should be closely monitored. The use of strong UGT1A9 inhibitors or inducers should be avoided. | Minor | EMA<sup>14</sup>, US FDA<sup>15</sup> |
| Sunitinib | CYP3A4 | CYP1A2 | 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<sup>14</sup>, US FDA<sup>15</sup> |
| Tivozanib | CYP3A4 | UGT1A1, CYP1A1 | CYP2B6, CYP2C8 | 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<sup>14</sup>, US FDA<sup>15</sup>, Cottereau and colleagues<sup>16</sup> |
| MKI | Major CYP | Minor CYPs and others | Inhibitory activity | Inducing activity | Inhibitory compound | Inducing compound | Change in \(C_{\text{max}}\) | Change in AUC | Clinical recommendations | Clinical relevance | References |
|-----|-----------|-----------------------|---------------------|------------------|--------------------|------------------|----------------|-------------|-------------------------|------------------|-----------|
| Trametinib | Deacetylation and glucuronidation | CYP3A4 | CYP2C8, CYP2C9, CYP2C19 (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; US FDA15 |
| Vandetanib | CYP3A4 | FMO1, FMO3 | CYP2D6 | CYP1A2, CYP2C8, 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; US FDA; Martin and colleagues92 |
| 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; US FDA15 |

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 > 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, cobcinivir, conivaptan, daspravir, elvitegravir, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, posaconazole, vincsir, saquinavir, telaprevir, tigantavir, troleandomycin, voriconazole, clarithromycin, diltiazem, efalzodine, nefazodone, netarinavir, itraconazole, ketoconazole; Major CYP inducers: CYP2B6: carbamazepine, CYP2C9: carbaizepine, enzalutamide, rifampin, ronavir CYP3A4: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. Johnswort, grapefruit juice; AUC, area under the curve; CYP, cytochrome P450 iso-enzyme; DDI, drug–drug interaction; EMA, European Medicines Agency; FMO, flavin-containing monoxygenase; 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\textsubscript{max}, respectively.\textsuperscript{14,15} Co-administration with rifampicin showed a 70% and 44% decrease in AUC and C\textsubscript{max}, respectively.\textsuperscript{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.\textsuperscript{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\textsubscript{max} was seen, respectively.\textsuperscript{14,15} A physiologically based pharmacokinetic (PBPK) model demonstrated rifampicin to decrease cobimetinib AUC by 83% and C\textsubscript{max} by 63%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14,15} Furthermore, dabrafenib is known to auto-induce CYP3A4 mediated metabolism.\textsuperscript{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\textsubscript{max} for S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4/CYP1A2 substrate), respectively.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14,15} Ibrutinib is mainly metabolized by CYP3A4. Ketoconazole gave 2800% and 2300% increase in C\textsubscript{max} and AUC respectively.\textsuperscript{14,15,51} Furthermore concomitant administration with rifampicin showed 92% and 90% decrease in C\textsubscript{max} and AUC respectively.\textsuperscript{14,15} Administration with a moderate inhibitor of CYP3A4 (e.g. erythromycin) led to 240% and 200% increase in C\textsubscript{max} and AUC respectively.\textsuperscript{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.\textsuperscript{14,15} When lenvatinib is administered with ketoconazole or rifampicin, only marginal changes in AUC and C\textsubscript{max} were observed.\textsuperscript{34,55} 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.\textsuperscript{14,15} Lenvatinib has an overall low DDI potential and dose modifications are currently not considered necessary.

\textit{Nintedanib}. Nintedanib is used in the treatment of NSCLC. It is a substrate and weak inhibitor of P-gp.\textsuperscript{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\%).\textsuperscript{14,15} Administration with ketoconazole resulted in 61\% and 83\% increase in AUC and $C_{\text{max}}$ respectively and administration with rifampicin demonstrated a decrease in AUC of 50\% and 60\% of $C_{\text{max}}$ respectively.\textsuperscript{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.

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

\textit{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.\textsuperscript{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.\textsuperscript{14,15} A study with concomitant ketoconazole administration showed an increase in $C_{\text{max}}$ of 47\% and 78\% in AUC of ponatinib.\textsuperscript{88} Multiple dosing of rifampicin demonstrated a decrease in AUC and $C_{\text{max}}$ of 42\% and 62\% respectively.\textsuperscript{89} As a consequence, concomitant administration with inhibitors of CYP3A4 and P-gp should be avoided or a dose reduction to 30mg 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.

\textit{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).\textsuperscript{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.\textsuperscript{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.

\textit{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.\textsuperscript{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.\textsuperscript{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.

\textbf{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.\textsuperscript{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 H2-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. 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. 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. 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.

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). 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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