



# Drug–drug interactions with tyrosine-kinase inhibitors: a clinical perspective

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In the past decade, many tyrosine-kinase inhibitors have been introduced in oncology and haemato-oncology. Because this new class of drugs is extensively used, serious drug–drug interactions are an increasing risk. In this Review, we give a comprehensive overview of known or suspected drug–drug interactions between tyrosine-kinase inhibitors and other drugs. We discuss all haemato-oncological and oncological tyrosine-kinase inhibitors that had been approved by Aug 1, 2013, by the US Food and Drug Administration or the European Medicines Agency. Various clinically relevant drug interactions with tyrosine-kinase inhibitors have been identified. Most interactions concern altered bioavailability due to altered stomach pH, metabolism by cytochrome P450 isoenzymes, and prolongation of the QTc interval. To guarantee the safe use of tyrosine-kinase inhibitors, a drugs review for each patient is needed. This Review provides specific recommendations to guide haemato-oncologists, oncologists, and clinical pharmacists, through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

## Introduction

To improve effectiveness and reduce adverse events of cancer treatment, specific targets have been identified in oncology in the past decade. One of the most promising groups in targeted therapy are the tyrosine-kinase inhibitors.<sup>1</sup> Tyrosine kinases are key components of signal transduction pathways in the cell that relay information about conditions in the extracellular domain or the cytoplasm to pass on to the nucleus. As a result, tyrosine-kinase inhibitors affect gene transcription and DNA synthesis. Many tumour cells show abnormal activity of specific tyrosine kinases and are therefore an appealing target in oncology.<sup>1</sup>

All tyrosine-kinase inhibitors are given orally, which makes administration flexible and convenient, and improves quality of life. Another advantage of oral administration is that the tyrosine-kinase inhibitors are often taken on a continuous daily basis (compared with intermittent use of most chemotherapy), which usually improves the exposure time of the tumour to the active drug.

Although tyrosine-kinase inhibitors have some advantages compared with traditional chemotherapy, new challenges have arisen in the use of these novel targeted drugs. First, tyrosine-kinase inhibitors have specific toxicity profiles that differ from those of cytotoxic drugs.<sup>2</sup> Toxic effects can be severe (eg, cardiovascular side-effects) and some tyrosine-kinase inhibitors can even cause secondary tumours (eg, vemurafenib). Because the tyrosine-kinase inhibitors are used chronically and are metabolised by cytochrome P450 (CYP) isozymes, patients given these drugs are at substantial risk of having drug–drug interactions. Furthermore, because of the oral administration route of tyrosine-kinase inhibitors, new drug–drug interactions concerning gastrointestinal absorption have become apparent (eg, cotreatment with proton pump and tyrosine-kinase inhibitors).

Drug–drug interactions might be associated with serious or even fatal adverse events, or can lead to reduced therapeutic effects of either drug. Interactions

can be classified into those that are pharmacokinetic and those that are pharmacodynamic.<sup>3</sup> Pharmacokinetic interactions arise when absorption, distribution, metabolism, or elimination of the involved drugs are altered, leading to changes in the amount and duration of drug availability at receptor sites. The most common pharmacokinetic drug–drug interactions concern absorption (incomplete drug absorption is a risk of drug interaction) and metabolism by the cytochrome P450 isozymes. Pharmacodynamic interactions usually refer to an interaction in which active compounds change each other's pharmacological effect. The effect can be synergistic, additive, or antagonistic.

In this Review we give an overview of existing data of known or suspected drug–drug interactions between tyrosine-kinase inhibitors approved by the US Food and Drug Administration or the European Medicines Agency and conventional prescribed drugs, over-the-counter drugs, and herbal medicines. Furthermore, we provide specific recommendations to guide oncologists, haemato-oncologists, and clinical pharmacists through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

## Pharmacokinetic drug interactions: absorption

Gastrointestinal absorption of a drug depends on its inherent characteristics (eg, solubility), but can also be affected by drug–drug interactions. At the absorption level, these interactions mainly take place with tyrosine-kinase inhibitors that have incomplete absorption (eg, bioavailability <50%, first pass effect, or dependence on influx or efflux transporters). Important factors that can affect absorption of tyrosine-kinase inhibitors are a change in stomach pH due to coadministration of an H<sub>2</sub> antagonist, proton-pump inhibitor, or antacid, and the inhibition of P-glycoprotein and intestinal CYP3A4 in enterocytes.

## Changes in stomach pH

Besides pH independent, chemical solubility properties, the most important factor that affects solubility and the

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resulting exposure to tyrosine-kinase inhibitors is stomach pH.

Because of their weakly basic properties, tyrosine-kinase inhibitors can be present in either the ionised or non-ionised form, depending on the pH in the stomach and the  $pK_a$  of the drug (ie, the pH at which the tyrosine-kinase inhibitor reaches equilibrium between the ionised and non-ionised form). Ionised forms normally dissolve more easily than do non-ionised forms. When a tyrosine-kinase inhibitor is coadministered with an acid suppressive drug (eg, a proton-pump inhibitor), the pH in the stomach will increase from 1 to about 4. Subsequently, the equilibrium of ionised or non-ionised drug will shift to the less soluble non-ionised form, and as a result, the bioavailability of the tyrosine-kinase inhibitor will decrease.<sup>4</sup> If the  $pK_a$  of a tyrosine-kinase inhibitor (eg, dasatinib) is near the pH range 1–4 the shift towards the non-ionised (less soluble) form, will be greater than that with an inhibitor with a higher  $pK_a$  (eg, sunitinib). As such, for tyrosine-kinase inhibitors with a  $pK_a$  of less than 4–5, co-administration of acid suppressive drugs (eg, antacids, proton-pump inhibitors,  $H_2$ -antagonists) will further reduce solubility and, subsequently, bioavailability and exposure to the tyrosine-kinase inhibitor.

In clinical practice, drug–drug interactions between acid suppressive drugs and tyrosine-kinase inhibitors can be clinically relevant. The oral absorption of crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, and pazopanib is substantially altered by concomitant use of acid suppressive treatment. If possible, the combination of these tyrosine-kinase inhibitors and an  $H_2$ -antagonist, proton-pump inhibitor, or antacid should be avoided. Table 1 provides detailed recommendations for the clinical management of these drug–drug interactions.

#### Inhibition or induction of intestinal enzymes and drug transporters

A tyrosine-kinase inhibitor needs to be transported across the gut wall to reach the portal blood circulation. This transmembrane transport of the drug is a complex multifactorial process mediated by passive diffusion, organic anion and cation transporting peptides, multidrug resistance-associated proteins (eg, ATP-binding cassette [ABC] transporter G2), efflux transporters (eg, P-glycoprotein or multidrug resistance protein 1 [ABCB1]) and intestinal metabolic enzymes (eg, CYP3A4).

After passive diffusion or active transport through the gut lumen (or apical membrane), the tyrosine-kinase inhibitor enters the enterocyte where some tyrosine-kinase inhibitors undergo cytochrome p450 (CYP)-mediated metabolism. Subsequently, the drug or its (active) metabolite will undergo either active countertransport (or efflux) back into the gut lumen, or uptake into the portal vein by passive diffusion, or active transport through the basolateral membrane (figure 1).

#### P-glycoprotein

The role of P-glycoprotein in the absorption of tyrosine-kinase inhibitors has been widely studied. Some tyrosine-kinase inhibitors (eg, crizotinib) are a substrate for P-glycoprotein, and consequently, inhibition or induction of this efflux transporter by coadministration of another drug might lead to a clinically relevant drug–drug interaction (table 2). Other tyrosine-kinase inhibitors (eg, pazopanib, lapatinib, and gefitinib) directly inhibit the activity of P-glycoprotein and can increase bioavailability of concomitantly used P-glycoprotein substrates. For instance, the area under the curve of digoxin is increased by 80% with P-glycoprotein inhibition by lapatinib.<sup>5,6</sup> Another example is the rise in SN-38 exposure (the active metabolite of irinotecan), which has been attributed to inhibition of P-glycoprotein by lapatinib and gefitinib.<sup>13,14</sup> The increased exposure to paclitaxel (roughly 26%) when used in combination with pazopanib can also be attributed to inhibition of P-glycoprotein by pazopanib.<sup>5,6</sup> Furthermore, the pazopanib area under the curve was increased by 59% with P-glycoprotein-related inhibition of lapatinib. However, at reduced doses of both drugs, no changes were noted in bioavailability.<sup>5,6</sup>

#### Intestinal CYP3A4

The intestinal metabolic enzyme CYP3A4 exerts its action in close proximity of P-glycoprotein in the enterocytes of the gut lumen (figure 1).<sup>15</sup> Simultaneous use of tyrosine-kinase inhibitors that are substrates for intestinal CYP3A4 together with CYP3A4 inhibitors and inducers can change the exposure and toxicity of tyrosine-kinase inhibitors. An example of a substance that inhibits intestinal CYP3A4 is grapefruit, which increases the area under the curve of sunitinib by 11%, or that of nilotinib by 29%.<sup>16,17</sup> By contrast, grapefruit juice did not seem to affect the area under the curve of imatinib.<sup>18</sup> A possible explanation is that grapefruit juice not only enhances absorption of CYP3A4 substrates at the enterocyte level, but also decreases absorption of organic anion transporting peptides substrates.

#### Other drug transporters

Besides P-glycoprotein, several tyrosine-kinase inhibitors (eg, imatinib) have been identified as substrates of other drug transporters (eg, organic anion transporting peptides, organic cation transporter, breast cancer resistance protein).<sup>5,6</sup> Some drugs might inhibit organic anion transporting peptides (eg, ciclosporin) or breast cancer resistance protein (eg, lapatinib), but involvement of other mechanisms, such as CYP3A4, cannot be ruled out in these drug–drug interactions.<sup>19</sup> Evidence for drug–drug interactions with tyrosine-kinase inhibitors through inhibition or induction of transporters is not yet available.

#### Other factors affecting absorption of tyrosine-kinase inhibitors

Another factor that might affect absorption of tyrosine-kinase inhibitors is the formation of an insoluble complex.

For instance, bile salt-sequestering drugs such as cholestyramine can interfere with regorafenib absorption by formation of insoluble complexes. The clinical significance of these drug–drug interactions is unknown.<sup>5,6</sup>

### Pharmacokinetic drug interactions: distribution

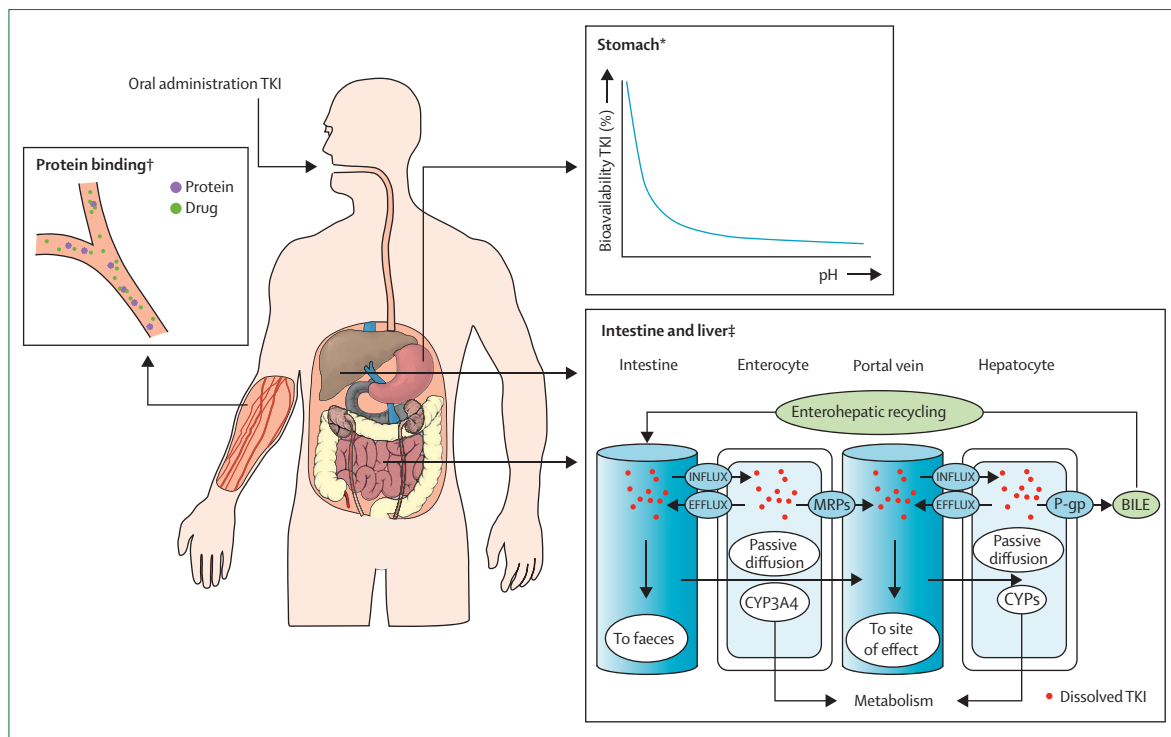
Distribution is largely measured by blood flow and the binding affinity for the plasma proteins albumin and

$\alpha$ 1-acid glycoprotein. If two drugs that are both highly bound to plasma proteins (>90%) are combined, one drug can displace the other from its protein binding site, therefore increasing the concentration of unbound drug (figure 1).

Although axitinib, lapatinib, and vemurafenib are all highly bound to plasma proteins ( $\geq 99\%$ ), and should theoretically be most susceptible for drug–drug

Acid-suppressive compound	Decreases in $C_{max}$	Decreases in area under the curve	Alternatives and recommendations	
Axitinib <sup>5,6</sup>	Rabeprazol 20 mg once daily	42%	15%	H <sub>2</sub> -antagonists, proton-pump inhibitors, and antacids can be used concomitantly with axitinib
Crizotinib <sup>5,6</sup>	..	..	..	The solubility of crizotinib is pH dependent. Solubility sharply decreases with increasing pH over the range of 1.6–8.2. No study of drug interaction has been done, but effects can be expected. Acid suppressive drugs should not be used concomitantly
Dasatinib <sup>5,7</sup>	Famotidine 40 mg, 10 h before dasatinib	63%	61%	H <sub>2</sub> -antagonists: can be used 2 h after dasatinib Antacids: can be used 2 h before and after dasatinib Proton-pump inhibitors: should not be used concomitantly with dasatinib
	Famotidine 40 mg, 2 h after dasatinib	..	..	
	Maalox (aluminium hydroxide, magnesium hydroxide, simethicone) 30 mL, 2 h before dasatinib	26%	..	
	Maalox (aluminium hydroxide, magnesium hydroxide, simethicone) 30 mL, concomitantly with dasatinib	58%	55%	
Erlotinib <sup>5,6</sup>	Omeprazole 40 mg twice daily concomitantly with dasatinib	42%	43%	H <sub>2</sub> -antagonists: can be used 2 h after erlotinib. Ranitidine should be given in a 150 mg twice daily regimen Antacids: can be used 4 h before or 2 h after erlotinib Proton-pump inhibitors: should not be used concomitantly with erlotinib
	Omeprazole 40 mg once daily, concomitantly with erlotinib	61%	46%	
	Ranitidine 300 mg once daily, concomitantly with erlotinib	54%	33%	
	Ranitidine 150 mg twice daily, concomitantly with erlotinib (erlotinib, 2 h before and 10 h after ranitidine)	17%	15%	
Gefitinib <sup>5,6</sup>	Two oral doses of 450 mg ranitidine (13 h and 1 h before gefitinib) followed by sodium bicarbonate was given if a pH of $\geq 5$ was not achieved.	71%	47%	H <sub>2</sub> -antagonists: should not be used concomitantly with gefitinib Antacids: can be used 2 h before or after gefitinib Proton-pump inhibitors: should not be used concomitantly with gefitinib
Imatinib <sup>8,9</sup>	Omeprazole 40 mg once daily, concomitantly with imatinib	..	..	H <sub>2</sub> -antagonists, proton-pump inhibitors, and antacids can be used concomitantly with imatinib
	Maalox (aluminium hydroxide, magnesium hydroxide, simethicone) 20 mL, 15 min before imatinib	..	..	
Lapatinib <sup>5,6</sup>	Esomeprazole 40 mg once daily 12 h before lapatinib	..	27%	H <sub>2</sub> -antagonists: should not be used concomitantly with lapatinib Antacids: can be used 2 h before or after lapatinib. Proton-pump inhibitors: should not be used concomitantly with lapatinib
Nilotinib <sup>10–12</sup>	Esomeprazole 40 mg once daily, concomitantly with nilotinib	27%	34%	H <sub>2</sub> -antagonists: can be used 10 h before or 2 h after nilotinib Antacids: can be used 2 h before or after nilotinib Proton-pump inhibitors: nilotinib can be used concomitantly
	Famotidine 20 mg twice daily, concomitantly with nilotinib (given 2 h after nilotinib)	..	..	
	Single oral dose of nilotinib and maalox (aluminium hydroxide, magnesium hydroxide, simethicone) 20 mL when antacid was given 2 h before and after nilotinib	..	..	
Pazopanib <sup>5,6</sup>	Esomeprazole (evening) concomitantly with pazopanib (morning) <sup>5,6</sup>	42%	40%	H <sub>2</sub> -antagonists: pazopanib should be taken at least 2 h before or 10 h after a dose of an H <sub>2</sub> -antagonist. Antacids: can be used 4 h before or 2 h after pazopanib. Proton-pump inhibitors: take the dose of pazopanib in the evening concomitantly
Regorafenib <sup>5,6</sup>	..	..	..	No data available
Ruxolitinib <sup>5,6</sup>	..	..	..	H <sub>2</sub> -antagonists, proton-pump inhibitors, and antacids can be used concomitantly with ruxolitinib
Sorafenib <sup>5,6</sup>	Esomeprazole concomitantly with sorafenib	..	..	H <sub>2</sub> -antagonists, proton-pump inhibitors, and antacids can be used concomitantly with imatinib
Sunitinib <sup>5,6</sup>	..	..	..	Because of the high solubility, no effect on sunitinib would be expected during H <sub>2</sub> -antagonist, antacid, or proton-pump inhibitor use; therefore, they can be used concomitantly
Vandetanib <sup>5,6</sup>	..	..	..	H <sub>2</sub> -antagonists, antacids, and proton-pump inhibitors can be concomitantly used with vandetanib, which has pH-dependent solubility, but this is not clinically significant
Vemurafenib <sup>5,6</sup>	..	..	..	H <sub>2</sub> -antagonists, antacids, and proton-pump inhibitors can be concomitantly used with vemurafenib, which has pH-dependent solubility, but this is not clinically significant

Table 1: Effects of acid-suppressive compounds on the bioavailability of tyrosine-kinase inhibitors



**Figure 1: Major sites of pharmacokinetic drug–drug interactions in treatment with TKIs**

TKI=tyrosine-kinase inhibitor. MRPs=multidrug resistance protein drug transporters, P-gp=P-glycoprotein. CYPs=cytochrome P450 enzymes. \*With increasing stomach pH the bioavailability of TKIs decreases. †Protein-bound molecules are not available to exert pharmacological effects. ‡Shows the association between CYPs and drug transporters in TKI absorption or metabolism.

interactions, little evidence is available to support a clinically relevant interaction on the basis of displacement of protein binding sites.<sup>5,6</sup> Imatinib used concomitantly with clindamycin leads to altered imatinib exposure because of displacement of protein-bound imatinib. As a result, the increased free plasma concentration of imatinib leads to a rapid redistribution of the unbound drug into the extravascular volume. The clinical relevance of this interaction is unknown.<sup>20</sup>

All tyrosine-kinase inhibitors are fairly highly bound to plasma proteins (90% to >99%; table 2), which, in theory, makes these inhibitors prone to interactions with other highly bound drugs, such as warfarin and phenytoin.<sup>5,6,21,22</sup> However, the evidence for drug–drug interactions concerning protein displacement is poor and, in reality, these interactions are more likely to be the consequence of other (metabolic) mechanisms.<sup>23</sup>

### Pharmacokinetic drug interactions: metabolism

Phase 1, mostly oxidative, metabolism by cytochrome P450 enzymes (CYPs) is the most important route of drug metabolism of drugs in vivo. Although some drugs are also metabolised by enterocyte CYP3A4 enzymes, the main site of metabolism in the human body is the liver (figure 1).

CYP enzymes can be inhibited in two ways: (1) competitive binding of two substrates at the same CYP-enzyme binding site and (2) uncompetitive inhibition of

CYP enzymes by an inhibitor coadministered with a substrate for the same CYP enzymes, leading to an increase in the serum area under the curve of the CYP substrate. The net effect on the area under the curve of the CYP substrate is dependent on the inhibitory and inducing potency of the coadministered drug. Increased or decreased exposure by alteration of CYP activity might cause clinically relevant toxic effects or ineffectiveness of treatment with tyrosine-kinase inhibitors. Table 2 provides an overview of CYPs involved in metabolism of tyrosine-kinase inhibitors.

Because drug–drug interactions concerning strong CYP3A4-inhibition or induction play a crucial part in treatment with tyrosine-kinase inhibitors, they are usually well described in the regulatory assessment report of the manufacturer or in primary literature (table 3).

### Other metabolic drug–drug interactions

#### Axitinib

The effects of strong CYP3A4 inhibition and induction on axitinib exposure have been thoroughly investigated. However, the effect on  $C_{max}$  and the area under the curve of moderate CYP3A4 inhibitors (eg, fluconazole) needs to be assessed in future studies. CYP1A2 and CYP2C19 have a minor role in axitinib elimination and so the risk of a clinically relevant drug–drug interaction via inhibition or induction of these enzymes is negligible. Furthermore, the effect of drug-transporter inhibitors (eg, ciclosporin)

	Target	Absolute bioavailability	Protein binding	CYPs major	CYPs minor and others	Inhibits	Inducer	P-glycoprotein
Axitinib	VEGFR 1,2,3	58%	>99%	CYP3A4	CYP1A2, CYP2C19, UGT	CYP1A2, CYP2C8	..	..
Crizotinib	HGFR; ALK	43%	91%	CYP3A4	CYP2D6, CYP2C19	CYP3A4	CYP2B6, CYP2C8, CYP2C9, UGT	Substrate, Inhibitor
Dasatinib	PDGFR $\beta$ ; c-KIT; SRC; BCR-ABL; EPH	Unknown	96%	CYP3A4	CYP2C8, FMO and UGT	CYP3A4	..	..
Erlotinib	HER1-(EGFR)	60%	95%	CYP3A4	CYP1A2, CYP2C8, CYP1A1, CYP2D6	CYP3A4, CYP2C8, CYP1A1	..	Substrate
Gefitinib	HER1-(EGFR)	60%	90%	CYP3A4, CYP2D6	CYP1A1	CYP2D6, CYP2C19	..	..
Imatinib	PDGFR $\beta$ ; c-KIT; FLT-3; BCR-ABL	98%	95%	CYP3A4	CYP2D6, CYP2C9	CYP3A4, CYP2D6, CYP2C9	..	..
Lapatinib	HER1-(EGFR); HER2, AKT	Unknown	>99%	CYP3A4	CYP2C8, CYP2C19, CYP2C9, CYP1A2, CYP2D6	CYP3A4, CYP2C8	..	Substrate, Inhibitor
Nilotinib	PDGFR $\beta$ ; c-KIT; BCR-ABL	31%	98%	CYP3A4	CYP2C8, CYP2C9, CYP1A1, CYP1A2, CYP2D6	CYP3A4	CYP2B6, CYP2C8, CYP2C9	..
Pazopanib	VEGFR 1,2,3; PDGFR $\beta$ ; c-KIT	14–39%	99%	CYP3A4	CYP1A2, CYP2C8	CYP2D6, CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1	..	Inhibitor
Regorafenib	VEGFR; PDGFR $\beta$ ; KIT; BRAF	69–83%	>99%	CYP3A4	UGT	CYP2C9; CYP2B6; CYP3A4; CYP2C8	..	Substrate, Inhibitor
Ruxolitinib	JAK 1,2	Unknown	97%	CYP3A4, CYP2C9	..	CYP3A4	..	..
Sorafenib	VEGFR 2,3; PDGFR $\beta$ ; c-KIT; FLT3; BRAF; CRAF	Unknown	99%	CYP3A4	..	CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4	..	..
Sunitinib	VEGFR 1,2,3; PDGFR $\beta$ ; c-KIT; FLT3; SRC	Unknown	90–95%	CYP3A4	CYP1A2	..	..	Inhibitor
Vandetanib	VEGFR 2; HER1-(EGFR); SRC	Unknown	90–94%	CYP3A4	FMO-1,3	CYP2D6	CYP3A4, CYP2C9, CYP1A2	..
Vemurafenib	BRAF	Unknown	>99%	CYP3A4*	..	CYP1A2, CYP2D6	CYP3A4, CYP2B6	Substrate, Inhibitor

This table is constructed from regulatory documents.<sup>4,5</sup> \*Only minor contribution of CYP3A4 (about 5%).

**Table 2: Pharmacological parameters of tyrosine-kinase inhibitors**

on the exposure of axitinib has not yet been investigated but deserves attention, because transporters of organic anion transporting peptide and breast cancer resistance protein might affect axitinib exposure.

### Crizotinib

Crizotinib is a strong CYP3A4 inhibitor; it increases the area under the curve of midazolam by 270%.<sup>5,6</sup> The combination of crizotinib and CYP3A4 substrates with a narrow therapeutic window (eg, ciclosporin or simvastatin) should therefore be avoided or closely monitored for toxic effects. For combined treatment with ciclosporin, therapeutic drug monitoring is recommended.<sup>5,6</sup> The product label also warns about co-administration of crizotinib with CYP2B6, CYP2C8, CYP2C9, UGT1A1, P-glycoprotein substrates, and drug transporter inhibitors, but the clinical significance of these combinations is unknown.<sup>5,6</sup>

### Dasatinib

Strong inhibitors of CYP3A4 have a profound effect on dasatinib exposure.<sup>5,6</sup> The effect of moderate CYP3A4 inhibitors on dasatinib exposure might also be clinically relevant, but such data are not available.<sup>5,6</sup> The product label warns about the combination of dasatinib and

simvastatin. Through (time-dependent) inhibition of CYP3A4 by dasatinib, simvastatin  $C_{max}$  is increased by 37%, and the area under the curve is increased by 20%.<sup>5,6</sup> However, because dasatinib is a time-dependent inhibitor of CYP3A4 and the dose was not at steady state, the above findings could underestimate the CYP3A4 inhibition and the effect on simvastatin. The combination of dasatinib and CYP3A4 substrates with a narrow therapeutic window should therefore be avoided (eg, change from simvastatin to pravastatin), or approached with caution.<sup>5,6</sup>

### Erlotinib

Profound reduction in erlotinib exposure has been reported for the potent CYP3A4 inducer rifampicin,<sup>5,6</sup> and reduced exposure of erlotinib might also take place with other strong inducers and moderate inducers (eg, enzalutamide, phenytoin, carbamazepine, barbiturates, or St John's wort).<sup>5,6</sup> The exposure to erlotinib is increased with concomitant use of the CYP1A2 inhibitor ciprofloxacin (increased  $C_{max}$  and area under the curve of 17% and 39%, respectively). In the case of combined ciprofloxacin and erlotinib treatment, recommendations state that the erlotinib dose should only be lowered (using 50 mg steps) if specific toxic effects are observed.<sup>5,6</sup>

Because of competition for CYPs (3A4 and 1A2), erlotinib might increase the international normalised ratio in patients given warfarin,<sup>22</sup> increase simvastatin exposure (rhabdomyolysis),<sup>37</sup> and augment phenytoin toxicity,<sup>21</sup> but evidence to support these changes is poor. Nevertheless, caution and awareness of these potential interactions is needed when coadministering these drugs. Carboplatin exposure was increased when concomitantly used with erlotinib, whereas no effect was noted with paclitaxel exposure.<sup>38</sup>

### Gefitinib

Concomitant gefitinib with phenytoin (a moderate-to-strong CYP3A4 inducer) results in a 26% decrease in  $C_{max}$  and a 47% decrease in the area under the curve.<sup>39</sup> A potential drug–drug interaction has been reported between herbal CYP3A4/5 inducers (eg, ginseng) and gefitinib. After discontinuation of the herbal medicines, a patient turned from being a non-responder to a (partial) responder.<sup>40</sup> In theory, this interaction could also be expected with St John's wort (CYP3A4 inducer).

	Inducing compound (CYP3A4)	Inhibitory compound (CYP3A4)	Changes in $C_{max}$	Changes in area under the curve	Alternatives and recommendations
Axitinib <sup>4,5,24</sup>	Rifampicin	..	71% decrease	79% decrease	Increase axitinib dose gradually and monitor toxicity to obtain optimum effectiveness
Axitinib <sup>4,5,25</sup>	..	Ketoconazole	50% increase	106% increase	Lower axitinib dose to 2 mg twice daily
Crizotinib <sup>4,5</sup>	Rifampicin	..	69% decrease	82% decrease	Increase crizotinib dose gradually and monitor toxicity to obtain optimum effectiveness
Crizotinib <sup>4,5</sup>	..	Ketoconazole	44% increase	216% increase	Avoid combination; if unavoidable, extreme caution should be taken, the crizotinib dose should be lowered, and toxicity must be monitored
Dasatinib <sup>4</sup>	Rifampicin	..	81% decrease	82% decrease	Initially increase the dasatinib dose by three times, then increase stepwise with 20 mg based on patient's tolerability and response
Dasatinib <sup>4,5,26</sup>	..	Ketoconazole	384% increase	256% increase	Reduce the dasatinib dose to 20–40 mg once daily
Erlotinib <sup>4,5</sup>	Rifampicin	..	29% decrease	67–69% decrease	Increase the erlotinib dose to 300 mg once daily, if well tolerated the dose can be increased after 2 weeks to 450 mg once daily with monitoring of side-effects
Erlotinib <sup>4,5,27</sup>	..	Ketoconazole	102% increase	86% increase	If combination is indicated and erlotinib toxic effects are noted, the erlotinib dose should be lowered in 50 mg steps
Gefitinib <sup>4,5,28</sup>	Rifampicin	..	65% decrease	83% decrease	Increase gefitinib dose to 500 mg once daily
Gefitinib <sup>4,5,28</sup>	..	Itraconazole	51% increase	78% increase	Avoid combination; if unavoidable, gefitinib toxic effects should be monitored; no clinical data available about the starting dose
Imatinib <sup>4,5,29</sup>	Rifampicin	..	54% decrease	74% decrease	Increase imatinib dose by at least 50%
Imatinib <sup>4,5,30</sup>	..	Ketoconazole	26% increase	40% increase	No intervention is needed, but regular monitoring for toxic effects is recommended
Lapatinib <sup>4,5,31</sup>	Carbamazepine	..	59% decrease	72% decrease	Gradually increase the lapatinib dose to 4500 mg once daily and monitor for liver toxicity
Lapatinib <sup>4,5,31</sup>	..	Ketoconazole	114% increase	257% increase	Lower the lapatinib dose to 500 mg once daily
Nilotinib <sup>32</sup>	Rifampicin	..	64% decrease	80% decrease	Increase the dose gradually dependent on toxic effects and effectiveness
Nilotinib <sup>32</sup>	..	Ketoconazole	84% increase	201% increase	Lower nilotinib dose to 400 mg once daily
Pazopanib <sup>4,5</sup>	Phenytoin or Carbamazepine	..	50% decrease	30% decrease	Gradually increase the pazopanib dose in 200 mg steps depending on patient's tolerance
Pazopanib <sup>4,5</sup>	..	Ketoconazole	45% increase	66% increase	Reduce the pazopanib dose by roughly 50% or 400 mg once daily
Regorafenib <sup>4,5</sup>	Rifampicin	..	50% decrease	20% decrease	Avoid the combination with strong CYP3A4 inducers; if unavoidable, gradually increase the regorafenib dose and monitor toxic effects
Regorafenib <sup>4,5</sup>	..	Ketoconazole	33% increase	40% increase	Avoid the combination with strong CYP3A4 inhibitors; if unavoidable, regorafenib toxicity should be monitored
Ruxolitinib <sup>4,5,33</sup>	Rifampicin	..	52% decrease	71% decrease	Increase the ruxolitinib dose gradually depending on toxic effects and efficacy.
Ruxolitinib <sup>4,5,33</sup>	..	Ketoconazole	33% increase	91% increase	Reduce the ruxolitinib dose by 50% and haematological toxicity should be monitored extensively (twice a week)
Sorafenib <sup>4,5</sup>	Rifampicin	..	..	37% decrease	Combination can be used safely
Sorafenib <sup>4,5,34</sup>	..	Ketoconazole	..	..	Combination can be used safely
Sunitinib <sup>35</sup>	Rifampicin	..	23% decrease	46% decrease	Gradually increase the sunitinib dose in 12.5 mg steps, with a maximum of 87.5 mg once daily, dependent on indication
Sunitinib <sup>35</sup>	..	Ketoconazole	49% increase	51% increase	Reduce the sunitinib dose to a maximum of 25 mg once daily
Vandetanib <sup>36</sup>	Rifampicin	..	..	40% decrease	Coadministration of rifampicin results in a moderate increase in the AUC of vandetanib. By contrast, exposure to the mean active metabolite N-desmethylvandetanib was profoundly increased (AUC 266% increase). CYP3A4 inducers should therefore be avoided during vandetanib treatment
Vandetanib <sup>36</sup>	..	Itraconazole	..	9% increase	Combination can be used safely
Vemurafenib <sup>4,5</sup>	..	..	..	..	No data about concomitant use of CYP3A4 inhibitors or inducers. Caution should be taken when coadministration of vemurafenib and CYP3A4 inhibitors or inducers is indicated

CYP=cytochrome P450.

Table 3: Effects of CYP3A4 inducers and inhibitors on the exposure of tyrosine-kinase inhibitors

If coadministration of gefitinib and a moderate-to-strong CYP3A4 inducer cannot be avoided, the gefitinib dose should be increased from 250 mg to 500 mg, both once daily. Through weak inhibition of CYP2D6, gefitinib can increase the  $C_{max}$  and the area under the curve of metoprolol by 10% and 35%, respectively, although increased metoprolol exposure does not seem to be clinically relevant.<sup>28</sup> Because of competition for CYP3A4, gefitinib might increase the international normalised ratio in warfarin treatment.<sup>41</sup> CYP3A4-inducing anti-epileptics significantly lowered gefitinib exposure.<sup>42</sup> Finally, sorafenib decreases the exposure to gefitinib (decrease in  $C_{max}$  and area under the curve of gefitinib by 38% and 26%, respectively) by an unknown mechanism, leaving sorafenib unaffected.<sup>43</sup>

### Imatinib

Drug–drug interactions described with phenytoin, St John's wort, and enzyme-inducing anti-epileptic drugs show a consistent decrease in imatinib exposure.<sup>44–46</sup> If co-administration of imatinib and a strong CYP3A4 inducer is needed, the imatinib dose should be increased by at least 50%. Concomitant use of single-dose ketoconazole results in a non-significant increase in imatinib single-dose exposure.<sup>30</sup> Furthermore, because of CYP3A4 auto-inhibition by imatinib at steady state, coadministration of ritonavir did not have an effect on imatinib exposure.<sup>47</sup> By contrast, severe toxic effects have been noted when imatinib was concomitantly used with the strong CYP3A4 inhibitor voriconazole.<sup>48</sup> Taking the safety profile into account, coadministration of imatinib and strong CYP3A4 inhibitors should be possible without dose adjustments. However, caution is needed, and regular monitoring for toxic effects is recommended.<sup>49</sup> Ciclosporin and imatinib can also mutually affect each other's exposure, but changes are small and regarded as clinically irrelevant.<sup>50</sup> Liver toxicity was noted during concomitant use of ginseng (a CYP3A4 inhibitor) and imatinib, but this outcome could also be caused by ginseng itself.<sup>51</sup> Because of strong inhibition of CYP3A4 by imatinib, simvastatin exposure was markedly increased.<sup>52</sup> If the combination is needed, simvastatin should be switched to another weakly CYP3A metabolised statin, such as rosuvastatin.<sup>53</sup> CYP3A4 inhibition by imatinib might lead to high nifedipine exposure, and thus form gallbladder stones; however, evidence is not convincing.<sup>54</sup> Through weak inhibition of CYP2D6, imatinib can increase the  $C_{max}$  and area under the curve of metoprolol by 8% and 23% respectively, but this finding has no clinical implications.<sup>55</sup> Because of possible competition for CYPs, imatinib might increase the international normalised ratio in warfarin treatment, but again, evidence is weak.<sup>56</sup>

### Lapatinib

If coadministration of lapatinib and a strong CYP3A4 inducer is needed, the once daily lapatinib dose should be gradually increased stepwise from 1250–1500 mg (normal

dose) to 4500 mg. Furthermore, if the lapatinib dose is increased to 4500 mg once daily, clinicians should be aware of the possible hepatotoxic effects of lapatinib metabolites with concomitant use of dexamethasone (a moderate CYP3A4 inducer).<sup>57</sup> CYP3A4 inducing anti-epileptics significantly lower lapatinib exposure.<sup>58</sup> When coadministered with irinotecan, the  $C_{max}$  of the active metabolite SN-38 was increased by 32% and the area under the curve was increased by 41%.<sup>13</sup> By contrast, no differences were noted in the exposure of lapatinib.<sup>13</sup> The reported effect is suspected to be multifactorial with contributions of, among others, inhibition of CYP3A4 by lapatinib.<sup>13</sup> When lapatinib was given in combination with paclitaxel, the exposure of both drugs was increased by 21% and 23%, respectively, possibly by inhibition of CYP2C8.<sup>59</sup> Because lapatinib is an inhibitor of CYP3A4 and CYP2C8, the product label recommends that the combination of lapatinib and CYP3A4 and CYP2C8 (eg, repaglinide) substrates with a small therapeutic window should therefore be avoided or approached with caution.<sup>5,6</sup>

### Nilotinib

By weak inhibition of CYP3A4, nilotinib can increase the  $C_{max}$  of midazolam by 20% and the area under the curve by 30%.<sup>5,6</sup> Nilotinib did not have a significant effect on warfarin or imatinib exposure, and so can be used concomitantly.<sup>60</sup>

### Pazopanib

By weak inhibition of CYP3A4 and CYP2D6, pazopanib might increase the exposure of midazolam and dextromethorphan.<sup>61</sup> In the same study, pazopanib did not have a significant effect on warfarin (CYP2C9 specific), omeprazole (CYP2C19 specific), and caffeine (CYP1A2 specific).<sup>61</sup> Coadministration of pazopanib eye drops with orally taken ketoconazole roughly doubled the pazopanib area under the curve.<sup>5,6</sup> Pazopanib increased the area under the curve and  $C_{max}$  of paclitaxel (a substrate for CYP2C8, CYP3A4, and P-glycoprotein) by 26% and 31%, respectively, without changing tolerability.<sup>5,6</sup> In combination with lapatinib 1500 mg (moderate, competitive CYP3A4, P-glycoprotein, and breast cancer resistance protein inhibitor), the pazopanib (800 mg) area under the curve and  $C_{max}$  were increased by 59% and 51%, respectively. However, at a lower pazopanib (400 mg) and lapatinib dose (1000 mg), no statistically significant effect was seen for the area under the curve or  $C_{max}$ .<sup>5,6</sup>

### Regorafenib

When given concomitantly with ketoconazole, the area under the curve of regorafenib was increased by 33% and the  $C_{max}$  by 40%. Furthermore, a decrease of more than 90% was noted in the area under the curve and  $C_{max}$  of the (active) regorafenib metabolite. According to the package label, concomitant use of strong inhibitors of CYP3A4 activity should be avoided because their effect on the steady state exposure of regorafenib and its active

metabolites has not been studied.<sup>5,6</sup> Co-administration with the strong CYP3A4 inducer rifampicin resulted in a reduction in the area under the curve and  $C_{max}$  of regorafenib of 50% and 20%, respectively. Furthermore, an increase of three to four times was noted in exposure of regorafenib's active metabolites. Because the net effect of the combination of strong CYP3A4 inducer and regorafenib is unknown, these combinations should preferably be avoided.<sup>5,6</sup> The inhibition of UGT1A1 by regorafenib resulted in an increase of 44% in area under the curve of SN-38 (active metabolite of irinotecan). An increase in area under the curve of irinotecan of roughly 28% was also noted. This finding shows that regorafenib can increase systemic exposure to UGT-substrates, such as irinotecan.<sup>62</sup> A study was done to evaluate the effect of regorafenib on probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (s-warfarin), CYP2C19 (omeprazole), and CYP3A4 (midazolam). No effects were reported.<sup>5,6</sup>

#### Ruxolitinib

Compared with strong CYP3A4 inhibitors, concomitant use of the moderate CYP3A4 inhibitor erythromycin results in a less profound increase in  $C_{max}$  of 8% and area under the curve of 27%. If coadministration with strong CYP3A4 inhibitors and inhibitors of both CYP3A4 and CYP2C9 (eg, fluconazole) is necessary, ruxolitinib dose should be reduced by 50% and haematological toxicity should be monitored extensively (eg, twice a week).<sup>5,6,33</sup> Concomitant use of the potent CYP3A4 inducer rifampicin decreased the area under the curve of ruxolitinib by 71%. However, only a 10% decrease in the overall pharmacodynamic activity was noted. This finding might be explained by the increased exposure to the active metabolites of ruxolitinib.<sup>33</sup>

#### Sorafenib

CYP3A4 inducers have an effect on sorafenib exposure.<sup>5,6</sup> By contrast, strong CYP3A4 inhibitors did not seem to have any effect on the  $C_{max}$  and area under the curve of sorafenib. However, this study was not done at steady state of sorafenib and inter-individual variation was high, with an increase in the area under the curve noted for some participants, and a decrease noted for others after co-administration of sorafenib with ketoconazole.<sup>34</sup> Substrates of CYP2C19 (omeprazole), CYP2D6 (dextromethorphan), and CYP3A4 (midazolam) were co-administered with sorafenib, with only minor, clinically insignificant, effects.<sup>63</sup> However, sorafenib reduced gefitinib exposure ( $C_{max}$  was reduced by 26% and area under the curve by 38%), but gefitinib had no effect on sorafenib exposure.<sup>43</sup> Sorafenib exposure was significantly decreased in the presence of CYP3A4-inducing anti-epileptic drugs.<sup>64</sup> The international normalised ratio should be monitored during concomitant use of warfarin and sorafenib.<sup>65</sup> When sorafenib was continuously coadministered with paclitaxel or carboplatin, increases in the area under the curves of paclitaxel, 6-OH paclitaxel, and sorafenib were reported,<sup>5,6</sup>

although the pharmacokinetics of carboplatin were unaffected.<sup>5,6</sup> Coadministration of paclitaxel and carboplatin with sorafenib, with a 3 day break in sorafenib dosing (2 days before and on the day of paclitaxel and carboplatin administration), had no significant effect on the pharmacokinetics of paclitaxel.<sup>5,6</sup> Thus, a drug–drug interaction might be bypassed by the introduction of a 3 day break from sorafenib. When co-administered with sorafenib, the area under the curve of doxorubicin was increased by 21%.<sup>5,6</sup> Furthermore, coadministration of capecitabine and sorafenib had no significant effect on sorafenib exposure, but increased the area under the curve exposure of capecitabine by 15–50%, and increased fluorouracil exposure by 0–52%.<sup>5,6</sup> The clinical significance of these findings is unknown, but changes in exposure of up to 50% could have an effect on clinical outcome. After co-administration of irinotecan with sorafenib (400 mg), the area under the curve of SN-38, roughly doubled.<sup>5,6</sup> Concomitant administration of low doses of sorafenib (100 mg or 200 mg twice daily) did not result in significant changes in SN-38.<sup>5,6</sup> In a small study in six patients, irinotecan had no significant effect on sorafenib exposure when sorafenib was given in low doses (100–200 mg twice daily), but when sorafenib was given at 400 mg twice daily together with 125 mg/m<sup>2</sup> irinotecan, sorafenib exposure increased by 68%.<sup>5,6</sup> Coadministration of sorafenib and dacarbazine led to decreased exposure of dacarbazine (the area under the curve reduced by 23%), but the clinical relevance of this drug–drug interaction remains unknown.<sup>66</sup> Neomycin decreased the area under the curve of sorafenib by 54%, probably because of eradication of gastrointestinal bacterial glucuronidase activity, resulting in a decrease in the enterohepatic recycling of sorafenib.<sup>5,6</sup>

#### Sunitinib

Coadministration of sunitinib and ifosfamide (CYP3A4 inducer) led to a significant decrease in sunitinib exposure.<sup>67</sup>

#### Vandetanib

Co-administration of rifampicin results in a moderate decrease of 40% in the area under the curve. By contrast, the exposure to the most important active metabolite N-desmethylvandetanib was profoundly increased during coadministration of rifampicin (increases of 266% in area under the curve and 414% in  $C_{max}$ ).<sup>36</sup> Because of the net effects of the decrease of vandetanib, and the major increase of its active metabolite are unknown, CYP3A4 inducers should be avoided during vandetanib treatment.<sup>36</sup> By contrast with the CYP3A4 inducer rifampicin, the CYP3A4 inhibitor itraconazole had no effect on vandetanib exposure. This finding implies that the effect of rifampicin on vandetanib exposure might be mediated by metabolic pathways other than CYP3A4, such as P-glycoprotein. The product label warns about the drug–drug interaction with warfarin, but no clinical evidence is available to support this.<sup>5,6</sup>



### Vemurafenib

No clinical data are available about the effect on vemurafenib exposure when concomitantly used with strong CYP3A4 inhibitors or inducers, and so caution should be taken when giving vemurafenib with either.<sup>5,6</sup> Vemurafenib had moderate, clinically insignificant, effects on exposure of dextromethorphan (CYP2D6), midazolam (CYP3A4), or caffeine (CYP1A2), and no effects on omeprazole (CYP2C19) or warfarin (CYP2C9).<sup>5,6</sup>

### Summary

In summary, all tyrosine-kinase inhibitors are metabolised by CYP enzymes, which make them prone to metabolic drug–drug interactions.<sup>5,6</sup> Regulatory assessment reports mainly investigate interactions with the most potent CYP inducers and inhibitors. Additional clinical studies should be done to fully assess the effect of moderate and strong CYP inducers and inhibitors at steady state, next to the present extrapolation of kinetic data from single-dose studies. On the basis of these results, adequate guidelines can be developed for dose adjustments of tyrosine-kinase inhibitors to counter drug–drug interactions.

### P-glycoprotein

Some tyrosine-kinase inhibitors are substrates or inhibitors of P-glycoprotein. In theory, the exposure of some tyrosine-kinase inhibitors (eg, erlotinib) could increase during coadministration of P-glycoprotein inhibitors (eg, verapamil or ciclosporin). Furthermore, because of P-glycoprotein inhibition by sunitinib, colchicines-related toxic effects were noted.<sup>68</sup> Clinical data are scarce and more research is needed to fully understand the role of P-glycoprotein in exposure to tyrosine-kinase inhibitors.

### Pharmacokinetic drug interactions: elimination

Drug–drug interactions related to elimination generally occur due to renal impairment, either caused by the parent drug or during concomitant use of other nephrotoxic comedication. Most tyrosine-kinase inhibitors are eliminated by liver metabolism and subsequently excreted in faeces as metabolites or unchanged, with minor contributions of renal clearance. Because tyrosine-kinase inhibitors are largely eliminated by hepatic metabolism, drug–drug interactions that take place through changes in renal elimination seem to be of minor importance. However, drug transporters (eg, P-glycoprotein, organic anion transporting peptides, organic cation transporter, and breast cancer resistance protein), that are also found in the kidneys, are important for the elimination of tyrosine-kinase inhibitors.<sup>69</sup> Because of the possible inhibition of the organic cation transporter by erlotinib, cellular accumulation of cisplatin in renal tubular cells might be restricted and, as a result, specific cisplatin-based nephrotoxic effects might be prevented.<sup>70</sup> Furthermore,

the drug–drug interaction between imatinib and methotrexate might affect methotrexate transport and elimination.<sup>71</sup> More research is needed to fully assess the positive effect of changes in expression of renal drug transporters on the pharmacokinetics of tyrosine-kinase inhibitors.

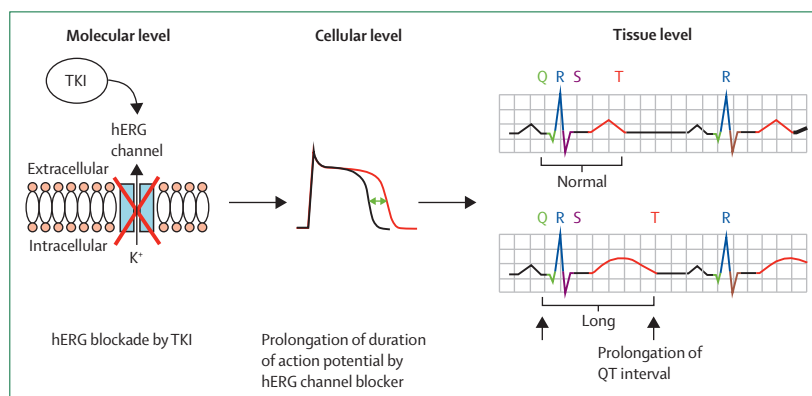
### Pharmacodynamic interactions

Pharmacodynamic drug–drug interactions can happen when the pharmacological effect of one drug is changed by another through action on mechanisms associated with the same physiological process or effect. Although pharmacodynamic interactions can be used intentionally (eg, methotrexate and folic acid), they can also be harmful (eg, cisplatin and lisdiuretics).

Some case reports describe pharmacodynamic interactions between tyrosine-kinase inhibitors and other drugs. For instance, imatinib can increase methotrexate toxicity by causing fluid retention, and sunitinib and imatinib can antagonise levothyroxine treatment by interference with thyroid hormones at the pituitary level.<sup>72,73</sup> Furthermore, concomitant use of antibiotics that affect the flora of the gastrointestinal tract might interfere with the enterohepatic circulation of regorafenib and might decrease regorafenib absorption.<sup>5,6</sup> Other, mainly additive, pharmacodynamic drug–drug interactions have been described between tyrosine-kinase inhibitors and other anticancer drugs, but this event is beyond the scope of this Review.

### Prolongation of the QTc interval

Many classic anticancer drugs can prolong the QTc interval (eg, anthracyclines). This prolongation is also frequently reported with use of tyrosine-kinase inhibitors,<sup>5,6</sup> which is probably caused by interaction with hERG K<sup>+</sup> channels. This interaction results in a change in electrical flow and delayed pulse conduction, and therefore, QTc prolongation (figure 2).<sup>74</sup> The potential of a tyrosine-kinase inhibitor to prolong the QTc interval is usually related to its chemical structure and plasma



**Figure 2:** Mechanism of action of QT<sub>c</sub> prolongation of TKIs, at the molecular, cellular, and tissue level  
TKI=tyrosine-kinase inhibitor.

concentration. Such QTc prolongation might be further increased by CYP3A4 inhibition by another drug, or by the simultaneous use of another drug that can prolong the QTc interval (eg, sotalol) alongside a tyrosine-kinase inhibitor.<sup>74</sup> Table 4 lists the QTc interval prolonging properties of tyrosine-kinase inhibitors. The Arizona CERT Index lists tyrosine-kinase inhibitors (eg, vandetanib, nilotinib, lapatinib, and sunitinib), and other drugs that might affect the QTc interval.<sup>75</sup>

Although rare, prolongation of the QTc interval and subsequent development of Torsades de pointes is a severe, life-threatening side-effect of treatment with tyrosine-kinase inhibitors. Medical oncologists should be better informed about the risk of coadministration of drugs that prolong the QTc interval in patients given tyrosine-kinase inhibitors. Pharmacists should routinely check for concomitant use of such prolonging drugs and CYP3A4 inhibitors. Special attention should be given to QTc interval-prolonging 5HT<sub>2</sub> antagonists, antibiotics, antifungals, and over-the-counter drugs (eg,

domperidone), because these drugs are frequently used by patients with cancer concomitantly with tyrosine-kinase inhibitors. Unless absolutely necessary, coadministration QTc-prolonging tyrosine-kinase inhibitors and drugs that prolong the QTc interval and CYP3A4 inhibitors should be avoided. If needed, an ECG should be obtained 24–48 h before, and 1 week after, the start of the concomitant treatment.

### Recommendations for clinical practice

In the past few years, tyrosine-kinase inhibitors have rapidly become an established part of oncology practice, but have also presented new challenges, such as the increased risk of drug–drug interactions.

Apart from sorafenib and vandetanib, tyrosine-kinase inhibitors' exposures are greatly affected by CYP3A4 inhibitors and inducers, and clinical intervention is often needed (table 3). Furthermore, acid-reducing drugs, such as proton-pump inhibitors, can profoundly affect the bioavailability of most tyrosine-kinase inhibitors and need clinical attention (table 1).

Drug–drug interactions that lead to prolongation of the QT<sub>c</sub> interval are rare, but can have fatal consequences and should be accounted for (table 4). Table 5 lists the main points about drug–drug interactions.

P-glycoprotein substrates with a narrow therapeutic window (eg, digoxin, ciclosporin, and tacrolimus) should be extensively monitored (eg, by therapeutic drug monitoring) during the use of tyrosine-kinase inhibitors that inhibit P-glycoprotein (table 2). The combination of grapefruit juice and sunitinib or nilotinib should be avoided.<sup>16,17</sup> Other product labels discourage intake of grapefruit juice only on theoretical assumptions (eg, pazopanib and lapatinib).<sup>5,6</sup>

To improve the safe use of tyrosine-kinase inhibitors in clinical oncology, a profound assessment of co-prescribed drugs, herbal supplements, lifestyle food and drinks (eg, grapefruit juice), cardiac risk factors, and physical examination is needed. To undertake this assessment, oncologists and haemato-oncologists should collaborate closely with clinical pharmacists, family doctors, and other medical specialists (eg, cardiologists). Additionally, more clinical research is needed (with for instance the

	QTc-interval prolongation?	Events?*
Axitinib	No	No
Crizotinib	Yes	No
Dasatinib	No	No
Erlotinib	No	No
Gefitinib	Yes	No
Imatinib	No	No
Lapatinib	Yes	No
Nilotinib	Yes	Yes
Pazopanib	Yes	Yes
Regorafenib	No	No
Ruxolitinib	No	No
Sorafenib	Yes	No
Sunitinib	Yes	Yes
Vandetanib	Yes	Yes
Vemurafenib	Yes	No

This table is constituted from regulatory documents.<sup>45</sup> \*Torsades de pointes or sudden (heart) death.

**Table 4: QTc-interval prolonging properties of tyrosine-kinase inhibitors**

Assessment of clinical relevance	
Interaction with acid suppressive drugs (proton-pump inhibitors, H <sub>2</sub> antagonists, and antacids): crizotinib, dasatinib, erlotinib, gefitinib, lapatinib and pazopanib	Concomitant use of acid suppressive drugs can significantly affect the drug absorption of these tyrosine-kinase inhibitors. If possible, the combination should be avoided, or the time of drug intake should be separated by several hours at least
Interaction with strong CYP3A4 inhibitors* and strong CYP3A4 inducers:† axitinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sunitinib, vemurafenib	Concomitant use of strong CYP3A4 inhibitors or inducers can significantly affect the exposure to these tyrosine-kinase inhibitors. Dose adjustments are highly recommended
Interaction with other QTc-interval-prolonging drugs: crizotinib, gefitinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib	Concomitant use of other QTc-interval-prolonging drugs along with these tyrosine-kinase inhibitors can significantly prolong the QTc interval. If indicated, an ECG should be obtained 24–48 h before and 1 week after initiating the concomitant therapy

See tables 1, 3, and 4 for detailed information. \*Ketoconazole, itraconazole, and voriconazole. †Rifampicin and enzalutamide.

**Table 5: Key points of the most significant drug–drug interactions in tyrosine-kinase inhibitor treatment**

### Search strategy and selection criteria

We screened the existing scientific literature about known or suspected drug–drug interactions between US Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved tyrosine-kinase inhibitors and conventional prescribed drugs, over-the-counter drugs, and herbal medicines. We identified references through searches of PubMed and Embase with the search terms [Drug interaction] OR [Drug combination] AND [Drug name]. We identified additional information was in the summary of product characteristics of the tyrosine-kinase inhibitors, that were FDA or EMA approved until Aug 1, 2013.<sup>4,5</sup> We reviewed only papers published in English. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

new anti-androgen enzalutamide; a strong CYP3A4 inducer) about drug–drug interactions in treatment with tyrosine-kinase inhibitors to provide a profound basis for drug reviews and to fully understand the interaction potential of these inhibitors. In case of a suspected interaction, and if pharmacokinetic data are not available, physicians and pharmacists should balance the available evidence, if possible, extrapolate available pharmacokinetic data for an individual patient, and monitor closely for toxic effects and response.

#### Contributors

RWFvL, RHJM, TvG, and FGAJ developed the idea for this Review. RvL and FGAJ reviewed the available data. RWFvL, TvG, RHJM, and FGAJ drafted the manuscript. All authors read, commented, and approved the final manuscript before submission.

#### Declaration of interests

We declare that we have no competing interests.

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