



Anti-Tumour Treatment

Oral epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer: Comparative pharmacokinetics and drug–drug interactions

Solange Peters^{a,*}, Stefan Zimmermann^a, Alex A. Adjei^b^a Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland^b Department of Medicine, Katherine Anne Gioia Chair in Cancer Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA

ARTICLE INFO

Article history:

Received 4 April 2014

Received in revised form 17 June 2014

Accepted 21 June 2014

Keywords:

Afatinib

Chemotherapy

Dacomitinib

Epidermal growth factor receptor

Erlotinib

Gefitinib

Non-small cell lung cancer

Pharmacokinetics

Tyrosine kinase inhibitors

ABSTRACT

The development of orally active small molecule inhibitors of the epidermal growth factor receptor (EGFR) has led to new treatment options for non-small cell lung cancer (NSCLC). Patients with activating mutations of the *EGFR* gene show sensitivity to, and clinical benefit from, treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs). First generation reversible ATP-competitive EGFR-TKIs, gefitinib and erlotinib, are effective as first, second-line or maintenance therapy. Despite initial benefit, most patients develop resistance within a year, 50–60% of cases being related to the appearance of a T790M gatekeeper mutation. Newer, irreversible EGFR-TKIs – afatinib and dacomitinib – covalently bind to and inhibit multiple receptors in the ErbB family (EGFR, HER2 and HER4). These agents have been mainly evaluated for first-line treatment but also in the setting of acquired resistance to first-generation EGFR-TKIs. Afatinib is the first ErbB family blocker approved for patients with NSCLC with activating EGFR mutations; dacomitinib is in late stage clinical development. Mutant-selective EGFR inhibitors (AZD9291, CO-1686, HM61713) that specifically target the T790M resistance mutation are in early development. The EGFR-TKIs differ in their spectrum of target kinases, reversibility of binding to EGFR receptor, pharmacokinetics and potential for drug–drug interactions, as discussed in this review. For the clinician, these differences are relevant in the setting of polymedicated patients with NSCLC, as well as from the perspective of innovative anticancer drug combination strategies.

© 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Introduction

Identification of different driver mutations that define new molecular subsets of non-small cell lung cancer (NSCLC) has been critical in defining novel targeted therapeutic approaches [1]. One of the most well-known examples is epidermal growth factor receptor (EGFR), a cell-surface receptor that is activated in more than half of NSCLC patients [2]. The EGFR receptor belongs to the ErbB family of transmembrane tyrosine kinase receptors, which includes EGFR (also known as ErbB1 or HER1), ErbB2 (HER2 or neu), ErbB3 (HER3) and ErbB4 (HER4) [3]. With the exception of HER3, all have tyrosine kinase activity. The EGFR/ErbB family tyrosine kinase receptors play an integral role in cell proliferation,

differentiation and apoptosis, and therefore represent a valid target for preventing tumour growth and metastasis.

The development of small-molecule tyrosine kinase inhibitors (TKIs) that target EGFR has revolutionised the management of NSCLC. The so-called “first generation” EGFR-TKIs, erlotinib and gefitinib, compete reversibly with adenosine triphosphate (ATP) for binding to the intracellular catalytic domain of EGFR tyrosine kinase and thus inhibit EGFR autophosphorylation and downstream signalling [4]. Erlotinib and gefitinib are especially effective in tumours with activating *EGFR* mutations, evident in 10–15% of Caucasians and 40% of Asians with NSCLC [5]. In 90% of cases, these mutations are exon 19 deletions or exon 21 L858R substitutions [5].

Reversible EGFR-TKIs

Clinical trials have demonstrated that treatment with gefitinib or erlotinib significantly improves progression-free survival (PFS) and quality-of-life compared with chemotherapy as first-line

* Corresponding author. Address: Department of Oncology, Lausanne University Hospital (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tel.: +41 795560192; fax: +41 213140737.

E-mail address: solange.peters@chuv.ch (S. Peters).

therapy in advanced *EGFR* mutation-positive NSCLC [6–10]. Gefitinib was approved in the US for third-line treatment of advanced NSCLC in 2003; however, its marketing application for use in new patients was withdrawn in 2005, after failure to show a benefit on overall survival (OS) in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial [11]. In Europe, gefitinib was approved in 2009 for all lines of treatment in patients with advanced NSCLC with *EGFR* mutations. Erlotinib was approved in 2004 (USA) and 2005 (Europe) for second- and third-line treatment of chemotherapy-resistant, advanced NSCLC. In 2010 its use was expanded to include maintenance therapy after platinum-based chemotherapy, followed by approval in 2012 (Europe) and 2013 (USA) for use as first-line treatment of NSCLC with *EGFR* activating mutations (exon 19 deletions or exon 21 L858R substitution) [12,13].

As erlotinib and gefitinib bind reversibly to the tyrosine kinase domain of *EGFR*, they are susceptible to mutations that affect the binding affinity of ATP or the kinase inhibitor itself. Thus, despite excellent tumour response to initial targeted therapy, *EGFR* mutation-positive patients eventually develop resistance to erlotinib or gefitinib after 9–12 months of treatment [6–10]. One important mechanism of acquired resistance is the T790M gatekeeper *EGFR* mutation in exon 20, which is found in about 50–60% of patients [14,15]. This mutation increases the affinity of the kinase for ATP, and thus reduces the inhibitor efficacy [15–17]. In addition, *c-MET* amplification, *HER2* amplification, small cell transformation, and *PIK3CA* mutations have been associated with the development of *EGFR*-TKI resistance [14,15]. Consequently, an unmet need exists for the development of novel targeted agents that are effective in this setting.

Irreversible ErbB family blockers

Agents that bind irreversibly to the *EGFR* receptor, and also target multiple ErbB-family members, including *HER2* which plays a key role in ErbB activation, also described as “second-generation *EGFR*-TKIs”, may overcome the acquired resistance observed with erlotinib and gefitinib [18]. Irreversible *EGFR*-TKIs, including afatinib, dacomitinib and neratinib, have demonstrated a higher affinity for the ATP-binding domain and form an irreversible covalent bond to the ATP-binding site, they also inhibit *HER2*, and some also inhibit *HER4* (see below).

Afatinib is the first irreversible ErbB family blocker approved for first-line treatment of metastatic NSCLC with *EGFR* mutations [19,20]. The LUX-Lung clinical trial programme investigated afatinib in the settings of second- or third-line treatment of patients with acquired resistance to gefitinib or erlotinib (LUX-Lung 1, 4 and 5) [21–23] as well as first-line treatment in patients with *EGFR*-activating mutations (LUX-Lung 2, 3 and 6) [24–26]. The phase IIb/III LUX-Lung 1 showed that treatment with afatinib prolonged PFS – but not OS – in patients refractory to both chemotherapy and either erlotinib or gefitinib [21]. The phase III LUX-Lung 3 and 6 trials showed that PFS was significantly prolonged with afatinib versus pemetrexed plus cisplatin (LUX-Lung 3) or gemcitabine plus cisplatin (LUX-Lung 6) in treatment naïve patients with advanced lung adenocarcinoma and activating *EGFR* mutations and improved tumour-related symptoms and global health status [25,26]. LUX-Lung 3 [25] provided the basis for approval of afatinib in the US, Taiwan and Europe in 2013, in the setting of first-line treatment of metastatic NSCLC with *EGFR*-activating mutations [19,20]. Preliminary results of a pooled analysis of these two trials show a significant improvement in OS (27.3 to 24.3 months; HR = 0.81, $p = 0.037$) with afatinib in patients with common *EGFR* mutations (Del19/L858R) compared with standard chemotherapy [27]. This was even more pronounced in patients whose tumours harbour a deletion in exon 19 (33.3 versus 21.1 months in LUX-Lung 3 [HR 0.54]; and 31.4 versus 18.4 months in LUX-Lung 6

[HR 0.64]). In addition, phase II trials have demonstrated benefit with another irreversible *EGFR*-TKI, dacomitinib (PF-00299804), in a number of settings including after failure of one or two chemotherapy regimens and failure on erlotinib [28,29] first-line treatment of patients with *EGFR*-mutant tumours or known T790M mutations [30] as well patients refractory to chemotherapy and TKIs [31]. Preliminary results for phase III trials comparing dacomitinib with erlotinib (ARCHER 1009) in advanced NSCLC previously treated with chemotherapy (second/third line); or with placebo after failure of TKI and chemotherapy (BR.26) were recently reported [32,33]. The ARCHER 1009 trial did not meet its objective of significant improvement in PFS versus erlotinib; the BR.26 trial also failed to show significant prolongation of OS versus placebo. A further phase III trial versus gefitinib in treatment-naïve patients with *EGFR*-mutation mutated tumours (ARCHER 1050, NCT01774721) is ongoing with results expected in 2015. Additionally, neratinib has been tested in patients with NSCLC and prior response to first-generation *EGFR*-TKIs and in TKI-naïve patients [34] but due to low response rates and dose-limiting diarrhoea, monotherapy treatment evaluation was discontinued. Benefit with the combination of neratinib and temsirolimus, an mTOR inhibitor, has been seen in patients with solid tumours [35]. Consequently, neratinib is now being evaluated in combination with weekly temsirolimus in patients with *HER2*-mutant NSCLC [36]. In view of the lack of benefit and future clinical development with neratinib monotherapy, further discussion about this drug is not included in this review.

Mutant-selective EGFR-TKIs

Newer, so called “third-generation” *EGFR*-TKIs targeting activating *EGFR* mutations and T790M but sparing wild-type *EGFR* are also in development as first-line or following resistance to treatment.

Three such compounds, AZD9291, CO-1686 and HM61713, are oral, irreversible, selective inhibitors of both *EGFR*-activating and resistance (T790M) mutations, while sparing wild-type *EGFR* [37–40]. Ongoing phase I dose-escalation trials show significant tumour shrinkage (by RECIST criteria) in patients with *EGFR*-mutant NSCLC tumours (mainly harbouring T790M) and acquired resistance to prior *EGFR*-TKI treatment [41–43]. Sparing of wild-type *EGFR* present in normal skin and gut cells is thought to be associated with an improved therapeutic index. An extensive phase II/III development program with CO-1686 (TIGER I–V trials) as second-line therapy for NSCLC patients with acquired resistance to *EGFR*-directed therapy due to T790M mutations and as a first-line treatment for *EGFR*-mutated tumours is planned from 2014. Further development of AZD9291 and HM61713 is yet to be officially announced.

In contrast to platinum-based systemic chemotherapy, oral *EGFR*-TKIs offer potential for extended first-line therapy, given evidence of good tolerability, and increased duration of PFS. Relevant to considerations for their clinical use, are the pharmacokinetic characteristics and potential for drug–drug interactions with the first and second-generation *EGFR*-TKIs, which is the focus of this review.

Profile of receptor activity

All of the *EGFR*-TKIs show a similar high affinity for the *EGFR* receptor (see Supplementary Table 1); [44–47] afatinib and dacomitinib also show high affinity for *HER2* and *HER4* receptors. Afatinib also inhibits transphosphorylation of *HER3*, thereby blocking signalling of all ErbB family members [45]. Compared with gefitinib and erlotinib, afatinib has shown superior *in vitro* activity in

cells expressing EGFR-activating mutations, anti-tumour activity in a variety of cancer xenograft models, including EGFR-mutant cell lines resistant to the currently available EGFR inhibitors or expressing T790M, and antitumor activity in animal models [45,46]. In preclinical studies, dacomitinib was shown to inhibit several EGFR mutants, including the common activating mutations and the T790M mutant, and was also effective in reducing the growth of gefitinib-resistant NSCLC xenografts [47,48].

The mutant-selective EGFR-TKIs all show high selectivity for the mutated EGFR receptors, both activating and T790M (Supplementary Table 1), but are less selective for wild-type EGFR [37–39]. *In vitro*, all are effective at inhibiting the proliferation of NSCLC cell lines expressing L858R EGFR or L858R/T790M EGFR, with less activity against wild-type EGFR lines. Similarly, *in vivo* studies demonstrate dose-dependent and significant tumour growth inhibition in different EGFR-mutant cell line xenograft models [37,38,40].

In summary, compared with erlotinib and gefitinib, afatinib and dacomitinib offer a wider spectrum of inhibitory activity including HER2 and HER4 receptors, as well as gefitinib- or erlotinib resistant NSCLC xenografts. Although the *in vitro* activity profile of afatinib and dacomitinib suggests potential in the setting of T790M-dependent acquired resistance, there is limited benefit clinically [21,28]. This could be due to dose-limiting toxicities associated with wild-type EGFR inhibition, such that they cannot be adequately dosed to inhibit the T790M drug-resistant mutation [49]. Here, mutant-selective EGFR-TKIs or dual targeting of EGFR (e.g. combining afatinib and cetuximab) show most promise in this setting.

Pharmacokinetic properties

Absorption and bioavailability

Oral absorption of the EGFR-TKIs is slow to moderate with substantial inter- and intra-individual variability in the extent of gastrointestinal tract absorption. Peak plasma levels of gefitinib are achieved ~3–7 h after dosing in healthy subjects and in patients with solid tumours (Table 1) [50]. Oral bioavailability of a single

250 mg gefitinib dose is ~60% [51]. This is independent of dose and unaffected by food [51]. However, due to limited solubility at high pH [52] co-administration of treatments that increase gastric pH such as histamine H₂-receptor antagonists and proton pump inhibitors can decrease absorption and bioavailability (Table 2). High doses of short-acting antacids may have a similar effect if taken regularly around the time of the gefitinib dose [52].

Erlotinib shows similar absorption characteristics to those of gefitinib [12,53]. However, as food increases bioavailability (from 60% to almost 100%), erlotinib should be taken at least 1 h before or 2 h after eating [12,53]. Like gefitinib, the solubility of erlotinib is pH-dependent and is subject to reduced absorption with acid-reducing agents (Table 2) [12].

Afatinib achieves peak plasma concentrations ~2–5 h after oral dosing in patients with solid tumours [54]. The absolute bioavailability of afatinib is not known [19]. Food has a moderate effect on afatinib exposure [55] and therefore patients should take afatinib at least 1 h before or 2–3 h after a meal [19,20]. Consistent with other approved oral EGFR-TKIs, there is substantial inter-patient variability in plasma concentrations [54]. Increases in maximum plasma concentration (C_{max}) and exposure (area under the plasma concentration–time curve [AUC]) values over the therapeutic range of 20–50 mg [54] are non-linear, potentially due to changes in the bioavailability of afatinib as a result of saturation of efflux transporters in the gut (see *drug–drug interactions*) [54]. Afatinib is highly soluble throughout the physiological pH range 1–7.5 [56] and therefore any interactions with acid-reducing drugs are not expected.

Dacomitinib has an oral bioavailability of 80% following a 45 mg dose and exhibits linear kinetics following single or multiple doses [57,58]. Food has only a mild effect on exposure but concomitant administration with acid suppressants should be avoided wherever possible [59]. As for the other EGFR-TKIs, inter-individual variability is high (coefficient of variation up to 50%), due in part to the low solubility of dacomitinib (BCS Class II compound with pH-dependent solubility) [59].

In summary, gefitinib, erlotinib, afatinib and dacomitinib all show extensive inter-individual variability in drug absorption.

Table 1

Pharmacokinetic parameters for EGFR tyrosine kinase inhibitors administered at the recommended doses in healthy adults or patients with solid tumours.^a

Parameter	Reversible EGFR-TKIs		Irreversible ErbB family blockers	
	Gefitinib	Erlotinib	Afatinib	Dacomitinib
Usual starting dose (mg/day)	250	150	40	45
t _{max} (h)	3–7 [51,120]	4 [12]	2–5 [54]	~6 ^b [58,121]
V _d /F (L)	1700 [51]	232 [65]	2870 ^c [54]	2600 ^b [58]
Protein binding (%)	~90 [68,122]	~95 [62]	~95 [64]	97–98 [63]
t _{1/2} (h)	48–72 [51]	36 [62]	37 [54]	72 ^b [58]
F absolute (%)	~60 [51]	~76 [123]	Not known ^d [54]	80 [57]
CL/F (L/h)	46 [122]	4.5 [62]	1070–1390 ^b [54]	26 [121]
Metabolism	Extensive [61,67]	Extensive [69]	Minimal [66]	Extensive [63]
Renal excretion	4% [61]	~9% [69]	<5% [66]	3% [63]
Accumulation	1.5 to ~4-fold [120]	1.5 to 5.4-fold [89]	2 to 3-fold [54]	~6-fold [58,121]
Gastric pH effect	Reduces absorption [52]	Reduces absorption [12]	Not known [56]	Reduces absorption [59]
Food effect	Not relevant [50]	AUC ↑34–66% ^e [124]	AUC ↓39% ^e [55]	Not relevant [59]
Age effect	None reported [125]	None reported [62]	None reported [74]	Not known
Weight effect	None reported [125]	None reported [62]	None reported [74]	Not known
Gender effect	None reported [125]	None reported [62]	None reported [74]	Not known
Race Effect	None reported [68]	None reported [89]	None reported [74]	Not known
Potential drug interactions	CYP enzymes	CYP enzymes	P-gp transporters [85]	Potent CYP2D6 substrates ^f [97]

AUC, area under curve plasma concentration curve; CL/F, apparent total oral clearance; C_{max}, maximum observed plasma concentration; CYP, cytochrome P-450 isoenzymes; F, bioavailability (systemic availability of the administered dose); P-gp, P-glycoprotein; t_{1/2}, terminal half-life; t_{max}, time to reach the C_{max}; V_d/F, apparent volume of distribution.

^a Data for AZD9291, CO-1686 and HM61713 are not included in the table as no information has been reported for most of the parameters.

^b Based on patients receiving dacomitinib 45 mg once-daily.

^c Based on patients receiving afatinib 40 once-daily.

^d The mean relative bioavailability of a 20 mg oral dose was 92% when compared with an oral solution.

^e Take without food.

^f CYP2D6 substrates include tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, anti-arrhythmics, antipsychotics, and some beta-blockers.

Table 2
Impact of acid-reducing agents on the absorption of the oral EGFR tyrosine kinase inhibitors in healthy subjects.

Drug (dose)	Acid-reducing agent and regimen	Mean change		Dosing implications	References
		AUC	C _{max}		
Gefitinib (250 mg)	Ranitidine (450 mg, 13 h and 1 h before gefitinib)	↓ 44%	↓ 70%	Co-administration with H ₂ receptor antagonists may reduce efficacy. Antacids if taken regularly close to administration of gefitinib may have a similar effect	[52]
Erlotinib (150 mg)	Omeprazole (40 mg) daily for 7 days	↓ 46%	↓ 61%	Avoid co-administration with proton pump inhibitors	[12]
	Ranitidine (300 mg daily for 5 days); erlotinib was given as a single dose after the ranitidine dose on the third day	↓ 33%	↓ 54%	Co-administration with H ₂ receptor antagonists may reduce efficacy. If required, erlotinib must be taken at least 2 h before or 10 h after ranitidine dosing	
	Ranitidine (150 mg twice daily for 5 days); erlotinib 150 mg was given 2 h before and 10 h after ranitidine on the third day	↓ 15%	↓ 17%	The effect of antacids on erlotinib absorption has not been investigated. If use of antacids is considered necessary, administer at least 4 h before or 2 h after erlotinib	
Afatinib	Not reported			Highly soluble at pH > 5 so unlikely to show any interaction	[56]
Dacomitinib	Rabepazole given with dacomitinib	↓ 29%	↓ 50%	Avoid co-administration with proton pump inhibitors	[59]

AUC, area under the plasma concentration curve; C_{max}, maximum observed plasma concentration.

Gefitinib, erlotinib and dacomitinib exhibit pH-dependent solubility influencing absorption (Table 2). Gefitinib, erlotinib and afatinib should be taken while fasting; data for dacomitinib indicate that food intake has no effect on bioavailability.

Limited pharmacokinetic data has been reported for the mutant selective EGFR-TKIs. CO-1686 was initially administered as free base formulation but is now administered as hydrobromide salt showing improved absorption and reduced pharmacokinetic variability [60]. The available evidence shows dose-proportional increases in exposure, with a plasma half-life of 4–5 h (CO-1686) [60] 8–11 h (HM61713) [40] and ~50 h (AZD9291) [37].

Distribution

The EGFR-TKIs are characterised by extensive tissue distribution and moderate to high plasma protein binding, ranging from ~90% for gefitinib to 97–98% for dacomitinib (Table 1) [61–64]. Consequently, the volume of distribution is high (generally ≥1700 L), resulting in a prolonged terminal half-life (2–3 days) in cancer patients [51,54,58] although half-life is shorter for erlotinib (36 h) [65] and afatinib (37 h) [54]. Steady-state plasma levels of afatinib are achieved within 8 days of once-daily dosing with no evidence of fluctuation in subsequent cycles. The elevated whole blood to plasma ratio is indicative of moderate distribution of afatinib into red blood cells [66]. Dacomitinib shows a similar distribution between red blood cells and plasma [63]. There is evidence of mild accumulation with dacomitinib after multiple dosing, as expected with a long half-life (72 h) [58].

Metabolism

In contrast to afatinib, gefitinib, erlotinib and dacomitinib undergo extensive hepatic metabolism predominantly by cytochrome P450 (CYP)-dependent enzymes (Table 3). Gefitinib is metabolised by CYP3A4 and to a lesser extent by CYP2D6 and CYP3A5 [67] and is excreted as both parent compound and metabolites, mostly O-desmethyl gefitinib, which is considered to be inactive [61,67,68]. Erlotinib is metabolised by CYP3A4/3A5 and, to a lesser extent by the CYP1A1/1A2 isoenzymes, to the active metabolite desmethyl erlotinib, which subsequently undergoes oxidation and glucuronidation [69,70]. Extra-hepatic metabolism by CYP3A4 in the intestine, CYP1A1 in the lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Erlotinib and its active desmethyl metabolite are considered to be equipotent in inhibiting EGFR tyrosine kinase activity. The metabolism of the new mutant-selective EGFR-TKIs has not been reported.

Cigarette smoking is well known to induce key CYP enzymes [71] and this in turn may impact both the pharmacokinetics and pharmacodynamics of therapeutic agents that are metabolised by these enzymes. In the current context, studies have shown that induction of CYP1A1/1A2 in smokers results in increased erlotinib metabolism and clearance and subsequent reduction in exposure after a standard therapeutic dose (see *drug–drug interactions*) [72]. In patients with solid tumours, erlotinib plasma clearance was 24% higher in current smokers than that in former smokers or those who never smoked [62]. In healthy volunteers, current smokers had increased

Table 3
Enzymes involved in the metabolism of oral EGFR tyrosine kinase inhibitors.

Drug	Metabolised by CYP enzymes								May inhibit ^a				May induce ^a	
	3A4	3A5	2D6	1A1	1A2	1B1	2C8	2C9	CYP2C19 (w)	CYP2D6 (w)	UGT1A9	BCRP	CYP1A1	CYP1A2
Gefitinib	+++	++	+++	++	+				CYP2C19 (w)	CYP2D6 (w)	UGT1A9	BCRP		
Erlotinib	+++	+++	+	+	++	+	+	–	CYP3A4 (m)	CYP2C8 (m)	CYP1A1 (s)	UGT1A1 (s)	CYP1A1	CYP1A2
Afatinib	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dacomitinib	++		++					+	CYP2D6 (s)					

BCRP, breast cancer-resistant protein; CYP, cytochrome P450; UGT, uridine diphosphate-glucuronosyltransferase.

+++ , major metabolic route; ++ , other significant metabolic route; + , minor metabolic route; – , no interaction.

Induction/inhibition activity: w: Weak; m: Moderate; s: Strong.

Table layout adapted from Shah and colleagues (2013) [126].

^a May inhibit/induce the metabolism of drugs that are substrates for the following enzymes.

Table 4

Clinical implications of effects of co-administered drugs on exposure of EGFR tyrosine kinase inhibitors.

Enzyme or transporter involved	Drugs	Impact on exposure	Dosing recommendations
H ₂ -receptor	Ranitidine	↓ Gefitinib	<ul style="list-style-type: none"> • H₂-antagonists may reduce exposure and plasma concentrations of gefitinib and, therefore, may reduce efficacy • Antacids if taken regularly close to administration of gefitinib may have a similar effect • If H₂-antagonists are considered, erlotinib must be taken at least 2 h before or 10 h after ranitidine dosing • Antacids should be taken at least 4 h before or 2 h after the daily dose of erlotinib
		↓ Erlotinib	
Proton pump	Omeprazole	↓ Gefitinib ↓ Erlotinib	<ul style="list-style-type: none"> • Proton-pump inhibitors may reduce exposure and hence efficacy • Combination of erlotinib and proton pump inhibitors should be avoided
CYP3A4	Potent inhibitor (azole antifungals, protease inhibitors, clarithromycin, telithromycin)	↑ Gefitinib ↑ Erlotinib	<ul style="list-style-type: none"> • Use with caution when combined with a potent CYP3A4 inhibitor due to the potential for increased plasma concentrations and hence adverse reactions. Dose reduction may be required • Patients with CYP2D6 poor metaboliser genotype are at greater risk • Avoid co-administration with a potent CYP3A4 inducer due to the potential for decreased plasma concentrations and hence reduced efficacy • For patients on erlotinib requiring concomitant treatment with a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while safety (renal and liver function and serum electrolytes) is closely monitored. If well tolerated for more than 2 weeks, a further increase to 450 mg could be considered with close safety monitoring
	Potent inducer (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St. John's wort/ <i>Hypericum perforatum</i>)	↓ Gefitinib ↓ Erlotinib	
CYP1A1/1A2	Cigarette smoking	↓ Erlotinib	<ul style="list-style-type: none"> • Advise patients to stop smoking • If continue to smoke, dose can be increased in 50 mg increments to a maximum of 300 mg
CYP1A2	Potent inhibitor (ciprofloxacin, fluvoxamine)	↑ Erlotinib	<ul style="list-style-type: none"> • Use with caution. If adverse reactions related to erlotinib are observed, the dose of erlotinib may be reduced
P-gp	Strong inhibitor (e.g. ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone)	↑ Afatinib	<ul style="list-style-type: none"> • Ritonavir can increase exposure if given 1 h before afatinib; no change in afatinib exposure is administered simultaneously with or 6 h after afatinib • Concomitant with other P-gp inhibitors can increase exposure • Recommended to administer strong P-gp inhibitors using staggered dosing, preferably 6 h (for P-gp inhibitors dosed twice-daily) or 12 h (for P-gp inhibitors dosed once-daily) apart from afatinib • Concomitant treatment with strong P-gp inducers with afatinib may decrease exposure to afatinib
	Inducer (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort)	↓ Afatinib	

BCRP, breast cancer-resistant protein; CYP, cytochrome P450; P-gp, P-glycoprotein; UGT, uridine diphosphate-glucuronosyltransferase.

Table compiled from data contained in regulatory documents [12,13,19,20,68].

erlotinib clearance compared with former smokers or non-smokers [72] with exposure (AUC) about 30–50% lower.

Of the irreversible ErbB family blockers, dacomitinib undergoes oxidative and glutathione-mediated conjugative metabolism involving CYP2D6 and CYP3A4, resulting in the active metabolite O-desmethyl dacomitinib which has similar *in vitro* activity to the parent compound [63]. In contrast, afatinib undergoes minimal biotransformation and oxidative CYP-mediated metabolism is of negligible importance [66]. Instead, metabolism is mainly governed by non-enzyme catalysed Michael adduct formation to proteins and nucleophilic small molecules [66].

Thus, with the exception of afatinib, there is important potential for interaction with other agents that are metabolised by, or are inhibitors or inducers of the CYP-related enzymes, as discussed later. The impact of smoking is also relevant and discussed further in *drug–drug interactions*. CYP-related enzyme interactions have not been reported for the mutant-selective EGFR-TKIs.

Excretion

All of the EGFR-TKIs discussed here undergo faecal excretion. For gefitinib, 86% of unchanged drug and metabolites is excreted in the faeces, with a minor proportion excreted in the bile [61]. Urinary recovery of unchanged drug accounts for <0.5% of the oral

doses [50,73]. Similarly, less than 10% of the erlotinib dose is recovered in the urine, with <1% excreted as parent drug [69]. The irreversible ErbB family blockers show a similar excretion profile, with faecal excretion of the unchanged parent drug accounting for 85% (afatinib) and 79% (dacomitinib) of the dose [63,66]. Renal elimination is responsible for <5% of the administered dose [63,66].

Special populations

Patient age, body weight, gender or ethnicity does not have a clinically relevant effect on clearance/exposure of gefitinib, erlotinib or afatinib [12,62,68,74]. Mild and moderate hepatic impairment do not appear to have a major impact on exposure to the EGFR-TKIs and therefore dose adjustment is not routinely required [64,75,76]. There are limited data for patients with severe hepatic impairment. Evidence suggests that the underlying aetiology of hepatic impairment may be relevant. In one study, patients with moderate to severe hepatic impairment due to cirrhosis or hepatitis had increased gefitinib exposure and reduced clearance, whereas in patients with hepatic metastases, there was no significant impact on gefitinib exposure [73].

As only a minor proportion of the dose is excreted in the urine, no prospective dose adjustment is required in patients with mild or moderate renal impairment (creatinine clearance [CrCl]

30–90 mL/min). In general, treatment of patients with severely impaired renal function ($\text{CrCl} < 30 \text{ mL/min}$) is not recommended. As a general recommendation, patients with moderate to severe renal impairment ($\text{CrCl} 30\text{--}50 \text{ mL/min}$) or severe hepatic impairment should be closely monitored and dosage adjusted in the event of poor tolerability [12,19,68].

Drug–drug interactions

Potential interactions to be considered for individual EGFR-TKIs include interactions with drug transporters, CYP enzymes (e.g. inhibitors, inducers or substrates) and acid-reducing drugs (e.g. H_2 -receptor antagonists and proton pump inhibitors) (Table 4).

Interactions with drug transporters

The ATP-binding cassette (ABC) drug transporter P-glycoprotein 1 (P-gp, also known as multidrug resistance protein 1 [MDR1] or ABC sub-family B member 1 [ABCB1]), breast cancer resistance protein (BCRP, also known as ABC sub-family G member 2 [ABCG2]), and multidrug resistance protein 2 (MRP2, also known as ABC sub-family C member 2 [ABCC2]) are recognised for their potential for drug–drug interactions [77–79]. The role of the uptake solute carrier (SLC) transporters (e.g. organic anion transporter [OAT], organic anion transporting polypeptide [OATP] and organic cation transporter [OCT]), in transporter-mediated drug interactions with EGFR-TKIs is less well defined [80,81].

In vitro studies show that gefitinib is a substrate of P-gp and inhibits the transporter protein BCRP [52,82] and erlotinib is both a substrate for and inhibitor of P-gp and BCRP [83,84] although the clinical relevance of these findings is not well defined. For gefitinib, available data do not suggest any clinically relevant consequences. With erlotinib, caution is advised in patients also receiving inhibitors of P-gp, such as verapamil or cyclosporine [13]. No data are available for interactions with the SLC transporters.

Afatinib is a substrate and inhibitor of P-gp and BCRP [85]. In healthy subjects, administration of ritonavir, a potent inhibitor of P-gp, given concomitantly or 6 h after afatinib (40 mg) had no clinically relevant effect on the pharmacokinetics of afatinib [85]. However, another study showed that administration of ritonavir 1 h before afatinib (20 mg) increased exposure by ~50% [85]. In contrast, co-administration of rifampicin, a potent P-gp inducer, and afatinib resulted in modest reduction (~by about one-third) in afatinib exposure in healthy subjects [85]. If P-gp inhibitors need to be taken concomitantly, the EU summary of product characteristics recommends that they should be administered using a staggered dosing regimen, i.e. taken with as large as possible interval from the afatinib dose. This means preferably 6 h (for P-gp inhibitors dosed twice-daily) or 12 h (for P-gp inhibitors dosed once-daily) apart from afatinib [20]. The US prescribing information recommends that clinicians can also consider a 10 mg decrease in the daily afatinib dose in patients concomitantly receiving a P-gp inhibitor, or an increase by 10 mg in patients concomitantly receiving a P-gp inducer [19]. The available clinical data indicate that it is unlikely that afatinib treatment results in changes in the plasma concentration of other P-gp substrates [20]. No data are available for dacomitinib.

Finally, while multiple *in vitro* studies have investigated possible interactions between these TKIs and other drug transporters, currently the clinical significance of polymorphic transporters and interactions between drugs on transporters are poorly defined.

Interactions with drugs metabolised by CYP enzymes

Most pharmacokinetic interactions involve the metabolism of EGFR-TKIs, especially those metabolised by CYP enzymes. Potent

inhibitors and inducers of CYP activity can modify the exposure (AUC and C_{max}) of the individual EGFR-TKI involved. Further, EGFR-TKIs that are CYP substrates can modify the metabolism of other medications.

Gefitinib is metabolised primarily by CYP3A4, and to a lesser extent by CYP3A5, CYP1A2 and CYP2D6 [67] suggesting that inhibition or induction of these isoenzymes has the potential to impact gefitinib exposure. This is most relevant for CYP3A4 as this is the dominant CYP isoform in the gastrointestinal tract and shares many substrates and inhibitors with ABC transporters [86]. Co-administration of itraconazole, a potent CYP3A4 inhibitor, may increase gefitinib exposure by up to 80%, whereas rifampicin, a potent CYP3A4 inducer, may decrease exposure by up to 83%; phenytoin, a less potent CYP3A4 inducer had a much smaller effect [87,88]. Thus, patients receiving gefitinib with potent inhibitors of CYP3A4 activity must be monitored carefully due to the potential for toxicity; conversely, those receiving a concomitant CYP3A4 inducer should be monitored for potential reduced efficacy (Table 4). Dose adjustments of the drug may be necessary.

In vitro studies show that gefitinib is only a weak inhibitor of CYP2D6 activity [87]. There are no data on concomitant treatment with CYP2D6 inhibitors. Co-administration of gefitinib with metoprolol (a CYP2D6 substrate) resulted in a 35% increase in metoprolol exposure, but this change was neither statistically significant nor clinically relevant [87]. However, co-administration with other CYP2D6 substrates with a narrow therapeutic index may require dose modification.

Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 *in vitro* [89]. Thus, there is potential for interactions with potent inhibitors and inducers of CYP3A4 activity. In clinical studies, inhibition of CYP3A4 by ketoconazole increased erlotinib exposure by 86%; [90] conversely, induction of CYP3A4 by co-treatment with rifampicin decreased exposure by >50% [91]. Furthermore, co-administration with ciprofloxacin, which inhibits both CYP3A4 and CYP1A2 may increase erlotinib exposure by up to 39%, suggesting the need for caution when ciprofloxacin or other potent CYP1A2 inhibitors (e.g. fluvoxamine) are co-administered [12]. Cigarette smoke induces CYP1A1 and CYP1A2 and may decrease erlotinib exposure by 50–60% [12,90]. Erlotinib does not appear to affect the pharmacokinetics of the CYP3A4/2C8 substrate paclitaxel [92]. Haemorrhage and elevated international normalised ratio (INR) levels have been reported in patients taking warfarin, a CYP3A4 substrate [12,93]. Case reports also suggest caution with coadministration with CYP3A4 or CYP2C8 substrates such as simvastatin and phenytoin [94,95]. The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues [96].

In contrast, *in vitro* studies have shown that afatinib is not an inhibitor or an inducer of CYP450 enzymes [19] and therefore is unlikely to affect the metabolism of drugs that are substrates of CYP-related enzymes.

Dacomitinib is a substrate and potent inhibitor of CYP2D6 *in vitro* [97]. Potent inhibition of CYP2D6 by paroxetine in healthy volunteers who were predominantly extensive CYP2D6 metabolisers increased dacomitinib exposure by 37% [98]. Dacomitinib exposure in poor CYP2D6 metabolisers was not studied but is likely to be similar or at most 10% higher [98]. The modest effect on dacomitinib exposure is unlikely to be clinically relevant, suggesting that dose adjustment of dacomitinib when coadministered with a CYP2D6 inhibitor may not be required [98]. Co-administration of dacomitinib with dextromethorphan (a CYP2D6 substrate) significantly increased dextromethorphan exposure (900% higher) in extensive CYP2D6 metabolisers, with no change in dacomitinib exposure [97]. This highlights the effect of dacomitinib as a strong CYP2D6 inhibitor. Thus, co-administration with drugs which are

highly dependent on CYP2D6 metabolism may require dose adjustment or substitution with an alternative medication.

Interactions with acid-reducing agents

As discussed above, concomitant use of H₂-receptor antagonists and proton pump inhibitors can substantially reduce the plasma levels of gefitinib, erlotinib or dacomitinib. Given that cancer patients frequently take acid-reducing treatments to counter symptoms of gastro-oesophageal reflux disease, this interaction is clinically relevant. However, a retrospective analysis of the BR.21 trial in patients with advanced NSCLC [99] demonstrated that co-administration of gastric acid suppressive medications and erlotinib ($n = 190$) did not have a significant impact on median plasma drug levels, clinical outcome (PFS or OS) or adverse events [100]. A further single-centre analysis showed that gastric secretion inhibitors did not influence the efficacy of gefitinib in patients with NSCLC ($n = 100$) [101] or those harboring EGFR activating mutations ($n = 43$) [102].

Smoking

As discussed, cigarette smoking reduces erlotinib exposure. In the BR.21 trial, current smokers had lower complete or partial response to erlotinib compared with never smokers (3.9 versus 24.7%; $p < 0.001$) [99] and experienced less toxicity [99]. Steady-state trough plasma concentrations were ~2-fold lower than in former smokers or patients who had never smoked [103]. Compared with NSCLC patients who had never smoked, current smokers showed a dose-proportional increase in erlotinib exposure at steady-state, as well as a doubling of maximum tolerated dose (from 150 mg/day to 300 mg/day) [104]. Steady-state plasma concentrations and the incidence of rash and diarrhoea in smokers at 300 mg/day were similar to those in never-smokers receiving 150 mg/day [104]. Based on these data, an increased dose of erlotinib (up to 300 mg) can be considered in patients who smoke [72,104]. However, so far there is no evidence to suggest that a dose of 300 mg/day erlotinib in smokers is associated with any significant improvement in PFS compared with the 150 mg/day dose [105]. Thus, the selection and dosing of erlotinib for patients who continue to smoke remains a clinical challenge. Smoking history has no significant effect on exposure to the other agents discussed here [68,74].

Pharmacogenetic effects

Genetic polymorphisms in the enzymes and transporters involved in the pharmacokinetics of gefitinib (CYP2D6) and erlotinib (CYP3A4, CYP3A5 and ABCG2) may potentially influence exposure, although data are limited. In one study, gefitinib exposure was ~2-fold higher in subjects with CYP2D6 poor metaboliser genotype compared with the extensive metaboliser genotype [106]. No specific dose adjustment is recommended in patients known to be CYP2D6 poor metabolisers, although such patients should be closely monitored for adverse events [68]. Conversely, for patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor has the potential for increased gefitinib exposure, and therefore patients should be closely monitored at initiation of CYP3A4 inhibitor treatment [68].

In another study, erlotinib exposure was shown to be higher in subjects with variants in the promoter region of the ABCG2 gene, conferring lower ABCG2 activity although the limited sample size did not permit meaningful conclusions [107]. A modest increase in dacomitinib exposure has been observed in healthy volunteers who were extensive CYP2D6 metabolisers [97]. Dacomitinib

exposure in poor CYP2D6 metabolisers would be expected to be similar or at most 10% higher [98]. Exploratory analyses looking at genetic P-gp polymorphisms for afatinib do not suggest any effects on exposure [85].

Tolerability profile

The adverse event profile of gefitinib, erlotinib, afatinib and dacomitinib is consistent with inhibition of wild-type-EGFR expressed predominantly on epithelial cells (e.g. skin and gastrointestinal tract), with diarrhoea and acneiform-like skin rash the most commonly observed treatment-related adverse events [108,109]. Less common drug-related EGFR-mediated adverse events include stomatitis, paronychia, dry skin, cheilitis, conjunctivitis and dry eyes [12,19,68]. Interstitial lung disease-like events have been reported in 1.1–1.5% of patients [12,19,68]. Symptomatic adverse reactions are generally managed by treatment interruption, dose reductions or rarely treatment discontinuation. Further aspects concerning the tolerability profile of these compounds are reviewed elsewhere [108,110,111].

Retrospective studies with erlotinib and afatinib suggest that the severity of rash or diarrhoea correlates with exposure [54,62,112–114]. Additional studies, particularly with erlotinib, have correlated skin rash onset with improved clinical outcome in patients with NSCLC [114,115]. There is less evidence to support the use of rash as a surrogate marker of EGFR inhibition and clinical benefit with gefitinib [116]. For erlotinib, the cut-off value for development of toxicity may be similar to therapeutic concentrations since erlotinib is dosed at its maximum tolerated dose, with a small therapeutic window [116,117].

Phase I studies with AZD9291, CO-1686 and HM61713 have so far shown low levels of dose-related diarrhoea and rash typically observed with gefitinib, erlotinib, afatinib and dacomitinib [41–43]. Asymptomatic hyperglycemia is the main dose-limiting toxicity reported with CO-1686 and interstitial lung disease has been observed with AZD9291 treatment [41,42]. Further details about the adverse event profile of these drugs will become apparent following the completion of phase III trials.

Recommended dosing

The recommended oral daily starting doses are 150 mg for erlotinib, 250 mg for gefitinib and 40 mg for afatinib. Gefitinib can be taken with or without food, whereas both erlotinib and afatinib should be dosed at least 1 h before or 2–3 h after ingestion of food. As discussed, in the event of potential drug–drug interaction, dose adjustment may be needed to avoid toxicity. Treatment should continue until disease progression or unacceptable toxicity. In phase III clinical trials, dacomitinib has been investigated at the maximum tolerated dose of 45 mg daily [32,33].

Clinical considerations

Gefitinib, erlotinib and afatinib are currently approved for the treatment of NSCLC. Afatinib is the first of the irreversible ErbB family blockers, offering a potentially beneficial novel approach with regard to resistance emergence even if no data clinically supporting this is currently available. From the clinical practice perspective, differences in the pharmacokinetics of these agents are relevant as they may impact the potential for drug–drug interaction, and thus the efficacy, optimum dose and tolerability of treatment (Table 4).

A key difference between afatinib and the reversible EGFR-TKIs is the extent to which they are metabolised by CYP-dependent enzymes. As discussed, both gefitinib and erlotinib undergo

extensive CYP-related metabolism, and thus, co-administration with a potent CYP3A4 inhibitor may substantially increase plasma levels of the EGFR-TKI. Conversely, co-administration with a potent CYP3A4 inducer may increase metabolism and decrease plasma levels, and consequently reduce efficacy. Clinicians should be cautious in treating patients with CYP3A4 inducers, and wherever possible avoid co-administration. Such considerations are not relevant for afatinib. As plasma concentrations of erlotinib are reduced in smokers, current smokers are advised to stop smoking. In those patients who continue to smoke, the erlotinib dose can be increased to a maximum of 300 mg per day [12]. Such considerations are not relevant for gefitinib and afatinib.

In addition, the potential for interactions with drug transporters, in particular P-gp, merits consideration. Gefitinib, erlotinib, and afatinib are substrates for this transporter *in vitro* [52,83,85] although *in vivo* the potential for interaction varies. Thus, while available clinical data suggest that this effect is probably not problematic for gefitinib or erlotinib, it is a potential drug–drug interaction for afatinib. Clinicians should be aware of the potential need for staggered administration or dose adjustment if afatinib is co-administered with a P-gp inhibitor or inducer.

Drug absorption interactions between the EGFR-TKIs and acid-reducing agents such as H₂-receptor antagonists, proton-pump inhibitors and antacids are also clinically important. As discussed, both gefitinib and erlotinib exhibit pH-dependent solubility, and therefore exposure is significantly decreased when co-administered with H₂-receptor antagonists or proton-pump inhibitors. Given that cancer patients routinely use acid-reducing agents, including over-the-counter agents that may transiently increase gastric pH, for palliation of gastro-oesophageal reflux, dyspepsia, gastritis or mucositis due to their disease and/or treatment [118,119] these differences between gefitinib, erlotinib and afatinib are important clinically.

Conclusions

In summary, the EGFR-TKIs offer a targeted therapeutic approach to the management of NSCLC. Review of the pharmacokinetics of gefitinib, erlotinib, afatinib and dacomitinib highlight differences in absorption and/or metabolism which influence their potential for drug–drug interactions, highly relevant in the setting of polymedicated cancer patients. In routine clinical practice, afatinib may offer a number of theoretical advantages, notably lack of CYP-related interaction potential as well as with acid-reducing agents (H₂-receptor antagonists, proton-pump inhibitors and antacids). Definitive statistical analysis of the pooled afatinib LUX-Lung 3 and -6 survival data and the related publication are awaited. Future mutant selective EGFR-TKIs, such as CO-1686, AZD9291 and HM61713, may offer potential benefit to patients, thereby preventing the onset of resistance seen with gefitinib and erlotinib, thereafter improving patient PFS.

Conflict of interest statement

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ctrv.2014.06.010>.

References

- [1] Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol* 2011;12:175–80.
- [2] Cataldo VD, Gibbons DL, Perez-Soler R, Quintas-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011;364:947–55.
- [3] Arteaga CL. Epidermal growth factor receptor dependence in human tumors: more than just expression? *Oncologist* 2002;7(Suppl. 4):31–9.
- [4] Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008;358:1160–74.
- [5] Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* 2007;7:169–81.
- [6] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
- [7] Maemondo M, Inoue A, Kobayashi K, et al. North-East Japan study group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–8.
- [8] Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–8.
- [9] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–42.
- [10] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
- [11] Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa survival evaluation in lung cancer). *Lancet* 2005;366:1527–37.
- [12] Tarceva [package insert] (2014) Genentech USA, Inc., South San Francisco, CA.
- [13] European Medicines Agency. Tarceva. Summary of Product Characteristics, 3 February 2014. Accessed at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000618/WC500033994.pdf. [20 Feb 2014].
- [14] Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
- [15] Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240–7.
- [16] Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006;12:5764–9.
- [17] Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci USA* 2008;105:2070–5.
- [18] Reid A, Vidal L, Shaw H, de Bono J. Dual inhibition of ErbB1 (EGFR/HER1) and ErbB2 (HER2/neu). *Eur J Cancer* 2007;43:481–9.
- [19] Boehringer Ingelheim. Gilotrif [prescribing information] (2014) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT. <http://www.gilotrif.com/>. [17 May 2014].
- [20] European Medicines Agency. Giotrif. Summary of Product Characteristics, 16 October 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002280/WC500152392.pdf. [20 Feb 2014].
- [21] Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528–38.
- [22] Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: A phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 2013;31:3335–41.
- [23] Schuler MH, Yang JC, Park K, et al. Continuation of afatinib beyond progression: Results of a randomized, open-label, phase III trial of afatinib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatinib-LUX-Lung 5 (LL5). *J Clin Oncol* 2014;32(Suppl):abstract 8019.
- [24] Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012;13:539–48.
- [25] Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327–34.
- [26] Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:213–22.
- [27] Yang JC, Sequist LV, Schuler MH, et al. Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (EGFR mut): Pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT). *J Clin Oncol* 2014;32(Suppl):abstract 8046.

- [28] Ramalingam SS, Blackhall F, Krzakowski M, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3337–44.
- [29] Reckamp KL, Giaccone G, Camidge DR, et al. A phase 2 trial of dacomitinib (PF-00299804), an oral, irreversible pan-HER (human epidermal growth factor receptor) inhibitor, in patients with advanced non-small cell lung cancer after failure of prior chemotherapy and erlotinib. *Cancer* 2014;120:1145–54.
- [30] Kris MG, Mok T, Ignatius OSH, et al. First-line dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor, for patients with EGFR-mutant lung cancers. *J Clin Oncol* 2012;30(Suppl):abstract 7530.
- [31] Park K, Heo DS, Cho B, et al. PF-00299804 (PF299) in Asian patients (pts) with non-small cell lung cancer (NSCLC) refractory to chemotherapy (CT) and erlotinib (E) or gefitinib (G): A phase (P) I/II study. *J Clin Oncol* 2010;28(Suppl):abstract 7599.
- [32] Ramalingam SS, Jänne PA, Mok T, et al. Randomized, double-blinded study of dacomitinib, an irreversible pan-human epidermal growth factor receptor (HER) inhibitor, versus erlotinib for second-line/third-line therapy of locally advanced/metastatic non-small cell lung cancer (ARCHER 1009). *J Clin Oncol* 2014;32(Suppl):abstract 8018.
- [33] Ellis PM, Liu G, Millward M, et al. NCIC CTG BR.26: A phase III randomized, double blind, placebo controlled trial of dacomitinib versus placebo in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who received prior chemotherapy and an EGFR TKI. *J Clin Oncol* 2014;32(Suppl):abstract 8036.
- [34] Sequist LV, Besse B, Lynch TJ, et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:3076–83.
- [35] Gandhi L, Bahleda R, Tolaney SM, et al. Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. *J Clin Oncol* 2014;32:68–75.
- [36] Gandhi L, Soria J-C, Bryce R, Besse B. Randomized phase II study of neratinib with or without temsirolimus in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2-activating mutations. *J Clin Oncol* 2013;31(Suppl):abstract TPS8124.
- [37] Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov* 2014;Jun 3. pii: CD-14-0337. [Epub ahead of print].
- [38] Walter AO, Sjin RT, Haringsma HJ, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. *Cancer Discov* 2013;3:1404–15.
- [39] Tjin Tham Sjin R, Lee K, Walter AO, et al. In vitro and in vivo characterization of irreversible mutant-selective EGFR inhibitors that are wild-type sparing. *Mol Cancer Ther* 2014;14:13:1468–79.
- [40] Kim DW, Kim SW, Kim TM, et al. Phase I study of HM61713, a novel epidermal growth factor receptor (EGFR) mutant selective inhibitor, in non-small cell lung cancer (NSCLC) patients having an activating EGFR mutation but failed to prior EGFR tyrosine kinase inhibitor (TKI) therapy (abstract). *J Thorac Oncol* 2013;8:S892–3.
- [41] Jänne PA, Ramalingam SS, Yang JC, Ahn MJ, Kim DW. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC). *J Clin Oncol* 2014;32(Suppl):abstract 8009.
- [42] Sequist LV, Soria J-C, Gadgeel SM, et al. First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). *J Clin Oncol* 2014;32(Suppl):abstract 8010.
- [43] Kim DW, Lee DH, Kang JH, Park K, Han JY. Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs). *J Clin Oncol* 2014;32(Suppl):abstract 8011.
- [44] Kitagawa D, Yokota K, Gouda M, et al. Activity-based kinase profiling of approved tyrosine kinase inhibitors. *Genes Cells* 2013;18:110–22.
- [45] Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008;27:4702–11.
- [46] Solca F, Dahl G, Zoepfel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012;343:342–50.
- [47] Engelman JA, Zejnullahu K, Gale CM, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res* 2007;67:11924–32.
- [48] Gonzales AJ, Hook KE, Althaus IW, et al. Antitumor activity and pharmacokinetic properties of PF-00299804, a second-generation irreversible pan-erbB receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2008;7:1880–9.
- [49] Chong CR, Jänne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. *Nat Med* 2013;19:1389–400.
- [50] 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;40:297–306.
- [51] Swaisland HC, Smith RP, Laight A, et al. Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005;44:1165–77.
- [52] European Medicines Agency. Iressa (gefitinib) Assessment Report, July 2009. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001016/WC500036361.pdf [20 Feb 2014].
- [53] 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;46:283–90.
- [54] Wind S, Schmid M, Erhardt J, Goeldner RG, Stopfer P. Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clin Pharmacokinet* 2013;52:1101–9.
- [55] Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. *J Clin Oncol* 2010;28:3965–72.
- [56] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Giotrif (afatinib). 16 October 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002280/WC500152394.pdf [20 Feb 2014].
- [57] Giri N, LaBadie RR, Liang Y, et al. Absolute bioavailability of dacomitinib (PF-00299804): Comparison of oral and intravenous administration in healthy volunteers. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5–9; San Diego, CA. Philadelphia (PA): Abstract CT208.
- [58] Jänne PA, Boss DS, Camidge DR, et al. Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors. *Clin Cancer Res* 2011;17:1131–9.
- [59] Ruiz-Garcia A, Masters JC, LaBadie RR, et al. Effect of food and antacid treatment on bioavailability of 45 mg tablet of dacomitinib relative to dacomitinib administration under fasted conditions (abstract PII-007). *Clin Pharmacol Ther* 2014;95:S63.
- [60] Sequist LV, Soria JC, Gadgeel SM, et al. First-in-human evaluation of CO-1686, an irreversible, selective, and potent tyrosine kinase inhibitor of EGFR T790M. *J Clin Oncol* 2013;31(Suppl):abstract 2524.
- [61] 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;34:917–34.
- [62] 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;80:136–45.
- [63] Bello CL, Smith E, Ruiz-Garcia A, et al. A phase I, open-label, mass balance study of [¹⁴C] dacomitinib (PF-00299804) in healthy male volunteers. *Cancer Chemother Pharmacol* 2013;72:379–85.
- [64] Schnell D, Buschke S, Fuchs H, et al. Pharmacokinetics of afatinib in subjects with mild or moderate hepatic impairment. *Cancer Chemother Pharmacol* 2014;Jun 7. [Epub ahead of print].
- [65] 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;11:6414–21.
- [66] Stopfer P, Marzin K, Narjes H, et al. Afatinib pharmacokinetics and metabolism after oral administration to healthy male volunteers. *Cancer Chemother Pharmacol* 2012;69:1051–61.
- [67] McKillop D, McCormick AD, Millar A, et al. Cytochrome P450-dependent metabolism of gefitinib. *Xenobiotica* 2005;35:39–50.
- [68] European Medicines Agency. Iressa (gefitinib). Summary of Product Characteristics. 30 July 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001016/WC500036358.pdf [20 Feb 2014].
- [69] 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;34:420–6.
- [70] 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;13:3731–7.
- [71] Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. *Pharmacotherapy* 2012;32:920–31.
- [72] Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res* 2006;12:2166–71.
- [73] Horak J, White J, Harris AL, et al. The effect of different etiologies of hepatic impairment on the pharmacokinetics of gefitinib. *Cancer Chemother Pharmacol* 2011;68:1485–95.
- [74] Freiwald M, Schmid U, Fleury A, et al. Population pharmacokinetics of afatinib, an irreversible ErbB family blocker, in patients with various solid tumors. *Cancer Chemother Pharmacol* 2014;73:759–70.
- [75] O'Bryant CL, Haluska P, Rosen L, et al. An open-label study to describe pharmacokinetic parameters of erlotinib in patients with advanced solid tumors with adequate and moderately impaired hepatic function. *Cancer Chemother Pharmacol* 2012;69:605–12.
- [76] Giri N, Plotka A, Liang Y, et al. Influence of mild and moderate hepatic impairment on the pharmacokinetics (PK) of the pan-HER inhibitor dacomitinib. *J Clin Oncol* 2013;31(Suppl):abstract 2568.
- [77] Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet* 2003;42:59–98.
- [78] Mizuno N, Niwa T, Yotsumoto Y, Sugiyama Y. Impact of drug transporter studies on drug discovery and development. *Pharmacol Rev* 2003;55:425–61.

- [79] Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clin Pharmacol Ther* 2004;75:13–33.
- [80] Oostendorp RL, Beijnen JH, Schellens JH. The biological and clinical role of drug transporters at the intestinal barrier. *Cancer Treat Rev* 2009;35:137–47.
- [81] van Erp NP, Gelderblom H, Guchelaar HJ. Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treat Rev* 2009;35:692–706.
- [82] 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;6:432–8.
- [83] 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;67:11012–20.
- [84] Marchetti S, de Vries NA, Buckle T, et al. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABC2 on erlotinib hydrochloride (Tarceva) disposition in vitro and in vivo pharmacokinetic studies employing Bcrp1-/-/Mdr1a/1b-/- (triple-knockout) and wild-type mice. *Mol Cancer Ther* 2008;7:2280–7.
- [85] Wind S, Giessmann T, Jungnick A, et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. *Clin Drug Invest* 2014;34:173–82.
- [86] Visentin M, Biason P, Toffoli G. Drug interactions among the epidermal growth factor receptor inhibitors, other biologics and cytotoxic agents. *Pharmacol Ther* 2010;128:82–90.
- [87] Swaisland HC, Ranson M, Smith RP, et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005;44:1067–81.
- [88] Chhun S, Verstuyft C, Rizzo-Padoin N, et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. *Br J Clin Pharmacol* 2009;68:226–37.
- [89] European Medicines Agency. Tarceva (erlotinib) Assessment Report, July 2005. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000618/WC500033991.pdf [20 Feb 2014].
- [90] 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;64:31–41.
- [91] Hamilton M, Wolf JL, Drolet DW, et al. The effect of rifampicin, a prototypical CYP3A4 inducer, on erlotinib pharmacokinetics in healthy subjects. *Cancer Chemother Pharmacol* 2014;73:613–21.
- [92] Tran HT, Zinner RG, Blumenschein Jr GR, et al. Pharmacokinetic study of the phase III, randomized, double-blind, multicenter trial (TRIBUTE) of paclitaxel and carboplatin combined with erlotinib or placebo in patients with advanced non-small cell lung cancer (NSCLC). *Invest New Drugs* 2011;29:499–505.
- [93] Thomas KS, Billingsley A, Amarshi N, Nair BA. Elevated international normalized ratio associated with concomitant warfarin and erlotinib. *Am J Health Syst Pharm* 2010;67:1426–9.
- [94] Grenader T, Gipps M, Shavit L, Gabizon A. Significant drug interaction: phenytoin toxicity due to erlotinib. *Lung Cancer* 2007;57:404–6.
- [95] Veeraputhiran M, Sundermeyer M. Rhabdomyolysis resulting from pharmacologic interaction between erlotinib and simvastatin. *Clin Lung Cancer* 2008;9:232–4.
- [96] Carcelero E, Anglada H, Tuset M, Creus N. Interactions between oral antineoplastic agents and concomitant medication: a systematic review. *Expert Opin Drug Saf* 2013;12:403–20.
- [97] Bello CL, LaBadie RR, Ni G, et al. The effect of dacomitinib (PF-00299804) on CYP2D6 activity in healthy volunteers who are extensive or intermediate metabolizers. *Cancer Chemother Pharmacol* 2012;69:991–7.
- [98] Ruiz-García A, Giri N, LaBadie RR, et al. A phase I open-label study to investigate the potential drug-drug interaction between single-dose dacomitinib and steady-state paroxetine in healthy volunteers. *J Clin Pharmacol* 2014;54:555–62.
- [99] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.
- [100] Hilton JF, Tu D, Seymour L, Shepherd FA, Bradbury PA. An evaluation of the possible interaction of gastric acid suppressing medication and the EGFR tyrosine kinase inhibitor erlotinib. *Lung Cancer* 2013;82:136–42.
- [101] Saeki S, Sasaki J, Sakata S, et al. The influence of gastric secretion inhibitors on gefitinib therapy in patients with non-small cell lung cancer (abstract P3.176). *J Thor Oncol* 2011;6(Suppl. 2):S1282–3.
- [102] Saeki S, Sasaki J, Morioka J, et al. The influence of gastric secretion inhibitors on gefitinib therapy in patients with non-small cell lung cancer harboring epidermal growth factor receptor activating mutations. *J Clin Oncol* 2012;30(Suppl):abstract e18059.
- [103] Hamilton M, Wolf JL, Zborowski D, et al. Tarceva™ (erlotinib) exposure/effects (EE) analysis from a Phase III study in advanced NSCLC: effect of smoking on the PK of erlotinib (abstract 6155). *Pro Am Assoc Cancer Res* 2005;46:1451.
- [104] 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;27:1220–6.
- [105] Smit EF, Gervais R, Zhou C, et al. Efficacy and safety results from CurrentS, a double-blind, randomized, phase III study of second-line erlotinib (150 mg versus 300 mg) in current smokers with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2014;32(Suppl):abstract 8046.
- [106] Swaisland HC, Cantarini MV, Fuhr R, Holt A. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. *Clin Pharmacokinet* 2006;45:633–44.
- [107] Rudin CM, Liu W, Desai A, et al. Pharmacogenomic and pharmacokinetic determinants of erlotinib toxicity. *J Clin Oncol* 2008;26:1119–27.
- [108] Hirsh V. Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Curr Oncol* 2011;18:126–38.
- [109] Yang JC, Sequist L, O'Byrne K, et al. Epidermal growth factor receptor (EGFR)-mediated adverse events (AEs) in patients (pts) with EGFR mutation positive (EGFR M+) non-small cell lung cancer treated with afatinib (abstract 895). *Eur J Cancer* 2013;49(Suppl. 2):S190.
- [110] Lucchini E, Pilotto S, Spada E, et al. Targeting the epidermal growth factor receptor in solid tumors: focus on safety. *Expert Opin Drug Saf* 2014;13:535–49.
- [111] D'Arcangelo M, Hirsch FR. Clinical and comparative utility of afatinib in non-small cell lung cancer. *Biologics* 2014;8:183–92.
- [112] Bruno R, Mass RD, Jones C, Lu JF, Wine E. Preliminary population pharmacokinetics (PPK) and exposure-safety (E-S) relationships of erlotinib HCL in patients with metastatic breast cancer (MBC) (abstract 823). *Proc Am Soc Clin Oncol* 2003;22:205.
- [113] Thomas F, Rochaix P, White-Koning M, et al. Population pharmacokinetics of erlotinib and its pharmacokinetic/pharmacodynamic relationships in head and neck squamous cell carcinoma. *Eur J Cancer* 2009;45:2316–23.
- [114] Tiseo M, Andreoli R, Gelsomino F, et al. Correlation between erlotinib pharmacokinetics, cutaneous toxicity and clinical outcomes in patients with advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 2014;83:265–71.
- [115] Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. *Lung Cancer* 2012;78:8–15.
- [116] Rukazenkov Y, Speake G, Marshall G, et al. Epidermal growth factor receptor tyrosine kinase inhibitors: similar but different? *Anticancer Drugs* 2009;20:856–66.
- [117] ter Heine R, Fanggiday JC, Lankheet NA, et al. Erlotinib and pantoprazole: a relevant interaction or not? *Br J Clin Pharmacol* 2010;70:908–11.
- [118] Budha NR, Frymoyer A, Smelick GS, et al. Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? *Clin Pharmacol Ther* 2012;92:203–13.
- [119] Smelick GS, Heffron TP, Chu L, et al. Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development. *Mol Pharm* 2013;10:4055–62.
- [120] Ranson M, Hammond LA, Fery 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;20:2240–50.
- [121] Takahashi T, Boku N, Murakami H, et al. Phase I and pharmacokinetic study of dacomitinib (PF-00299804), an oral irreversible, small molecule inhibitor of human epidermal growth factor receptor-1, -2, and -4 tyrosine kinases, in Japanese patients with advanced solid tumors. *Invest New Drugs* 2012;30:2352–63.
- [122] 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;24:291–7.
- [123] Ranson M, Shaw H, Wolf J, et al. A phase I dose-escalation and bioavailability study of oral and intravenous formulations of erlotinib (Tarceva, OSI-774) in patients with advanced solid tumors of epithelial origin. *Cancer Chemother Pharmacol* 2010;66:53–8.
- [124] Ling J, Fettner S, Lum BL, Riek M, Rakhit A. Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. *Anticancer Drugs* 2008;19:209–16.
- [125] 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;98:1714–23.
- [126] Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf* 2013;36:295–316.