



Universiteit  
Leiden  
The Netherlands

## Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

Erp, P.H. van

### Citation

Erp, P. H. van. (2009, December 16). *Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib*. Retrieved from <https://hdl.handle.net/1887/14515>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/14515>

**Note:** To cite this publication please use the final published version (if applicable).

**Clinical Pharmacokinetics  
of Tyrosine Kinase Inhibitors**

**2**

**Chapter 2**



Nielka P. van Erp, Hans Gelderblom, Henk-Jan Guchelaar  
**Cancer Treatment Reviews 2009 (in press)**

## Summary

In the recent years, eight tyrosine kinase inhibitors (TKIs) have been approved for cancer treatment and numerous are under investigation. These drugs are rationally designed to target specific tyrosine kinases that are mutated and/or over-expressed in cancer tissues. Post marketing study commitments have been made upon (accelerated) approval such as additional pharmacokinetic studies in patients with renal- or hepatic impairment, in children, additional interactions studies and studies on the relative or absolute bioavailability. Therefore, much information will emerge on the pharmacokinetic behavior of these drugs after their approval.

In the present manuscript, the pharmacokinetic characteristics; absorption, distribution, metabolism and excretion (ADME), of the available TKIs are reviewed. Results from additional studies on the effect of drug transporters and drug-drug interactions have been incorporated. In general, TKIs reach their maximum plasma levels relatively fast; have an unknown absolute bioavailability, are extensively distributed and highly protein bound. The drugs are primarily metabolized by cytochrome P450 (CYP) 3A4 with other CYP-enzymes playing a secondary role. They are predominantly excreted with the feces and only a minor fraction is eliminated with the urine. All TKIs appear to be transported by the efflux ATP binding cassette transports (ABC) B1 and G2. Additionally these drugs can inhibit some of their own metabolizing enzymes and transporters making steady-state metabolism and drug-drug interactions both complex and unpredictable.

By understanding the pharmacokinetic profile of these drugs and their similarities, factors that influence drug exposure will be better recognized and this knowledge may be used to limit sub- or supra-therapeutic drug exposure.

## Introduction

In 1960, a minute chromosome, later known as the Philadelphia chromosome, was discovered in human chronic granulocytic leukemia and a causal relationship was suggested between this abnormal chromosome and the disease<sup>1-3</sup>. Later, a translocation between the long arm of the 22 and the long arm of the 9 chromosome was found and which was associated with an altered heavier human *c-abl* protein with tyrosine kinase activity and assumingly a growth stimulating effect<sup>4-6</sup>. The group of Heisterkamp et al. discovered the linkage between *c-abl*, positioned at chromosome 9 and the breakpoint cluster region (*bcr*) on chromosome 22 resulting in the *bcr-abl* oncogene and corresponding protein supposedly important for the generation and/ or maintenance of the disease<sup>7-10</sup>. Ninety-five percent of all chronic myelogenous leukemia (CML) was suggested to be the result of the altered tyrosine kinase that, under physiological conditions, is under tight control but in fusion is deregulated and expressed constitutively resulting in indefinite proliferation<sup>11</sup>. The involvement of protein tyrosine kinase activity in the development of tumors made them interesting targets for selective chemotherapy and thus for rational drug design. As a result the first series of low molecular weight compounds (tyrphostins) that display specificity for individual tyrosine kinase receptors were synthesized<sup>12</sup>.

Also a novel compound (CGP57148, STI571, imatinib) was synthesized that specifically inhibits Bcr-Abl cell proliferation. It competes with ATP for the ATP binding site of the tyrosine kinases. In *in vitro* tests imatinib inhibits Bcr-Abl, c-Abl and platelet-derived growth factor receptor (PDGFR) tyrosine kinase<sup>13, 14</sup>. Only five years after the presentation of the *in vitro* and *animal study* data, the results of the phase I studies were presented<sup>15-17</sup>. Based on the results from three additional phase II studies, the drug that was rationally designed to inhibit the *Bcr-Abl* protein appeared substantially active and received accelerated approval by the FDA on the 5<sup>th</sup> of May 2001 for the treatment of three Philadelphia chromosome positive leukemia subtypes<sup>18-20</sup>. Additionally imatinib potentially inhibits the kinase activity of the mutated and wild-type c-kit receptor *in vitro* and an effect on malignancies that is completely or partly dependent on c-kit activity was hypothesized and confirmed<sup>21, 22</sup>. The phase I study, presented in 2001, showed imatinib activity in c-kit receptor positive gastrointestinal stromal tumor (GIST)<sup>23</sup>. On the 18<sup>th</sup> of April 2003 the registration of imatinib was extended to treatment of patients with c-KIT receptor positive unresectable and/or metastatic GISTs and was reassigned to the first line treatment of patients with CML in the chronic phase<sup>24</sup>. With the introduction of imatinib a whole new era of tumor treatment started, with therapy that is rationally designed and given orally on a daily basis. Since the introduction of imatinib seven additional TKIs have been approved (Table I). All TKIs are designed to compete with ATP for the ATP binding pocket of similar or different tyrosine kinases that are mutated and/or over-expressed in specific tumors.

**Table I**      Approved tyrosine kinase inhibitors

Name	Tradename (FDA)	Registration date (FDA)	Research name	Targeted tyrosine kinases
Imatinib	Gleevec	10 May 2001	STI571	Bcr-Abl, PDGFR $\alpha$ , - $\beta$ , c-KIT
Gefitinib	Iressa	5 May 2003	ZD1839	EGFR
Erlotinib	Tarceva	18 Nov. 2004	OSI774	EGFR
Sorafenib	Nexavar	20 Dec. 2005	BAY 43-9006	C-RAF, B-RAF, c-KIT, FLT3, VEGFR2, -3, PDGFR- $\beta$
Sunitinib	Sutent	26 Jan. 2006	SU11248	PDGFR $\alpha$ , - $\beta$ , VEGFR1, -2, -3, c-KIT, RET, CSF-1R, FLT3
Dasatinib	Sprycel	28 June 2006	BMS354825	Bcr-Abl, SCR-family kinases, PDGFR $\beta$ , c-KIT, ephrin (EPH)receptor kinases
Lapatinib	Tykerb	13 March 2007	GW572016	EGFR (HER-1), HER-2
Nilotinib	Tasigna	29 Oct. 2007	AMN107	Bcr-Abl, c-KIT, PDGFR $\alpha$ , - $\beta$

**Absorption**

**Imatinib**

Imatinib is rapidly absorbed after oral administration with a peak plasma concentration at 2 hrs<sup>25</sup>. For imatinib, the bioavailability is surprisingly well investigated for a drug with no intravenously registered formulation. The exposure after intravenous infusion and after intake of oral capsule or solution was measured to determine the absolute bioavailability<sup>26</sup>. The intravenous formulation was specially made for investigational purposes and the capsule was used at the time the study was performed. The later registered tablet formulation was compared to the capsules to determine the relative bioavailability<sup>27</sup>. The bioavailability of imatinib is ~ 98% which is irrespective of oral formation (solution, capsule or tablet) or dosage (100mg or 400mg)<sup>26-28</sup>. Imatinib absorption is not influenced by food or concomitant antacid use<sup>29</sup>. Long-term exposure might influence the bioavailability since imatinib inhibits efflux transporters (ABCB1 and ABCG2) and enzymes (CYP3A4 and CYP3A5) present at the intestinal wall, but conflicting data are reported on this matter<sup>30, 31</sup>. The exact gastrointestinal site of absorption is not known yet. In a case of a woman with short bowel syndrome only 20% of the imatinib exposure was measured indicating that absorption takes place over a

longer part of the gastrointestinal tract<sup>32</sup>. Another case report describes the absorption from the rectum; the exposure (AUC) was approximately 40% of the orally achieved exposure indicating that absorption of the drug in the rectum takes place<sup>33</sup>. The interpatient variability in imatinib clearance is large ~ 40% and mainly unexplained<sup>34</sup>.

**Gefitinib**

The peak plasma levels of gefitinib occur within 3-7 hrs<sup>35</sup>. The absolute bioavailability is ~ 60% in healthy volunteers and cancer patients<sup>36</sup>. Administration of a granular formulation, a dispersion of the classic tablets or administration by nasogastric tube did not significantly influence the bioavailability<sup>37,38</sup>. Food has only a moderate and clinical non-significant effect on gefitinib exposure. Data of a study with 50 mg gefitinib showed a 14% decrease in AUC, another study with 250 mg of the drug showed a 37% increase in AUC after co-administration with food; this combined with the large interpatient variability (45-70%) makes the effect of food negligible<sup>35, 36, 39</sup>.

**Erlotinib**

The peak plasma levels of erlotinib occur 4 hrs after dosing<sup>40</sup>. The bioavailability following a 150 mg dose is 100% when applying a noncompartmental approach and ~ 60% using a 2-compartment nonlinear model<sup>41</sup>. The assumed nonlinearity in the compartmental approach is not confirmed by the data from the phase I dose escalation study<sup>42</sup>. Food increases the bioavailability to almost 100%<sup>40</sup>. Since the effect of food on erlotinib exposure is highly variable, the drug should be taken without food<sup>41</sup>. Erlotinib shows a large interpatient variability (~60%) which is unexplained yet<sup>43</sup>.

**Sorafenib**

The peak plasma levels of sorafenib occurs ~3 hrs after dosing<sup>44</sup>. The absolute bioavailability is unknown. The relative bioavailability of tablets compared to oral solution is 38-49%<sup>45</sup>. Conflicting data are published on the effect of food on the pharmacokinetics of sorafenib. In the phase I studies no major effect of food was observed<sup>46</sup>. However, the FDA approval reports a reduction of the bioavailability of 29% when taken with food and advices to take sorafenib without food <sup>47</sup>. Sorafenib pharmacokinetics show a large interpatient variability<sup>44</sup>. The large interpatient variability is supposed to be the result of slow dissolution in the gastrointestinal tract and enterohepatic circulation<sup>46</sup>. The drug shows a less than proportional increase in exposure with dose escalation. The underlying reason for this nonlinearity is not known yet<sup>46</sup>.

**Sunitinib**

The maximum plasma concentration of sunitinib is achieved within 6-12 hrs and the absolute bioavailability is unknown. The drug may be taken with or without food since food only has

a marginal effect on the exposure<sup>48</sup>. The interpatient variability is large ~40%<sup>49</sup>. A recent case report describes a significant decrease in sunitinib exposure (AUC) in an obese patient, which might indicate that body mass index has a pronounced effect on drug exposure and might thereby explain partly the large interpatient variability<sup>50</sup>.

**Dasatinib**

The maximum plasma concentration of dasatinib is achieved within 3-5 hrs and the bioavailability in humans is unknown. A 14% AUC increase may occur in patients taking the drug with a high-fat meal, however, this effect is not supposed to be clinically significant<sup>51</sup>. The interpatient and inter-occasion variability is large and ranges from 32-118%. A substantial proportion of the inter-occasion variability is supposed be explained by the bioavailability<sup>52</sup>. The origin of the interpatient variability has not been elucidated yet.

**Lapatinib**

The maximum plasma concentration of lapatinib is achieved within 3-4 hrs<sup>53</sup>. The absolute bioavailability has not been studied. However, the bioavailability of the drug must be low since food has such an extraordinary effect on the bioavailability. The largest effect is seen with a high-fat meal, which increased the exposure of lapatinib by 325% while a low-fat meal increased the exposure by 167%<sup>54</sup>. Possible explanations for this pronounced effect are: 1] A delayed gastric emptying induced by food allows more time for the tablets to dissolve and/ or 2] Food increases the formation of micelles by bile salts of hydrophobic substances such as lapatinib which might be of great influence on the bioavailability. Food does not influence the half life which suggests that the increased exposure is mainly caused presystemically<sup>54</sup>. The interpatient variability is large (68%) and not significantly reduced by the co-administration of food (52%)<sup>54</sup>.

**Nilotinib**

The maximum plasma concentration of nilotinib is reached 3 hrs after oral administration<sup>55</sup>. The absolute bioavailability is unknown but again cannot be high since the systemic exposure is increased by 82% when the drug is given with a high fat meal compared to fasted state<sup>56</sup>. The interpatient variability in exposure is 32-64% and unexplained yet<sup>57</sup>. In the phase I dose escalation study a saturation of serum levels was observed with doses ranging from 400 – 1200mg daily. A possible explanation might be that the uptake of nilotinib is saturated at doses exceeding 400mg since a modified dose schedule to a twice-daily regimen results in an increased exposure<sup>55</sup>.

**Absorption: In summary** most TKIs reach the maximum plasma concentration relatively fast (3-6 hrs) with sunitinib as the only exception (6-12 hrs) (Table II). The absolute bioavailability

**Table II** Pharmacokinetic parameters of the individual tyrosine kinase inhibitors

Name	F (%)	Protein binding (%)	t <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)	AUC <sub>0-24</sub> (ug*hr/mL)	Vd/F (L)	Cl/F (L/hr)	C <sub>trough</sub> (ng/mL)	Ref.
Imatinib	98	~95	2 - 4	18	40.1	295	11.8	1215.8	15, 26, 34
Gefitinib	60	~91	3 - 7	48	5.6	1400	35.7	60	36, 39, 153
Erlotinib	60 - 100	~93	4	36.2	26.5	232	5.3	1168	40, 41
Sorafenib	unknown	~99.5	3	25 - 48	143.4	unknown	unknown	unknown	46, 47
Sunitinib	unknown	~95	6 - 12	40 - 60	1.11	2230	34-62	44	49, 93
Dasatinib	unknown	~96	0.5 - 6	3 - 5	unknown	2505	unknown	unknown	51
Lapatinib	unknown	>99	3 - 4	24	14.3 - 36.2	>2200	unknown	300	53, 79, 154, 155
Nilotinib	unknown	~98	3	17	36.0	579	29.1	900.2	57, 156

Abbreviations: F, absolute bioavailability; T<sub>max</sub>, time to peak concentration; t<sub>1/2</sub>, elimination half-life; AUC, area under the concentration-time curve; Vd/F, apparent volume of distribution; Cl/F, apparent oral clearance; C<sub>trough</sub>, trough concentration

is only known for the three earliest registered TKIs (imatinib, gefitinib and erlotinib). It is remarkable that the bio-availability is not mandatory for registration since this information is used in the clinical practice to treat patients with altered gastrointestinal anatomy/physiology. TKIs are generally well soluble in acidic environment and the solubility rapidly declines above pH 4-6. A pronounced effect of food was expected for all TKIs since food can rapidly buffer gastric acid and thereby negatively influence the drug's solubility. However, food has an effect on only a few TKIs and even then in the opposite direction, indicating that other possible factors such as micelle formation or a hydrophobic vehicle (fat) are more important for the absorption of TKIs than the drug's solubility is. The bioavailability of lapatinib and nilotinib was pronouncedly increased by food, the bio-availability of erlotinib was marginally increased, the bio-availability of gefitinib, sorafenib and dasatinib is not clinically significant increased by food and food has no effect on the bioavailability of imatinib and sunitinib. Only sorafenib and

nilotinib showed a less than proportional increase in exposure with dose escalation which could be result of multiple mechanisms e.g. saturation at the absorption site, solubility aspects and transporter interactions. This non-proportionality distinguishes them from the other TKIs and might be addressed in future research. Also the large and unexplained inter-patient variability of all TKIs warrants further research..

## Distribution

### **Imatinib**

Imatinib is extensively distributed into tissues and highly protein bound, predominantly to albumin and  $\alpha$ 1-glycoprotein (AGP), which is translated into a large volume of distribution of 435 L and a long half life of 18 hrs<sup>26, 58-60</sup>. Changes in the unbound drug fraction had a large effect on the intracellular drug concentration in *in vitro* experiments<sup>61</sup>. The role of AGP on the pharmacokinetics is underscored in *in vivo* studies, and a possible relation was suggested between imatinib-free plasma levels and the treatment efficacy<sup>62-65</sup>. Imatinib only penetrates in the cerebrospinal fluid (CSF) to a limited extent; ~100-fold lower levels were measured in the central nervous system (CNS) compared to plasma<sup>61, 66-70</sup>. This limited penetration in the CNS was confirmed in a non-human primate model. The drug appears to concentrate in the sinuses and tissues surrounding the brain<sup>58, 71</sup>. ABCB1 and to a lesser extent ABCG2 are suggested to strongly regulate the uptake in the CNS and malignant cells. Inhibition of ABCB1 in *in vitro* and *animal* studies resulted in a 2-10 fold increase in CNS penetration<sup>66, 67, 69, 70</sup>. However, the clinical relevance of the efflux transporters has to be investigated in humans. In *in vivo* and *in vitro* studies a 5-8 cell/plasma ratio was observed which indicates that imatinib is actively transported into the leukemia cells and a possible role for the organic cation transporter (OCT) 1 is hypothesized<sup>61, 62</sup>.

### **Gefitinib**

Gefitinib is extensively distributed into the tissues and highly protein bound (to albumin and AGP) which results in a large volume of distribution of 1400L and a long half life of 48hrs<sup>72</sup>. The blood to plasma ratio of 0.76 suggests that the drug mainly binds to plasma proteins, with a preference for AGP, and to a lesser degree to blood cells<sup>72</sup>. The penetration in the CNS is poor, probably as a result of ABCB1 mediated efflux at the blood-brain barrier<sup>73</sup>. The drug preferably distributes into highly perfused tissues (lung, liver, kidney and gastrointestinal tract) including tumor tissues<sup>73</sup>. In mice bearing human tumor xenografts the tumor cell/plasma ratio was 11-fold as was the skin/plasma ratio which points into the direction of active transport into specific tissues<sup>74</sup>.

### **Erlotinib**

Erlotinib and gefitinib have a common chemical backbone structure and are distributed very similarly in the human body. Erlotinib is also extensively protein bound, predominantly to albumin and AGP, has a long half life of 36.2 hrs and an accompanying large volume of distribution of 232 L<sup>40</sup>. AGP concentration and steady state exposure (AUC) are tightly linked<sup>43</sup>. AGP together with total bilirubin and smoking status were the most important factors affecting the drug clearance<sup>75</sup>. The penetration of erlotinib in the CNS is poor, with CNS levels that represent ~7% of the plasma exposure<sup>76</sup>.

### **Sorafenib**

The volume of distribution of sorafenib is not reported. However, since the drug is highly protein bound (~99.5%) and has a long half life of 25-48hrs, a large volume of distribution is expected<sup>47</sup>.

### **Sunitinib**

Sunitinib has a large volume of distribution of 2230 L and is highly (95%) protein bound. The half life of the drug is 40-60 hrs<sup>49</sup>.

### **Dasatinib**

Dasatinib is extensively distributed in the extravascular space and is highly protein bound (~94%) which results in a large volume of distribution of 2505 L and a half life of 3-5 hrs<sup>77</sup>. The distribution between plasma and blood cells was equal in *in vitro* experiments<sup>77</sup>. The brain penetration is poor. In three patients the CSF: plasma ratios ranged from 0.05-0.28. However, dasatinib appears to be more potent against CNS tumors than imatinib which might be the result of a much greater potency (325-fold) along with the low amount of proteins in the CNS resulting in a relatively large fraction of unbound drug<sup>78</sup>.

### **Lapatinib**

The volume of distribution of the terminal phase of lapatinib is >2200 L and the half life is 24 hrs. The drug is highly protein bound (> 99%) to albumin and AGP<sup>79</sup>. *Rat* and *mouse* studies demonstrated a very limited penetration of the drug in the CNS which was increased with 40-fold in ABCB1/ ABCG2 knockout mice though single transporter knockout mice have only limited effect on the CNS penetration<sup>80, 81</sup>. The translation of the results of these animal studies to human remains difficult and therefore additional studies in humans are warranted.

### **Nilotinib**

The volume of distribution of nilotinib is not reported. Although the high level of protein binding (98%) and the long half life (~17 hrs) suggest that the volume of distribution is presumably large.

**Distribution: In summary** TKIs are extensively distributed into tissues and are highly protein bound, resulting in a large volume of distribution and a long terminal half life (Table II). The volume of distribution, the affinity for specific plasma proteins and the CNS penetration is not reported for all TKIs yet. However, since the TKIs share multiple pharmacokinetic characteristics, parallels might be drawn between the TKIs. Especially, the influence of AGP on the pharmacokinetics and efficacy of TKIs might be interesting, since TKIs are preferably bound to this plasma protein and AGP is often elevated in cancer patients and could therefore interfere with an effective treatment.

## Metabolism

### Imatinib

Imatinib is primarily metabolized through CYP3A4 and CYP3A5 with CYP2D6, CYP2C9, CYP2C19 and CYP1A2 playing a minor role<sup>28, 82-84</sup>. A recent study identified two extrahepatic enzymes (CYP1A1 and CYP1B1) and the flavin-containing monooxygenase 3 (FMO3) enzyme as being capable of extensively metabolizing the drug<sup>83</sup>. Additionally, imatinib can inhibit CYP3A4 and CYP2D6 metabolism<sup>34, 84, 85</sup>. Patients carrying a polymorphism in CYP2D6 (\*4 allele) show a reduced apparent clearance indicating that CYP2D6 appears to be important *in vivo* in the metabolism of imatinib<sup>86</sup>. The clinical relevance of these enzymes at steady-state pharmacokinetics, under auto inhibition of metabolic pathways, is mainly unsolved and needs to be addressed in additional studies. The main metabolite is CGP74588 which represents approximately 10% of the imatinib AUC and has similar potency *in vitro*<sup>25</sup>.

### Gefitinib

*In vitro* studies indicate that gefitinib is metabolized by CYP3A4, CYP3A5, CYP2D6 and by the extrahepatic enzyme CYP1A1<sup>39, 87</sup>. The drug inhibits CYP2C19 and CYP2D6 although the clinical relevance is questioned<sup>88</sup>. The main metabolite is the O-desmethyl derivate (M523595) which is present at concentrations similar to gefitinib and is formed through CYP2D6 metabolism<sup>87, 89</sup>. M523595 and gefitinib have similar potency against epithelial growth factor receptor (EGFR) tyrosine kinase activity in isolated enzyme assays. However, the metabolite has lower activity in a cell based assay due to the poor penetration into the cell and is therefore unlikely to contribute significantly to the therapeutic activity<sup>74</sup>. In CYP2D6 poor metabolizers a higher exposure to gefitinib was observed compared to the extensive metabolizers. Additionally, M523595 was undetectable in poor metabolizers. CYP3A4 activity and CYP3A5 polymorphisms did not explain the large interindividual variability<sup>89</sup>. *In vitro* studies claim that CYP3A4 is the most prominent enzyme in gefitinib metabolism though conflicting data are presented<sup>73, 87, 88</sup>. However *in vivo* data suggests that besides CYP3A4 also CYP2D6 activity has a significant influence on the exposure<sup>89, 90</sup>.

### Erlotinib

The overall metabolism of erlotinib, and formation of O-desmethyl-erlotinib (OSI-420), is predominantly through CYP3A4 and CYP3A5 and to a lesser extent by CYP1A2 and the extrahepatic isoform CYP1A1 and CYP1B1, with only a minor role for CYP2D6 and CYP2C8<sup>40, 75, 87, 91</sup>. However, induction of the enzymes CYP1A2 and CYP1A1 has a pronounced effect on the drug exposure, indicating that both enzymes might have a more prominent role in the *in vivo* erlotinib metabolism as suggested by the *in vitro* results<sup>91</sup>. Erlotinib is a moderate pregnane X receptor (PXR) inducer and strongly induces CYP3A4 mRNA levels, although the formation of 1-hydroxymidazolam is decreased in *in vitro* experiment showing the potency of erlotinib to inhibit CYP3A4 metabolism<sup>92</sup>. Conflicting data are published on the effect the drug has on CYP3A4 metabolism<sup>87</sup>.

### Sorafenib

Oxidative metabolism of sorafenib is mediated by CYP3A4, additionally the drug is glucuronidated by UDP glucuronosyltransferase (UGT) 1A9<sup>47</sup>. Around 50% is eliminated in the unchanged form which is either the result of poor metabolism capacity or the result of a low fraction of the drug that is absorbed from the intestines.

### Sunitinib

Sunitinib is primarily metabolized by CYP3A4 to produce its primary active metabolite SU12662 which is further metabolized by CYP3A4 into inactive metabolites<sup>93</sup>. Data on additional enzymes involved in the metabolism are lacking.

### Dasatinib

Dasatinib is extensively metabolized and thus relatively small amount of unchanged drug is excreted<sup>94</sup>. Dasatinib is primarily metabolized by CYP3A4 to produce its pharmacologically active metabolites; M4, M5, M6, M20 and M24 that represent around 5% of the parent compound AUC. Flavin-containing mono-oxygenase 3 (FMO-3) and UGT are also involved in the formation drug metabolites<sup>51</sup>. *In vitro* data demonstrate that multiple CYP isoforms (e.g. CYP1A1, 1B1 and 3A5) are capable of metabolizing dasatinib, however the relevance of these other CYP-enzymes *in vivo* requires further investigation<sup>95</sup>.

### Lapatinib

*In vitro* studies indicate that lapatinib is primarily metabolized to oxidation products by CYP3A4, 3A5, 2C19 and 2C8<sup>79</sup>. The major enzyme is CYP3A4 which accounts for approximately 70% of the metabolism. One metabolite GW690006 remains active against EGFR however it has lost activity against HER2, whereas other metabolites appear to be inactive<sup>79</sup>. Lapatinib is an inhibitor of CYP3A4 and CYP2C8 and may therefore interact with substrates of these



enzymes; additional studies to investigate this effect are ongoing<sup>79</sup>.

**Nilotinib**

Nilotinib is mainly metabolized through CYP3A4. *In vitro* data demonstrate that the drug is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1. Additional *in vitro* data show that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9<sup>57</sup>. *In vivo* data have been presented on the clinical relevance of CYP3A4 inhibition in an interaction study with midazolam and for UGT1A1 in a genetic polymorphism study describing an increased risk of nilotinib induced hyperbilirubinemia for the UGT1A1 \*28 genotype<sup>56, 96</sup>.

**Metabolism: In summary** all TKIs are metabolized in a very similar way (Table III, Figure I). All TKIs are primarily metabolized by CYP3A4, with other CYP-enzymes and for some TKIs (sorafenib, dasatinib) UGT playing only a minor role. The enzymes that show affinity are mostly identified in *in vitro* experiments, whereas the clinical effects of the major enzymes is typically investigated in *in vivo* interaction studies in healthy volunteers. The clinical relevance of the involvement of minor enzymes is largely unsolved at the time of registration and needs to be addressed in additional studies after registration. Several TKIs (imatinib, gefitinib, lapatinib and nilotinib) are inhibitors of enzymes by which they are primarily metabolized themselves, this could alter their metabolism substantially upon multidose use at steady-state. There is little insight in the steady-state metabolism at this point, which is surprising since these drugs are used on a daily basis. Some TKIs (erlotinib, sorafenib, sunitinib and dasatinib) are thought to have no effect on CYP-enzyme activity which might be the result of a lack of data rather than an absent effect. Additional research to investigate the effect of these drugs on CYP-enzyme activity is needed.

**Excretion**

**Imatinib**

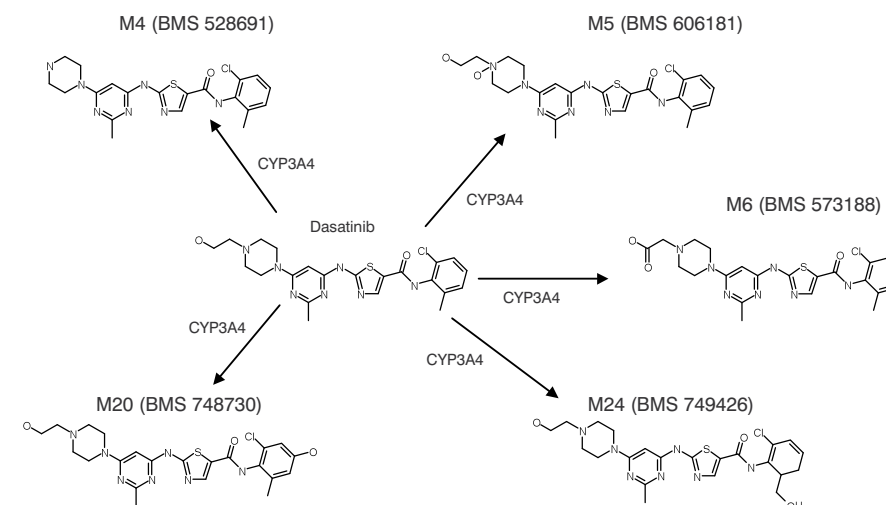
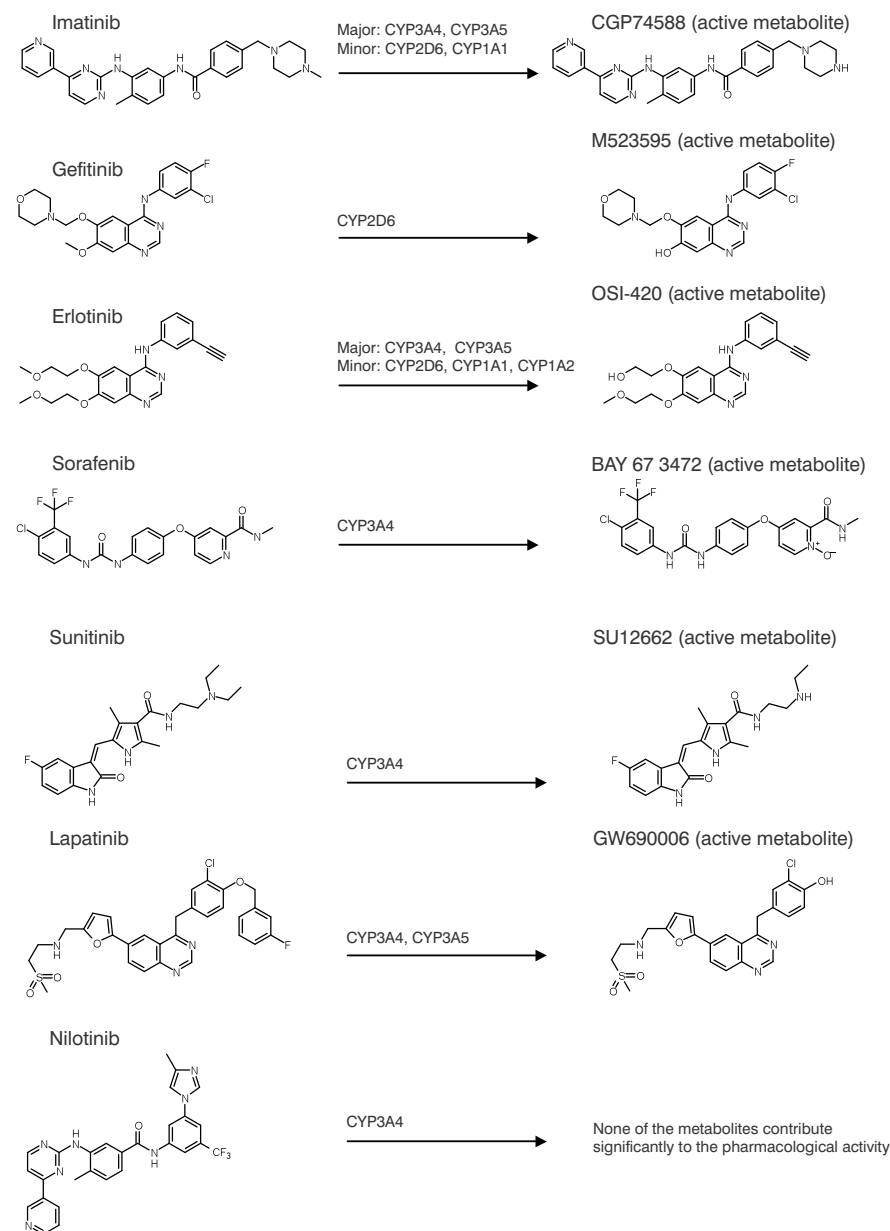
Imatinib is mainly eliminated through the liver. The kidneys only excrete a minimal amount of the drug and its metabolites. At this point there is still a discussion ongoing whether the apparent clearance increases, decreases or remains the same at steady-state<sup>97-100</sup>. However, a decrease in clearance seems more plausible since imatinib is capable of inhibiting its own metabolic pathways. Of a single dose imatinib in healthy volunteers 81% of the dose was recovered in urine (13.2%; 5% as unchanged imatinib) and feces (67.8%; 23% as unchanged imatinib) in 7 days<sup>25</sup>. This suggests that the drug clearance will more likely be affected by hepatic impairment than by renal dysfunction<sup>61</sup>. Surprisingly, two independent groups found that renal impairment has a pronounced effect on imatinib pharmacokinetics<sup>62, 101</sup>. In contrary

**Table III** enzymes and transporters involved in the pharmacokinetics

Name	Enzymes Phase I - oxidation	Enzymes Phase II - conjugation	Efflux transporters	ref
Imatinib	Major: CYP3A4 and CYP3A5 Minor: CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP1A1, CYP1B1	Minor: FMO3	ABCB1, ABCG2, ABCG4 Suggested: OCT1, OATP1B3 and OCTN2	28, 117, 120, 122
Gefitinib	Major: CYP3A4, CYP3A5, CYP2D6 & CYP1A1		ABCG2 Suggested: ABCB1	39, 123
Erlotinib	Major: CYP3A4 and CYP3A5, Minor CYP1A1, CYP1A2, CYP2C8, CYP2D6		ABCB1, ABCG2	40, 87, 127
Sorafenib	CYP3A4	UGT1A9		47
Sunitinib	CYP3A4		ABCB1, ABCG2	49, 130
Dasatinib	Major: CYP3A4	Minor FMO-3, UGT	ABCB1, ABCG2 Suggested: OCT1	51, 77, 132
Lapatinib	Major: CYP3A4, CYP3A5 Minor CYP2C19, CYP2C8		ABCB1, ABCG2	79, 80
Nilotinib	CYP3A4		ABCB1, ABCG2	57, 134



**Figure I** Tyrosine kinase inhibitors with their active metabolites



The tyrosine kinase inhibitors with only their active metabolites are demonstrated. The enzymes involved according to literature are presented, possible other enzymes involved in the formation of the metabolite are absent.

a case study in an end-stage renal function patient claims no effect on the pharmacokinetics, however the clearance in this patient was significantly reduced compared to patients with normal renal function<sup>102</sup>. Two possible explanations for this apparent discrepancy were put forward: a correlation between renal failure and AGP levels and an effect of elevated levels of uremic toxins in renal failure on the organic anion transporting polypeptide (OATP) 1B3 and hereby influencing the hepatic elimination<sup>101, 103, 104</sup>. Moreover, there was no effect observed of mild and moderate liver dysfunction on the pharmacokinetics of imatinib and CGP74588 in three independent studies<sup>105-107</sup>. Severe liver dysfunction resulted in elevated drug exposure levels<sup>106</sup>. Renal and hepatic impairment is no reason for abstaining patients from imatinib treatment though patients with moderate renal failure should start at a 50% decreased dose and patients with severe liver dysfunction are advised to start with a 25% dose reduction<sup>24</sup>.

### Gefitinib

About 90% of gefitinib is recovered in feces (86%) and urine (0.5%) over 10 days indicating that renal excretion is not a major route of elimination<sup>35</sup>. Surprisingly, in patients with moderate and severe elevated liver tests the pharmacokinetics was not altered. No data are available on the influence of renal impairment on the pharmacokinetics<sup>39</sup>.

**Erlotinib**

Following a 100 mg oral dose of erlotinib, 91% of the dose was recovered over 11 days: 83% in feces and 8% in urine of which 1% and 0.3% as parent drug respectively<sup>108</sup>. No data are available regarding the influence of hepatic dysfunction and/or hepatic metastases and renal dysfunction on the drug pharmacokinetics<sup>40</sup>.

**Sorafenib**

Sorafenib is eliminated primarily through the liver. Of a 100mg dose 77% is excreted with the feces and 19% is excreted as glucuronidated metabolites in the urine<sup>47</sup>. Approximately 50% of an oral dose is recovered as unchanged drug in the feces, due to either inefficient metabolism or lack of absorption<sup>47</sup>. Mild to moderate hepatic impairment does not significantly alter the exposure. Sorafenib pharmacokinetics has only recently been studied in patients with severe hepatic and renal impairment<sup>109</sup>. After a single dose of 400mg no significant alterations were observed in drug and metabolite AUC regardless of the severity of renal or hepatic impairment. However, only patients with normal or mild hepatic and renal dysfunction tolerated (without experiencing dose limiting toxicities) a dose of 400mg twice daily at steady state. Patients with moderate renal and hepatic dysfunction needed a dose reduction of 50%, while patients with severe hepatic impairment did not tolerate sorafenib. Patients with very severe hepatic and renal dysfunction only tolerated 200mg once daily, no explanation for the discrepancy between the tolerance in severe and very severe hepatic impairment is provided<sup>109</sup>. This recent study provides valuable information since sorafenib is used for the treatment of patients with hepatocellular carcinoma that is often accompanied by severe hepatic impairment.

**Sunitinib**

Sunitinib is primarily eliminated with the feces (61%), with renal elimination accounting for only 16% of the administered dose. There are no studies on the pharmacokinetics in patients with serious hepatic or renal insufficiency. However, in pharmacokinetic studies where also the creatinine clearance was assessed, there appeared to be no pharmacokinetic alterations in volunteers with a wide range of creatinine clearances<sup>110</sup>. Additionally in a case report describing two hemodialyzed patients on sunitinib therapy the plasma concentration of the drug and its major metabolite at steady-state were comparable to patients with normal renal function<sup>111</sup>.

**Dasatinib**

Dasatinib is mainly excreted via feces, 85% of which 19% as intact drug. Urine excretion is around 4% of which <1% as unchanged dasatinib<sup>51, 112</sup>. No data are available on the effect of hepatic and renal impairment on dasatinib pharmacokinetics<sup>51</sup>.

**Lapatinib**

Lapatinib is primarily eliminated hepatically, with 27% of the oral dose recovered in the feces and <2% recovered in the urine<sup>79</sup>. It is suggested that a large part of the oral dose remains in the intestines and is not absorbed which may contribute to the most prevalent dose limiting toxicity diarrhea. Indeed, diarrhea showed no relation to serum levels of lapatinib<sup>113</sup>. In patients with severe hepatic impairment the AUC of lapatinib was increased by > 60% and the half life was ~3-fold increased compared to patients with normal hepatic function<sup>79</sup>. No data are available on the influence of severe renal impairment.

**Nilotinib**

Nilotinib recovery was assessed over 7 days after a single dose and showed 4.4% of the drug being recovered in urine and 93.5% in feces (69% unchanged nilotinib). A large amount (31%) of unchanged nilotinib excreted via the feces was suggested to be the result of unabsorbed drug<sup>114</sup>. Nilotinib pharmacokinetics has not been studied in patients with hepatic or renal impairment, however the drug label warns for the possible risk of giving nilotinib to patients with hepatic impairment<sup>57</sup>.

**Excretion: In summary** all TKIs are predominantly excreted via the feces and only a minor fraction is eliminated with the urine. The fraction of unchanged drug in the feces can vary widely among the TKIs. Large fraction of unchanged drug in the feces can either be the result of a relatively large fraction that is not absorbed and directly eliminated or by a low efficient metabolism. Without data on the absolute bioavailability or the time frame of the fecal elimination it is difficult to distinguish between both mechanisms. Data on the effects of mild, moderate or severe renal and hepatic impairment on the pharmacokinetics of TKIs are mainly absent. For the few TKIs where the effect is studied some unexpected results are observed. Mild to moderate hepatic impairment did not affect the pharmacokinetics of imatinib and gefitinib whereas severe hepatic impairment did affect the pharmacokinetics of imatinib and lapatinib and did not affect the pharmacokinetics of gefitinib. Surprisingly, mild to moderate renal impairment did affect the pharmacokinetics of imatinib pharmacokinetics. Since the patients treated with these drugs are at risk to develop renal or hepatic impairment at any stage of their disease it is necessary that more data become available on the possible influence of these impairments on the pharmacokinetics of these drugs.

**Drug transporters**

The ABCB1 (P-glycoprotein; P-gp), ABCC1 (multidrug resistance-associated protein; MRP1) and ABCG2 (breast cancer resistance protein; MXR) are efflux transporters and are now

recognized to have an important role in the absorption, distribution, excretion and toxicity of xenobiotics<sup>115</sup>. Also the solute carrier family (SLC) transporters, which are influx transporters, are receiving more attention although their effect on drug kinetics is less well established at this point<sup>116</sup>. Members of the SLC family are the solute carrier OATP, solute carrier peptide transporter family (PepT1), and organic zwitterion/cation transporters (OCTNs)<sup>116</sup>. Also for the disposition of TKIs efflux and influx transporters are gaining interest.

### **Imatinib**

The high bioavailability of imatinib, a substrate for multiple CYP enzymes (especially CYP3A4 and CYP3A5), and also for ABCB1, ABCG2 with ambiguous affinity for SLC transporters, is remarkable and can only be explained by a low hepatic extraction and low efficient transport of imatinib by the efflux transporters<sup>115, 117-119</sup>. Although conflicting results have been published, imatinib is most likely a substrate and an inhibitor of ABCB1 and ABCG2<sup>120</sup>. The *ABCG2* 421C/A polymorphism is associated with a reduced clearance in humans<sup>65</sup>. A recent study in 90 CML patients showed a pronounced effect of *ABCB1* 1236C/T and 2677G/T polymorphisms on trough drug levels and an corresponding clinical effect (major molecular response)<sup>121</sup>. However, additional studies are necessary to conclusively determine the role of ABC-transporters on imatinib pharmacokinetics and efficacy. There appears to be a modest role for the organic cation transporter 1 (OCT1) as observed in *in vitro* experiments. OAT1, OAT3 and OCT2 do not transport imatinib *in vitro* which is consistent with their presence on the kidneys and the relative low renal clearance<sup>117, 122</sup>. OATP1B3 and OCTN2 appeared to have affinity for the drug, however the *in vivo* relevance is not yet studied [Oostendorp RL The role of Organic Cation Transporter 1 and 2 in the *in vivo* pharmacokinetics of imatinib Submitted]. Since the precise role of the transporters on imatinib disposition and the effect of transporter inhibition by the drug is not completely understood, no additional warnings have been added to the drug label. However, alertness is necessary for possible drug interactions on drug transporter level. Moreover, the highly polymorphic transporters might explain at least in part the large interpatient variability.

### **Gefitinib**

Gefitinib also interacts with ABCG2 and to a lesser extend with ABCB1<sup>123</sup>. In *in vitro* experiments the drug appeared to reverse ABCG2 mediated resistance by inhibiting ABCG2 at relatively high drug concentrations<sup>123-125</sup>. It is a substrate of ABCG2 in *in vitro* experiments at clinically relevant drug concentration. Additionally patients carrying the *ABCG2* 421C/A polymorphism have higher gefitinib exposure and more diarrhea compared to those carrying the wild-type *ABCG2* genotype<sup>125, 126</sup>. No association was found between the *ABCB1* 3435 C/T genotype and gefitinib pharmacokinetics<sup>125</sup>.

### **Erlotinib**

In *in vitro* experiments erlotinib was shown to be a substrate for ABCB1 and ABCG2 but not for ABCC2. In mice studies the absence of ABCB1 and ABCG2 significantly affected the oral bioavailability<sup>127</sup>. Erlotinib also inhibits the ABCB1 and ABCG2 drug efflux function<sup>128</sup>. In a recent study in humans the *ABCG2* -15622C/T and 1143C/T polymorphisms, resulting in a reduced expression of the transporter, were associated with increased AUC and Cmax<sup>129</sup>.

### **Sorafenib**

The role of transporters on the disposition of sorafenib is yet unknown.

### **Sunitinib**

Recently, an *in vitro* study demonstrated that sunitinib is a high affinity inhibitor of ABCG2 and inhibits ABCB1, albeit more weakly. Moreover, the drug is also a substrate of both transporters<sup>130</sup>. The bioavailability might therefore be affected by polymorphisms in the genes encoding for these transporters but this needs to be addressed in clinical studies<sup>130</sup>.

### **Dasatinib**

*In vitro* data demonstrated that dasatinib is a substrate of ABCB1 and ABCG2 but not a potent inhibitor of these transporters<sup>77, 131, 132</sup>. Additional *in vitro* studies suggested that the drug is also a substrate for hOCT1 however the uptake is much less hOCT1 dependent compared to imatinib. Inhibitors of hOCT1 did not interfere with the uptake of dasatinib and it is hypothesized that the uptake *in vivo* is more likely driven by diffusion than by active transport<sup>131, 132</sup>.

### **Lapatinib**

Results from *in vitro* studies indicated that lapatinib is a substrate and an inhibitor of the efflux transporters ABCB1, ABCG2 and solely an inhibitor of OATP1B1<sup>80</sup>. It has the potency to reverse the ABCB1 and ABCG2 driven resistance on multi drug resistant cells *in vitro*<sup>133</sup>. In addition, lapatinib did not inhibit nor was a substrate of OAT, OCT and uric acid transporter (URAT) transporters which is in line with the marginal renal clearance of the drug<sup>80</sup>. Further studies in humans are warranted to further clarify the role of transporters on the efficacy, disposition, toxicity and drug interactions<sup>80</sup>.

### **Nilotinib**

Nilotinib appears to be a substrate and an inhibitor of ABCB1 and ABCG2, however the clinical relevance of these *in vitro* assessments need to be addressed<sup>57, 134</sup>.

**Drug transporters:** *In summary* all TKIs are substrates and inhibitors of ABCB1 and ABCG2, except for dasatinib which appears to be no inhibitor of these transporters and for sorafenib of which no data are available. Additionally, imatinib and dasatinib might interact with OCT1. No data are available on the affinity of the other TKIs for the SLC transporter family. Multiple *in vitro* studies have been published on the effect TKIs have on drug transporters and *visa versa*. At this point the clinical significance of polymorphic transporters and interactions between drugs on transporters are mainly undefined.

## Drug-drug interactions

### Imatinib

The drug label of imatinib warns for co-administration of potent CYP3A4 inhibitors and for co-administration of substrates of CYP3A4 with a narrow therapeutic window. This warning makes the clinical practice difficult since a large group of drugs is either a substrate or an inhibitor of CYP3A4. The inhibitory effect of the drug on CYP3A4 was investigated by an interaction study with simvastatin. Simvastatin clearance was reduced by 70% indicating a clinically relevant strong CYP3A4 inhibitory effect<sup>85</sup>. Contrary results are presented in interaction studies with CYP3A4 inhibitors after a single dose (ketoconazole) and at steady-state (ritonavir)<sup>84, 135</sup>. CYP3A4 inducers (rifampicin, St. John's wort, phenytoin and enzyme inducing anti-epileptic drugs (EIAED's)) very constantly show a decrease in imatinib exposure<sup>15, 100, 136-139</sup>. Administration of the drug together with metoprolol, a CYP2D6 substrate, resulted in an increase in metoprolol exposure of 23% with moderate differences between the intermediate and extensive metabolizers<sup>140</sup>. Smoking does not alter imatinib exposure, indicating no major contribution of CYP1A2 in the metabolism of the drug<sup>141</sup>. An interaction between imatinib and warfarin is hypothesized since both increases and decreases in INR have been reported after starting therapy. Warfarin is a substrate of CYP2C9 and CYP3A4 and both enzymes are involved in the metabolism of imatinib<sup>28</sup>. Interactions through the other enzymes are hypothesized and warned for in the drug label but not yet investigated. Also the effect of drug transporter inhibitors (e.g. pantoprazol, cyclosporine) on the disposition of the drug in humans is not evolved yet and neither is the influence of imatinib on drugs that are transported by ABCB1 (e.g. digoxine) or ABCG2 (e.g. nitrofurantoin). The cellular uptake of nilotinib is enhanced by the co-administration of imatinib due to ABCB1 and possibly ABCG2 inhibition in *in vitro* studies<sup>142</sup>. The drug label does not include warnings with regard to risks related to drug transporter interactions though alertness is on its place.

### Gefitinib

Inhibitors and inducers of CYP3A4 interfere with gefitinib exposure. Itraconazole elevated the exposure (AUC) with 78%. Concomitant administration of rifampicin reduced the AUC

with 83%<sup>88</sup>. In *in vitro* experiments gefitinib stimulates midazolam metabolism through CYP3A4. An explanation for this observation is not provided yet<sup>87</sup>. High doses of ranitidine, inducing a gastric pH > 5.0, resulted in a decreased gefitinib AUC<sup>143</sup>. Gefitinib co-administration resulted in a 35% increase in metoprolol exposure indicating that the drug is a CYP2D6 inhibitor at therapeutic levels<sup>88</sup>. In a case report the possible interaction between herbal medicines (e.g. ginseng) and gefitinib is suggested since interruption of the herbal medicine treatment turned the patient from a non-responder into a responder. Unfortunately, in this case the gefitinib plasma levels were not measured<sup>144</sup>. Surprisingly, sorafenib reduced the AUC of gefitinib by 38%, where gefitinib has no effect on sorafenib exposure<sup>145</sup>. There is no explanation for this observation.

### Erlotinib

Inhibitors and inducers of CYP3A4 interfere with erlotinib exposure. Co-administration of rifampicin results in a 67% decreased drug exposure (AUC)<sup>146</sup>. Ketoconazole increases the drug exposure (AUC<sub>0-∞</sub>) and C<sub>max</sub> with 86% and 102% respectively<sup>147</sup>.

Co-administration of BAS 100, a substance in grapefruit juice, resulted in a 2.1 fold increase in the AUC of erlotinib in mice, most likely due to an increased uptake by inhibiting CYP3A4 or ABCB1<sup>148</sup>. Smoking results in a decreased erlotinib AUC (35.9%) possibly by inducing CYP1A1 and CYP1A2 metabolism<sup>91</sup>. The maximum tolerated dose in smokers was 300 mg compared to 150 mg in non-smokers. Additionally the steady-state trough levels and incidence of rash and diarrhea in smokers at 300mg were similar as the data for non smokers receiving 150mg erlotinib<sup>149</sup>.

### Sorafenib

Since sorafenib is metabolized by CYP3A4, an interaction with CYP3A4 inhibitors was expected. In a drug interaction study with ketoconazole and sorafenib, ketoconazole did not alter the exposure. However it did decrease the plasma concentration of sorafenib-N-oxide which is formed through CYP3A4. This finding is consistent with an earlier mass-balance study showing that 15% of the administered dose was eliminated by glucuronidation where only 5% was eliminated as oxidative metabolites<sup>150</sup>. Co-administration of sorafenib with gefitinib causes an decrease in gefitinib exposure of 38%. The interaction can not be mediated through CYP3A4 inhibition since sorafenib does not influence the exposure of midazolam which is suggested to be solely metabolized through CYP3A4<sup>145</sup>. *In vitro* data demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6 and CYP3A4 although the inhibitory potency does not appear in clinical studies where the drug was given concomitantly with midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate) or omeprazol (CYP2C19 substrate)<sup>45, 47</sup>. Sorafenib is also a competitive inhibitor of CYP2B6 and CYP2C8 though the clinical relevance of this inhibition is not studied yet<sup>151</sup>. The hypothetical effect

on CYP2C9 was indirectly measured by the effect on warfarin therapy. The INR in sorafenib treated patients was similar in placebo treated patients. The effect of CYP3A4 inducers (e.g. rifampicin) is not studied, however a warning is included in the drug label of sorafenib<sup>47</sup>. The drug does interfere with the pharmacokinetics of concomitantly administered antineoplastic agents doxorubicin and irinotecan. The exposure of doxorubicin was increased by 21%. The increase in SN-38 exposure was 67-120% most likely through competition or inhibition of UGT1A1 and additionally the irinotecan exposure increased with 26-41%<sup>47</sup>.

### **Sunitinib**

Since sunitinib is primarily metabolized through CYP3A4, the influence of ketoconazole and rifampicin was investigated in healthy volunteers. Co-administration of ketoconazole increased the cumulative exposure of sunitinib and SU12662 with ~ 50%. Rifampicin coadministration resulted in a 50% decrease in combined systemic exposure<sup>110</sup>. It is suggested that sunitinib has no influence on other co-administered drugs.

### **Dasatinib**

The exposure of dasatinib is increased five fold on the co-ingestion of ketoconazole in healthy volunteers. Rifampicin decreased the exposure by 82%. *In vitro* data demonstrated that the drug does not induce human CYP-enzymes. It however does appear to be a time dependent CYP3A4 inhibitor. As a result, the co-ingestion of dasatinib with simvastatin (a CYP3A4 substrate) resulted in a 20% increased exposure to simvastatin. The solubility of dasatinib appears to be pH dependent. Famotidine reduced the exposure by 61%, the co-administration of agents that provide prolonged gastric acid suppression is therefore not recommended<sup>51</sup>.

### **Lapatinib**

Lapatinib is a substrate and an inhibitor of CYP3A4 and an inhibitor of CYP2C8. A single dose of a CYP3A4 inhibitor (ketoconazole) increases the exposure by 3.6-fold. In contrast carbamazepine, a CYP3A4 inducer, decreases the exposure by ~75%<sup>79</sup>. An extrapolation is made to other CYP3A4 inhibitors and inducers although no clinical data are available on these interactions. Dose adjustment advices are given in the package insert when combining lapatinib with an inducer or an inhibitor. These advices are not tested in clinical setting and/or on steady-state lapatinib exposure.

In the combination of lapatinib with folinic acid, 5-fluorouracil and irinotecan the AUC of SN-38, the active metabolite of irinotecan, was increased by 41%. There are multiple suggested explanations for this interaction. Lapatinib showed inhibition of CYP3A4, OATP1B1, ABCB1 and ABCG2 *in vitro* which are enzymes and transporters important in the metabolism and disposition of SN-38. However, further investigation is needed to determine whether

one or all mechanisms are responsible for this *in vivo* interaction<sup>152</sup>. In the combination of lapatinib with paclitaxel the exposure of lapatinib as well as paclitaxel was increased with 21% and 23% respectively<sup>79</sup>. The mechanism behind the described interactions is yet unknown. Since *in vitro* data suggest that lapatinib is an inhibitor of ABCB1, alertness may be warranted when the drug is co-administered with ABCB1 substrates<sup>79</sup>. However, no clinical studies are available to confirm this interaction.

### **Nilotinib**

Nilotinib is mainly metabolized through CYP3A4. The concomitant administration of ketoconazole with nilotinib produces a 3-fold increase in systemic exposure. Nilotinib itself appears to be a weak inhibitor of CYP3A4<sup>56</sup>. The co-administration of midazolam with the drug in healthy volunteers resulted in a 30% increase in the systemic exposure of midazolam<sup>56</sup>.

**Drug-drug interactions: In summary** most clinical interaction studies investigate interactions in healthy volunteers with a single dose of the TKI given together with a CYP3A4 inhibitor (e.g. ketoconazole, itraconazole) or a single dose of the TKI given after a few days of CYP3A4 inducing therapy (e.g. rifampicin, carbamazepine) (Table IV, V). This study design might not represent the metabolism at steady-state pharmacokinetics, since most TKIs are capable of inhibiting at least partly the enzymes by which they are metabolized. Auto-inhibition could result in the shunting of the metabolism through less prominent metabolic pathways at steady-state. Therefore, interaction studies performed at steady-state pharmacokinetics are more informative and representative for the clinical relevance of the investigated enzymes. Fortunately, the FDA is becoming stricter and demands additional research at steady-state for the newer TKIs (lapatinib, nilotinib) that have potency to inhibit enzymes and transporters.

**Table IV**      Drugs that interact with tyrosine kinase exposure

Name	Inducing drug	Inhibitory drug	Effect observed	ref
Imatinib	Phenytoin		Decreased imatinib AUC	15
	Rifampicin		Decreased imatinib C <sub>max</sub> (54%) and AUC <sub>24&amp;∞</sub> (68%; 74%)	136
	St. John's Wort		Increased Cl/F (44%) of imatinib	137
	Enzyme-inducing antiepileptic drug (carbamazepine, oxcarbazepine, phenytoin, phenobarbital or primidone)		Decreased C <sub>max</sub> , AUC, T <sub>max</sub> and t <sub>1/2</sub> Increased Cl/F	100
Gefitinib	Rifampicin	Ketoconazole	Decreased clearance (28.6%) and increased C <sub>max</sub> (26%) and AUC <sub>24&amp;∞</sub> (40%; 40%)	135
		Cyclosporin	Increased exposure (2-10%) of imatinib	28
		Elacridar*	Brain penetration increases, increased systemic exposure	67, 157
		Pantoprazol*	Brain penetration increases, increased systemic exposure	157
		Valspodar*	Brain penetration increases	67
		Zosuquidar*	Brain penetration increases	67
Erlotinib	High dose ranitidine Rifampicin	Itraconazol	Decreased gefitinib AUC (83%)	88
		Sorafenib	Increased gefitinib AUC (78%)	88
			Increased gefitinib AUC (38%)	145
			Decreased gefitinib exposure	143
Sorafenib Sunitinib Dasatinib Lapatinib Nilotinib	Smoking Phenytoin	Ketoconazole BAS 100*	Decreased erlotinib AUC, C <sub>max</sub> and C <sub>trough</sub>	91
			Highest Cl/F and lowest AUC observed in patient treated with phenytoin	43
			Increased erlotinib AUC (86%) and C <sub>max</sub> (102%)	147
			2.1-fold increase in erlotinib AUC	148
	Rifampicin	Ketoconazole	Decreased combined AUC (sunitinib + metabolite) (46.5%)	49
			Increased combined AUC (sunitinib + metabolite) (51%)	49
			Decreased dasatinib AUC (82%)	51
			Increased dasatinib AUC (5-fold)	51
	Famotidine Carbamazepine	Ketoconazole	Decreased dasatinib exposure (61%)	51
			Decreased lapatinib AUC (75%)	79
			Increased lapatinib AUC (3.6-fold)	79
			Increased lapatinib AUC (21%)	79
Nilotinib	Rifampicin	Ketoconazole	Decreased nilotinib AUC (80%)	57
			Increased nilotinib AUC (3-fold)	56

Abbreviations: C<sub>max</sub>, peak concentration; AUC, area under the concentration-time curve; Cl/F, apparent oral clearance; T<sub>max</sub>, time to peak concentration; t<sub>1/2</sub>, elimination half-life; C<sub>trough</sub>, trough concentration  
\* Results from animal studies





## Conclusions

TKIs are a relatively new and fast growing group of anticancer drugs developed as oral formulations and administered on a daily basis. In general, these TKIs are substrates of several drug transporters and metabolizing enzymes. Some of them are also capable to inhibit drug transporters and enzymes making their disposition and metabolism at steady-state pharmacokinetics rather complex and unpredictable. Most of the available pharmacokinetic information is based on information obtained from *in vitro* experiments, animal studies, drug-drug interaction studies and mass balance studies in healthy volunteers with a single dose of the aimed TKI. However, it is difficult to translate the results of these studies to the clinical oncology practice where these drugs are administered on a daily basis with possible auto-inhibiting mechanisms significantly altering the pharmacokinetics outcomes as well as the relevance of claimed drug interactions. Most information is available for the TKIs that are used for the longest time in clinical practice. A question that arises is whether the knowledge obtained for one TKI should not be used for the rational design of studies with the other TKIs and whether translations between these drugs are possible when confronted with unexpected low or high drug exposure.

In this review the current knowledge on the pharmacokinetic aspects; ADME, drug transporters and drug-drug interactions of the individual TKIs are described. Similarities and differences between the TKIs are summarized. It appears that several pharmacokinetic aspects are unfortunately not investigated yet for these drugs. While awaiting the results the only way to anticipate on clinical features and drug interaction potential in the clinical practice is by translating the knowledge obtained from the other TKIs as described in this review.

## References

- Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science* 1960; 132:1497.
- Rudkin CT, Hungerford DA, Nowell PC. DNA contents of chromosome PH1 and chromosome 21 in human chronic granulocytic leukemia. *Science* 1964; 144:1229-1231.
- A proposed standard system of nomenclature of human mitotic chromosomes. *Lancet* 1960; 1(7133):1063-1065.
- Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973; 243(5405):290-293.
- Mayall BH, Carrano AV, Moore DH, Rowley JD. Quantification by DNA-based cytophotometry of the 9q+/22q-chromosomal translocation associated with chronic myelogenous leukemia. *Cancer Res* 1977; 37(10):3590-3593.
- Konopka JB, Watanabe SM, Witte ON. An alteration of the human c-abl protein in K562 leukemia cells unmasks associated tyrosine kinase activity. *Cell* 1984; 37(3):1035-1042.
- Heisterkamp N, Stam K, Groffen J, De KA, Grosveld G. Structural organization of the bcr gene and its role in the Ph' translocation. *Nature* 1985; 315(6022):758-761.
- Stam K, Heisterkamp N, Grosveld G et al. Evidence of a new chimeric bcr/c-abl mRNA in patients with chronic myelocytic leukemia and the Philadelphia chromosome. *N Engl J Med* 1985; 313(23):1429-1433.
- Grosveld G, Hermans A, De KA, Bootsma D, Heisterkamp N, Groffen J. The role of the Philadelphia translocation in chronic myelocytic leukemia. *Ann N Y Acad Sci* 1987; 511:262-269.
- Naldini L, Stacchini A, Cirillo DM, Aglietta M, Gavosto F, Comoglio PM. Phosphotyrosine antibodies identify the p210c-abl tyrosine kinase and proteins phosphorylated on tyrosine in human chronic myelogenous leukemia cells. *Mol Cell Biol* 1986; 6(5):1803-1811.
- Comoglio PM, Di Renzo MF, Gaudino G. Protein tyrosine kinases associated with human malignancies. *Ann N Y Acad Sci* 1987; 511:256-261.
- Yaish P, Gazit A, Gilon C, Levitzki A. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. *Science* 1988; 242(4880):933-935.
- Buchdunger E, Zimmermann J, Mett H et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Res* 1996; 56(1):100-104.
- Druker BJ, Tamura S, Buchdunger E et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996; 2(5):561-566.
- Peng B, Hayes M, Resta D et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. *J Clin Oncol* 2004; 22(5):935-942.
- Druker BJ, Talpaz M, Resta DJ et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; 344(14):1031-1037.
- Druker BJ, Sawyers CL, Kantarjian H et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; 344(14):1038-1042.
- Sawyers CL, Hochhaus A, Feldman E et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002; 99(10):3530-3539.
- Kantarjian H, Sawyers C, Hochhaus A et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002; 346(9):645-652.
- Talpaz M, Silver RT, Druker BJ et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002; 99(6):1928-1937.
- Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 2000; 96(3):925-932.
- Tuveson DA, Willis NA, Jacks T et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* 2001; 20(36):5054-5058.
- van Oosterom AT, Judson I, Verweij J et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; 358(9291):1421-1423.
- FDA. Drug label Gleevec approved on 05/20/2003. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> Accessed on 01/19/2009.
- Gschwind HP, Pfaar U, Waldmeier F et al. Metabolism and disposition of imatinib mesylate in healthy volunteers. *Drug Metab Dispos* 2005; 33(10):1503-1512.
- Peng B, Dutreix C, Mehning G et al. Absolute bioavailability of imatinib (Gleevec) orally versus intravenous infusion. *J Clin Pharmacol* 2004; 44(2):158-162.
- Nikolova Z, Peng B, Hubert M et al. Bioequivalence, safety, and tolerability of imatinib tablets compared with capsules. *Cancer Chemother Pharmacol* 2004; 53(5):433-438.
- Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005;

- 44(9):879-894.
29. Sparano BA, Egorin MJ, Parise RA et al. Effect of antacid on imatinib absorption. *Cancer Chemother Pharmacol* 2009; 63(3):525-528.
30. Gurney H, Wong M, Balleine RL et al. Imatinib disposition and ABCB1 (MDR1, P-glycoprotein) genotype. *Clin Pharmacol Ther* 2007; 82(1):33-40.
31. Burger H, Nooter K. Pharmacokinetic resistance to imatinib mesylate: role of the ABC drug pumps ABCG2 (BCRP) and ABCB1 (MDR1) in the oral bioavailability of imatinib. *Cell Cycle* 2004; 3(12):1502-1505.
32. Beumer JH, Natale JJ, Lagattuta TF, Raptis A, Egorin MJ. Disposition of imatinib and its metabolite CGP74588 in a patient with chronic myelogenous leukemia and short-bowel syndrome. *Pharmacotherapy* 2006; 26(7):903-907.
33. van Erp NP, Oostendorp RL, Guchelaar HJ, Schellens JH, Gelderblom H. Is rectal administration an alternative route for imatinib? *Cancer Chemother Pharmacol* 2007; 60(4):623-624.
34. Cohen MH, Williams G, Johnson JR et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. *Clin Cancer Res* 2002; 8(5):935-942.
35. Swaisland H, Laight A, Stafford L et al. Pharmacokinetics and tolerability of the orally active selective epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in healthy volunteers. *Clin Pharmacokinet* 2001; 40(4):297-306.
36. Swaisland HC, Smith RP, Laight A et al. Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005; 44(11):1165-1177.
37. Cantarini MV, McFarquhar T, Smith RP, Bailey C, Marshall AL. Relative bioavailability and safety profile of gefitinib administered as a tablet or as a dispersion preparation via drink or nasogastric tube: results of a randomized, open-label, three-period crossover study in healthy volunteers. *Clin Ther* 2004; 26(10):1630-1636.
38. Cantarini MV, Bailey CJ, Collins B, Smith RP. The relative bioavailability of gefitinib administered by granular formulation. *Cancer Chemother Pharmacol* 2008; 62(2):203-208.
39. Cohen MH, Williams GA, Sridhara R et al. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. *Clin Cancer Res* 2004; 10(4):1212-1218.
40. Johnson JR, Cohen M, Sridhara R et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. *Clin Cancer Res* 2005; 11(18):6414-6421.
41. Frohna P, Lu J, Eppler S et al. Evaluation of the absolute oral bioavailability and bioequivalence of erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in a randomized, crossover study in healthy subjects. *J Clin Pharmacol* 2006; 46(3):282-290.
42. Hidalgo M, Siu LL, Nemunaitis J et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001; 19(13):3267-3279.
43. Tan AR, Yang X, Hewitt SM et al. Evaluation of biologic end points and pharmacokinetics in patients with metastatic breast cancer after treatment with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor. *J Clin Oncol* 2004; 22(15):3080-3090.
44. Moore M, Hirte HW, Siu L et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol* 2005; 16(10):1688-1694.
45. FDA. Drug label Nexavar approved 12/20/2005. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> Accessed on 02/03/2009.
46. Strumberg D, Richly H, Hilger RA et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol* 2005; 23(5):965-972.
47. Kane RC, Farrell AT, Saber H et al. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res* 2006; 12(24):7271-7278.
48. Bello CL, Sherman L, Zhou J et al. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects. *Anticancer Drugs* 2006; 17(3):353-358.
49. Goodman VL, Rock EP, Dagher R et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; 13(5):1367-1373.
50. Desai IM, Burger DM, Van Hoesel QG, Beijnen JH, Van Herpen CM, Van der Graaf WT. Pharmacokinetics of sunitinib in an obese patient with a GIST. *Ann Oncol* 2009; 20(3):599-600.
51. Brave M, Goodman V, Kaminskas E et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. *Clin Cancer Res* 2008; 14(2):352-359.
52. Dai G, Pfister M, Blackwood-Chirchir A, Roy A. Importance of characterizing determinants of variability in exposure: application to dasatinib in subjects with chronic myeloid leukemia. *J Clin Pharmacol* 2008; 48(11):1254-1269.
53. Burris HA, III, Hurwitz H, Dees EC et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005; 23(23):5305-5313.
54. Koch KM, Reddy NJ, Cohen RB et al. Effects of Food on the Relative Bioavailability of Lapatinib in Cancer Patients. *J Clin Oncol* 2009; 27(8):1191-1196.
55. Kantarjian H, Giles F, Wunderle L et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; 354(24):2542-2551.
56. Tanaka C, Smith T, Kantarjian H et al. Clinical pharmacokinetics (PK) of AMN107, a novel inhibitor of Bcr-Abl, in healthy subjects and patients with imatinib resistant or intolerant chronic myelogenous leukemia (CML) or relapsed/refractory Ph+ acute lymphocytic leukemia (Ph+ALL). *J.Clin.Oncol.*, 2006 ASCO Annual Meeting Proceedings Part I Vol. 24, No. 18S, 3095.
57. Hazarika M, Jiang X, Liu Q et al. Tasigna for chronic and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukemia resistant to or intolerant of imatinib. *Clin Cancer Res* 2008; 14(17):5325-5331.
58. Kil KE, Ding YS, Lin KS et al. Synthesis and positron emission tomography studies of carbon-11-labeled imatinib (Gleevec). *Nucl Med Biol* 2007; 34(2):153-163.
59. Gambacorti-Passerini C, Barni R, le CP et al. Role of alpha1 acid glycoprotein in the in vivo resistance of human BCR-ABL(+) leukemic cells to the abl inhibitor STI571. *J Natl Cancer Inst* 2000; 92(20):1641-1650.
60. Gambacorti-Passerini C, Zucchetti M, Russo D et al. Alpha1 acid glycoprotein binds to imatinib (STI571) and substantially alters its pharmacokinetics in chronic myeloid leukemia patients. *Clin Cancer Res* 2003; 9(2):625-632.
61. le Coutre P, Kreuzer KA, Pursche S et al. Pharmacokinetics and cellular uptake of imatinib and its main metabolite CGP74588. *Cancer Chemother Pharmacol* 2004; 53(4):313-323.
62. Widmer N, Decosterd LA, Csajka C et al. Population pharmacokinetics of imatinib and the role of alpha-acid glycoprotein. *Br J Clin Pharmacol* 2006; 62(1):97-112.
63. Widmer N, Decosterd LA, Leyvraz S et al. Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability. *Br J Cancer* 2008; 98(10):1633-1640.
64. Delbaldo C, Chatelut E, Re M et al. Pharmacokinetic-pharmacodynamic relationships of imatinib and its main metabolite in patients with advanced gastrointestinal stromal tumors. *Clin Cancer Res* 2006; 12(20 Pt 1):6073-6078.
65. Petain A, Kattygnarath D, Azard J et al. Population pharmacokinetics and pharmacogenetics of imatinib in children and adults. *Clin Cancer Res* 2008; 14(21):7102-7109.
66. Dai H, Marbach P, Lemaire M, Hayes M, Elmquist WF. Distribution of STI-571 to the brain is limited by P-glycoprotein-mediated efflux. *J Pharmacol Exp Ther* 2003; 304(3):1085-1092.
67. Bihorel S, Camenisch G, Lemaire M, Scherrmann JM. Modulation of the brain distribution of imatinib and its metabolites in mice by valspodar, zosuquidar and elacridar. *Pharm Res* 2007; 24(9):1720-1728.
68. Wolff NC, Richardson JA, Egorin M, Ilaria RL, Jr. The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. *Blood* 2003; 101(12):5010-5013.
69. Breedveld P, Pluim D, Cipriani G et al. The effect of Bcrp1 (Abcg2) on the in vivo pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. *Cancer Res* 2005; 65(7):2577-2582.
70. Bihorel S, Camenisch G, Lemaire M, Scherrmann JM. Influence of breast cancer resistance protein (Abcg2) and p-glycoprotein (Abcb1a) on the transport of imatinib mesylate (Gleevec) across the mouse blood-brain barrier. *J Neurochem* 2007; 102(6):1749-1757.
71. Neville K, Parise RA, Thompson P et al. Plasma and cerebrospinal fluid pharmacokinetics of imatinib after administration to nonhuman primates. *Clin Cancer Res* 2004; 10(7):2525-2529.
72. Li J, Brahmer J, Messersmith W, Hidalgo M, Baker SD. Binding of gefitinib, an inhibitor of epidermal growth factor receptor-tyrosine kinase, to plasma proteins and blood cells: in vitro and in cancer patients. *Invest New Drugs* 2006; 24(4):291-297.
73. McKillop D, Hutchison M, Partridge EA et al. Metabolic disposition of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in rat, dog and man. *Xenobiotica* 2004; 34(10):917-934.
74. McKillop D, Partridge EA, Kemp JV et al. Tumor penetration of gefitinib (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2005; 4(4):641-649.
75. Lu JF, Eppler SM, Wolf J et al. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clin Pharmacol Ther* 2006; 80(2):136-145.
76. Broniscer A, Panetta JC, O'Shaughnessy M et al. Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite OSI-420. *Clin Cancer Res* 2007; 13(5):1511-1515.
77. Kamath AV, Wang J, Lee FY, Marathe PH. Preclinical pharmacokinetics and in vitro metabolism of dasatinib (BMS-354825): a potent oral multi-targeted kinase inhibitor against SRC and BCR-ABL. *Cancer Chemother Pharmacol* 2008; 61(3):365-376.

78. Porkka K, Koskenvesa P, Lundan T et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood* 2008; 112(4):1005-1012.
79. Medina PJ, Goodin S. Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. *Clin Ther* 2008; 30(8):1426-1447.
80. Polli JW, Humphreys JE, Harmon KA et al. The role of efflux and uptake transporters in [N-(3-chloro-4-[(3-fluorobenzyl)oxy]phenyl)-6-[5-[[[2-(methylsulfonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine] (GW572016, lapatinib) disposition and drug interactions. *Drug Metab Dispos* 2008; 36(4):695-701.
81. Polli JW, Olson KL, Chism JP et al. An unexpected synergist role of P-glycoprotein and breast cancer resistance protein on the central nervous system penetration of the tyrosine kinase inhibitor lapatinib (N-(3-chloro-4-[(3-fluorobenzyl)oxy]phenyl)-6-[5-[[[2-(methylsulfonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine; GW572016). *Drug Metab Dispos* 2009; 37(2):439-442.
82. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. *Clin Pharmacokinet* 2005; 44(4):349-366.
83. Rochat B, Zoete V, Grosdidier A, von GS, Marull M, Michielin O. In vitro biotransformation of imatinib by the tumor expressed CYP1A1 and CYP1B1. *Biopharm Drug Dispos* 2008; 29(2):103-118.
84. van Erp NP, Gelderblom H, Karlsson MO et al. Influence of CYP3A4 inhibition on the steady-state pharmacokinetics of imatinib. *Clin Cancer Res* 2007; 13(24):7394-7400.
85. O'Brien SG, Meinhardt P, Bond E et al. Effects of imatinib mesylate (ST1571, Glivec) on the pharmacokinetics of simvastatin, a cytochrome p450 3A4 substrate, in patients with chronic myeloid leukaemia. *Br J Cancer* 2003; 89(10):1855-1859.
86. Gardner ER, Burger H, van Schaik RH et al. Association of enzyme and transporter genotypes with the pharmacokinetics of imatinib. *Clin Pharmacol Ther* 2006; 80(2):192-201.
87. Li J, Zhao M, He P, Hidalgo M, Baker SD. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. *Clin Cancer Res* 2007; 13(12):3731-3737.
88. Swaisland HC, Cantarini MV, Smith RP et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005; 44(10):1067-1081.
89. Swaisland HC, Cantarini MV, Fuhr R, Holt A. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. *Clin Pharmacokinet* 2006; 45(6):633-644.
90. Li J, Karlsson MO, Brahmer J et al. CYP3A phenotyping approach to predict systemic exposure to EGFR tyrosine kinase inhibitors. *J Natl Cancer Inst* 2006; 98(23):1714-1723.
91. Hamilton M, Wolf JL, Rusk J et al. Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res* 2006; 12(7 Pt 1):2166-2171.
92. Harmsen S, Meijerman I, Beijnen JH, Schellens JH. Nuclear receptor mediated induction of cytochrome P450 3A4 by anticancer drugs: a key role for the pregnane X receptor. *Cancer Chemother Pharmacol* 2008; 64(1): 35-43.
93. Faivre S, Delbaldo C, Vera K et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; 24(1):25-35.
94. Christopher LJ, Cui D, Li W et al. Biotransformation of [14C]dasatinib: in vitro studies in rat, monkey, and human and disposition after administration to rats and monkeys. *Drug Metab Dispos* 2008; 36(7):1341-1356.
95. Wang L, Christopher LJ, Cui D et al. Identification of the human enzymes involved in the oxidative metabolism of dasatinib: an effective approach for determining metabolite formation kinetics. *Drug Metab Dispos* 2008; 36(9):1828-1839.
96. Singer JB, Shou Y, Giles F et al. UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. *Leukemia* 2007; 21(11):2311-2315.
97. Schmidli H, Peng B, Riviere GJ et al. Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study. *Br J Clin Pharmacol* 2005; 60(1):35-44.
98. Judson I, Ma P, Peng B et al. Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. *EORTC Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol* 2005; 55(4):379-386.
99. Menon-Andersen D, Mondick JT, Jayaraman B et al. Population pharmacokinetics of imatinib mesylate and its metabolite in children and young adults. *Cancer Chemother Pharmacol* 2009; 63(2):229-238.
100. Reardon DA, Egorin MJ, Quinn JA et al. Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. *J Clin Oncol* 2005; 23(36):9359-9368.
101. Gibbons J, Egorin MJ, Ramanathan RK et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. *J Clin Oncol* 2008; 26(4):570-576.
102. Pappas P, Karavasili V, Briasoulis E, Pavlidis N, Marselos M. Pharmacokinetics of imatinib mesylate in end stage renal disease. A case study. *Cancer Chemother Pharmacol* 2005; 56(4):358-360.
103. Judson IR. Imatinib for patients with liver or kidney dysfunction: no need to modify the dose. *J Clin Oncol* 2008; 26(4):521-522.
104. Franke RM, Sparreboom A. Inhibition of imatinib transport by uremic toxins during renal failure. *J Clin Oncol* 2008; 26(25):4226-4227.
105. Eckel F, von DS, Mayr M et al. Pharmacokinetic and clinical phase II trial of imatinib in patients with impaired liver function and advanced hepatocellular carcinoma. *Oncology* 2005; 69(5):363-371.
106. Ramanathan RK, Egorin MJ, Takimoto CH et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. *J Clin Oncol* 2008; 26(4):563-569.
107. Treiber G, Wex T, Schleyer E, Troeger U, Hosius C, Malfertheiner P. Imatinib for hepatocellular cancer--focus on pharmacokinetic/pharmacodynamic modelling and liver function. *Cancer Lett* 2008; 260(1-2):146-154.
108. Ling J, Johnson KA, Miao Z et al. Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. *Drug Metab Dispos* 2006; 34(3):420-426.
109. Miller AA, Murry DJ, Owzar K et al. Phase I and Pharmacokinetic Study of Sorafenib in Patients With Hepatic or Renal Dysfunction: CALGB 60301. *J Clin Oncol* 2009; 27(11):1800-1805.
110. Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. *Clin Ther* 2007; 29(7):1338-1353.
111. Izzedine H, Etienne-Grimaldi MC, Renee N, Vignot S, Milano G. Pharmacokinetics of sunitinib in hemodialysis. *Ann Oncol* 2009; 20(1):190-192.
112. Christopher LJ, Cui D, Wu C et al. Metabolism and disposition of dasatinib after oral administration to humans. *Drug Metab Dispos* 2008; 36(7):1357-1364.
113. Ratain MJ, Cohen EE. The value meal: how to save \$1,700 per month or more on lapatinib. *J Clin Oncol* 2007; 25(23):3397-3398.
114. Kagan M, Tran P, Fischer V et al. Safety, Pharmacokinetics (PK), Metabolism, and Mass Balance of [<sup>14</sup>C]-AMN107, a Novel Aminopyrimidine Inhibitor of Bcr-Abl Tyrosine Kinase, in Healthy Subjects. *Blood ASH Annual Meeting Abstracts* 2005 106 abstract 4887.
115. Lepper ER, Nooter K, Verweij J, Acharya MR, Figg WD, Sparreboom A. Mechanisms of resistance to anticancer drugs: the role of the polymorphic ABC transporters ABCB1 and ABCG2. *Pharmacogenomics* 2005; 6(2):115-138.
116. Oostendorp RL, Beijnen JH, Schellens JH. The biological and clinical role of drug transporters at the intestinal barrier. *Cancer Treat Rev* 2008; 35(2):137-147.
117. Hu S, Franke RM, Filipinski KK et al. Interaction of imatinib with human organic ion carriers. *Clin Cancer Res* 2008; 14(10):3141-3148.
118. White DL, Saunders VA, Dang P et al. OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. *Blood* 2006; 108(2):697-704.
119. Wang L, Giannoudis A, Lane S, Williamson P, Pirmohamed M, Clark RE. Expression of the uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. *Clin Pharmacol Ther* 2008; 83(2):258-264.
120. Shukla S, Sauna ZE, Ambudkar SV. Evidence for the interaction of imatinib at the transport-substrate site(s) of the multidrug-resistance-linked ABC drug transporters ABCB1 (P-glycoprotein) and ABCG2. *Leukemia* 2008; 22(2):445-447.
121. Dulucq S, Bouchet S, Turcq B et al. Multidrug resistance gene (MDR1) polymorphisms are associated with major molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood* 2008; 112(5):2024-2027.
122. Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. *Blood* 2004; 104(12):3739-3745.
123. Ozvegy-Laczka C, Hegedus T, Varady G et al. High-affinity interaction of tyrosine kinase inhibitors with the ABCG2 multidrug transporter. *Mol Pharmacol* 2004; 65(6):1485-1495.
124. Nakamura Y, Oka M, Soda H et al. Gefitinib ("Iressa", ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, reverses breast cancer resistance protein/ABCG2-mediated drug resistance. *Cancer Res* 2005; 65(4):1541-1546.
125. Li J, Cusatis G, Brahmer J et al. Association of variant ABCG2 and the pharmacokinetics of epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients. *Cancer Biol Ther* 2007; 6(3):432-438.
126. Cusatis G, Sparreboom A. Pharmacogenomic importance of ABCG2. *Pharmacogenomics* 2008; 9(8):1005-1009.
127. Marchetti S, de Vries NA, Buckle T et al. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCG2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1-/- Mdr1a/1b-/- (triple-knockout) and wild-type mice. *Mol Cancer Ther* 2008; 7(8):2280-2287.
128. Shi Z, Peng XX, Kim IW et al. Erlotinib (Tarceva, OSI-774) antagonizes ATP-binding cassette subfamily B member 1 and ATP-binding cassette subfamily G member 2-mediated drug resistance.

- Cancer Res 2007; 67(22):11012-11020.
129. Rudin CM, Liu W, Desai A et al. Pharmacogenomic and pharmacokinetic determinants of erlotinib toxicity. *J Clin Oncol* 2008; 26(7):1119-1127.
  130. Shukla S, Robey RW, Bates SE, Ambudkar SV. Sunitinib (Sutent, SU11248), a small-molecule receptor tyrosine kinase inhibitor, blocks function of the ATP-binding cassette (ABC) transporters P-glycoprotein (ABCB1) and ABCG2. *Drug Metab Dispos* 2009; 37(2):359-365.
  131. Giannoudis A, Davies A, Lucas CM, Harris RJ, Pirmohamed M, Clark RE. Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): implications for the treatment of imatinib-resistant chronic myeloid leukemia. *Blood* 2008; 112(8):3348-3354.
  132. Hiwase DK, Saunders V, Hewett D et al. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. *Clin Cancer Res* 2008; 14(12):3881-3888.
  133. Dai CL, Tiwari AK, Wu CP et al. Lapatinib (Tykerb, GW572016) reverses multidrug resistance in cancer cells by inhibiting the activity of ATP-binding cassette subfamily B member 1 and G member 2. *Cancer Res* 2008; 68(19):7905-7914.
  134. Brendel C, Scharenberg C, Dohse M et al. Imatinib mesylate and nilotinib (AMN107) exhibit high-affinity interaction with ABCG2 on primitive hematopoietic stem cells. *Leukemia* 2007; 21(6):1267-1275.
  135. Dutreix C, Peng B, Mehring G et al. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* 2004; 54(4):290-294.
  136. Bolton AE, Peng B, Hubert M et al. Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, ST1571) in healthy subjects. *Cancer Chemother Pharmacol* 2004; 53(2):102-106.
  137. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004; 76(4):323-329.
  138. Wen PY, Yung WK, Lamborn KR et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consortium Study 99-08. *Clin Cancer Res* 2006; 12(16):4899-4907.
  139. Pursche S, Schleyer E, von BM et al. Influence of enzyme-inducing antiepileptic drugs on trough level of imatinib in glioblastoma patients. *Curr Clin Pharmacol* 2008; 3(3):198-203.
  140. Wang Y, Zhou L, Dutreix C et al. Effects of imatinib (Glivec) on the pharmacokinetics of metoprolol, a CYP2D6 substrate, in Chinese patients with chronic myelogenous leukaemia. *Br J Clin Pharmacol* 2008; 65(6):885-892.
  141. van Erp NP, Gelderblom H, Van GM et al. Effect of cigarette smoking on imatinib in patients in the soft tissue and bone sarcoma group of the EORTC. *Clin Cancer Res* 2008; 14(24):8308-8313.
  142. White DL, Saunders VA, Quinn SR, Manley PW, Hughes TP. Imatinib increases the intracellular concentration of nilotinib, which may explain the observed synergy between these drugs. *Blood* 2007; 109(8):3609-3610.
  143. AstraZenica. Drug Label Gefitinib approved 05/05/2003. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> Accessed 03/02/2009.
  144. Hwang SW, Han HS, Lim KY, Han JY. Drug interaction between complementary herbal medicines and gefitinib. *J Thorac Oncol* 2008; 3(8):942-943.
  145. Adjei AA, Molina JR, Mandrekas SJ et al. Phase I trial of sorafenib in combination with gefitinib in patients with refractory or recurrent non-small cell lung cancer. *Clin Cancer Res* 2007; 13(9):2684-2691.
  146. Abbas R, Fettner S, Riek M et al. A drug-drug interaction study to evaluate the effect of rifampicin on the pharmacokinetics of epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib in healthy subjects [abstract 548]. *Proc Am Soc Clin Oncol* 22, 137. 2003.
  147. Rakhit A, Pantze MP, Fettner S et al. The effects of CYP3A4 inhibition on erlotinib pharmacokinetics: computer-based simulation (SimCYP) predicts in vivo metabolic inhibition. *Eur J Clin Pharmacol* 2008; 64(1):31-41.
  148. Smith NF, Baker SD, Gonzalez FJ, Harris JW, Figg WD, Sparreboom A. Modulation of erlotinib pharmacokinetics in mice by a novel cytochrome P450 3A4 inhibitor, BAS 100. *Br J Cancer* 2008; 98(10):1630-1632.
  149. Hughes AN, O'Brien ME, Petty WJ et al. Overcoming CYP1A1/1A2 Mediated Induction of Metabolism by Escalating Erlotinib Dose in Current Smokers. *J Clin Oncol* 2009; 27(8):1220-1226.
  150. Lathia C, Lettieri J, Cihon F, Gallentine M, Radtke M, Sundaresan P. Lack of effect of ketoconazole-mediated CYP3A inhibition on sorafenib clinical pharmacokinetics. *Cancer Chemother Pharmacol* 2006; 57(5):685-692.
  151. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist* 2008; 13(10):1084-1096.
  152. Midgley RS, Kerr DJ, Flaherty KT et al. A phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. *Ann Oncol* 2007; 18(12):2025-2029.
  153. Ranson M, Hammond LA, Ferry D et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J Clin Oncol* 2002; 20(9):2240-2250.
  154. Chu QS, Schwartz G, de BJ et al. Phase I and pharmacokinetic study of lapatinib in combination with capecitabine in patients with advanced solid malignancies. *J Clin Oncol* 2007; 25(24):3753-3758.
  155. LoRusso PM, Jones SF, Koch KM et al. Phase I and pharmacokinetic study of lapatinib and docetaxel in patients with advanced cancer. *J Clin Oncol* 2008; 26(18):3051-3056.
  156. Novartis. Scientific Discussion Tasigna Approved on 11/19/2007. <http://www.emea.europa.eu/> Accessed on 03/06/2009.
  157. Oostendorp RL, Buckle T, Beijnen JH, van TO, Schellens JH. The effect of P-gp (MDR1a/1b), BCRP (BCRP1) and P-gp/BCRP inhibitors on the in vivo absorption, distribution, metabolism and excretion of imatinib. *Invest New Drugs* 2009; 27(1):31-40.
  158. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; 21(8):1637-1647.
  159. Van Hest RM, Schnog JB, Van't Veer MB, Cornelissen JJ. Extremely slow methotrexate elimination in a patient with t(9;22) positive acute lymphoblastic leukemia treated with imatinib. *Am J Hematol* 2008; 83(9):757-758.
  160. Yang CH, Huang CJ, Yang CS et al. Gefitinib reverses chemotherapy resistance in gefitinib-insensitive multidrug resistant cancer cells expressing ATP-binding cassette family protein. *Cancer Res* 2005; 65(15):6943-6949.
  161. Stewart CF, Leggas M, Schuetz JD et al. Gefitinib enhances the antitumor activity and oral bioavailability of irinotecan in mice. *Cancer Res* 2004; 64(20):7491-7499.
  162. OSI Pharms. Drug Label Erlotinib approved 11/18/2004. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/> Accessed 03/02/2009.