Drug-Drug Interactions, Safety, and Pharmacokinetics of EGFR Tyrosine Kinase Inhibitors for the Treatment of Non–Small Cell Lung Cancer

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Inhibitors of the epidermal growth factor receptor (EGFR) are important treatment options for non–small cell lung cancer (NSCLC) patients with activating *EGFR* mutations. Erlotinib, gefitinib, afatinib, and osimertinib are approved for use in NSCLC patients, and several other agents are in clinical development. The objectives of this article are to review the pharmacokinetic and known drug interaction data for EGFR tyrosine kinase inhibitors (TKIs) available for use in NSCLC patients, as well as adverse events (AEs) commonly observed with EGFR-TKI treatment, and to discuss relevant management strategies. The importance of this information for patient care is explored from the perspective of advanced practitioners. Pharmacokinetic, drug-interaction, and safety data are included for EGFR inhibitors approved for NSCLC (erlotinib, gefitinib, afatinib, and osimertinib). Relevant dose modifications and AE management strategies are also reviewed. The interdisciplinary health-care team plays an essential role in patient education, care planning, and medication administration. As such, it is essential that advanced practitioners understand the safety profiles and the potential for drug interactions with EGFR TKIs to ensure patients achieve the maximum benefit from these agents.

The identification of activating mutations in the epidermal growth factor receptor (EGFR) has expanded treatment options for non–small cell lung cancer (NSCLC), where the presence of these mutations can sensitize tumors to EGFR inhibitors (Rosell et al., 2010). For patients whose tumors have sensitizing *EGFR* mutations, EGFR tyrosine kinase inhibitors (TKIs) are important components of the NSCLC treatment landscape. Four EGFR TKIs

are approved by the US Food and Drug Administration (FDA) for use in NSCLC patients (erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], and osimertinib [Tagrisso]), and several others are in development. A thorough understanding of the safety profiles and drug interactions of EGFR TKIs is critical for advanced practitioners, who have a key role in educating patients on their safe and effective use. Here, we review relevant pharmacokinetic (PK) data and known drug interactions for each of the FDA-approved EGFR TKIs. We also summarize the most common EGFR-TKI–associated adverse events (AEs) and discuss management strategies, highlighting the role of advanced practitioners in safely managing EGFR-TKI use to ensure maximum patient benefit.
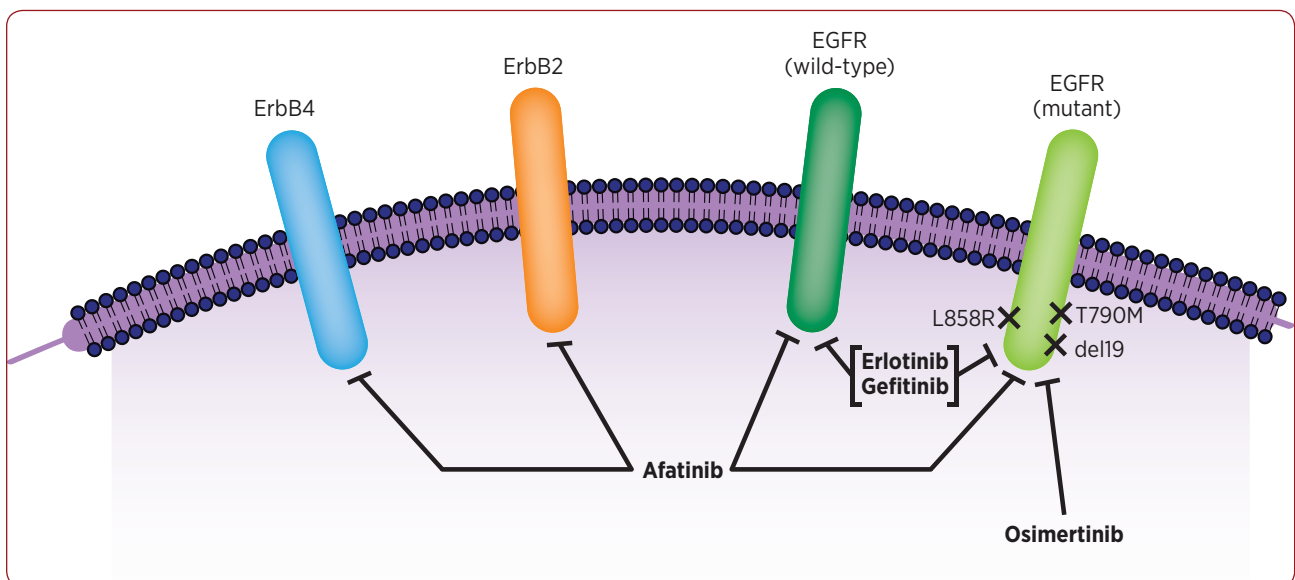
APPROVED EGFR TKIs

Erlotinib

Erlotinib is an oral, reversible inhibitor of wild-type and mutant EGFR (Figure 1) indicated for the first-line treatment of metastatic NSCLC harboring deletion 19 (del19) or exon 21 (L858R) substitution *EGFR* mutations (OSI Pharmaceuticals, LLC, 2015). Erlotinib is also indicated for the treatment of locally advanced NSCLC after che-motherapy failure and for maintenance treatment of locally advanced or metastatic NSCLC that has not progressed after 4 cycles of platinum-based therapy (OSI Pharmaceuticals, LLC, 2015). The recommended erlotinib dose is 150 mg/day on an empty stomach, as PK studies have demonstrated that bioavailability is increased with food (Katsuya et al., 2015; OSI Pharmaceuticals, LLC, 2015). Additional PK analyses (Table 1) have shown that erlotinib is ~60% bioavailable, has a long half-life (> 36 hours), and is metabolized primarily by cytochrome P450 (CYP) enzymes, particularly CYP3A4, in the liver (Lu et al., 2006; OSI Pharmaceuticals, LLC, 2015).

Generally, no significant effects on PK were observed with age, gender, or weight differences (Lu et al., 2006; OSI Pharmaceuticals, LLC, 2015), although one study (N = 55) demonstrated lower erlotinib exposure in African-American NSCLC patients (Phelps et al., 2014). Patients with mild or moderate hepatic impairment had similar PK as patients with normal liver function; thus, erlotinib dose modifications are not recommended for impaired hepatic function, but patients should be monitored closely (O'Bryant et al., 2012). Hepatotoxicity can occur with erlotinib, and patients with

Figure 1. Mechanisms of action of approved EGFR TKIs for NSCLC. Erlotinib and gefitinib are reversible EGFR inhibitors that bind to both wild-type and mutant EGFR, including L858R and del19 forms. In contrast, afatinib irreversibly binds to wild-type and mutant EGFR, as well as to the ErbB family members ErbB2 and ErbB4. The recently approved, mutant-specific, EGFR inhibitor osimertinib binds preferentially to mutant forms of the receptor, particularly T790M. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non–small cell lung cancer; L858R = exon 21; del19 = deletion 19.

Table 1. Pharmacokinetic Parameters for EGFR TKIs Approved for the Treatment of NSCLC

PK parameter	Erlotinib[a]	Gefitinib[b]	Afatinib[c]	Osimertinib[d]
Available dosage strengths (mg)	25, 100, 150	250	20, 30, 40	40, 80
Recommended dose (mg/day)	150	250	40	80
Recommended administration	With fasting	With fasting or with food	At least 1 hour before or 2 hours after food	With fasting or with food
Time to maximum plasma concentration (hr)	4	3–7	2–5	6
Bioavailability (%)	60	60	92	N/A
Plasma protein binding (%)	93	> 90	95	N/A
Hepatic metabolism	Extensive	Extensive	Minimal	N/A
Mean elimination half-life (hr)	36.2	48.0	37.0	48.0
Time to steady-state level (days)	7–8	7–10	8	15
Mode of excretion	Fecal	Fecal	Fecal	Fecal

Note. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non–small cell lung cancer; PK = pharmacokinetic; N/A = not available.
[a]Based on information from Katsuya et al. (2015); Lu et al. (2006); OSI Pharmaceuticals, LLC (2015); Scheffler, Di Gion, Doroshyenko, Wolf, & Fuhr (2011); van Erp, Gelderblom, & Guchelaar (2009).
[b]Based on information from AstraZeneca Pharmaceuticals LP (2015a); Ranson et al. (2002); Scheffler, Di Gion, Doroshyenko, Wolf, & Fuhr (2011); Swaisland et al. (2005a); van Erp, Gelderblom, & Guchelaar (2009).
[c]Based on information from Boehringer Ingelheim Pharmaceuticals, Inc. (2016); Stopfer et al. (2012); Shibata & Chiba (2015); Wind, Schmid, Erhardt, Goeldner, & Stopfer (2013).
[d]Based on information from AstraZeneca Pharmaceuticals LP (2015b); Janne et al. (2015).

baseline hepatic impairment have increased risk. Periodic liver testing should be performed, and erlotinib should be withheld for total bilirubin levels greater than three times the upper limit of normal or transaminases greater than five times the upper limit of normal. No studies have been conducted in patients with renal failure, although a case study reported that erlotinib was tolerated in three NSCLC patients with chronic renal failure (Gridelli, Maione, Galetta, & Rossi, 2007). Accordingly, there are no dose modifications recommended for these patients (OSI Pharmaceuticals, LLC, 2015).

Erlotinib exposure may be affected by concomitant use of other drugs (Table 2). Drugs that decrease acid can decrease erlotinib exposure. Patients should avoid use of proton pump inhibitors, such as pantoprazole and omeprazole, while taking erlotinib due to potential effects on erlotinib concentration (Kletzl et al., 2015; OSI Pharmaceuticals, LLC, 2015; Ter Heine et al., 2010). When histamine H2-receptor antagonists (H2 antago-

nists), such as ranitidine, are used concomitantly, erlotinib should be given 10 hours after the H2 antagonist and ≥ 2 hours before the next antagonist dose (Kletzl et al., 2015; OSI Pharmaceuticals, LLC, 2015). Antacids should be administered several hours before or after erlotinib (Kletzl et al., 2015; OSI Pharmaceuticals, LLC, 2015). It is important that these recommendations are followed, as decreased erlotinib efficacy was reported in NSCLC patients using gastric acid–suppressing medications (Chu et al., 2015). Alternate means of managing gastroesophageal reflux disease include sucralfate and limiting gastric irritants and foods high in acidity.

Due to its extensive metabolism by CYP3A4, erlotinib may be affected by other drugs that enhance or inhibit CYP activity or undergo CYP-mediated metabolism (Table 2). Advanced practitioners should be aware if patients are taking CYP inhibitors, including certain antifungal, antibiotic, and antiretroviral medications, as these agents can

Table 2. Drug Interactions and Suggested Modifications for Administration of EGFR TKIs in Patients With NSCLC[a]

Drug/ interactor class	Examples	Relevant EGFR TKI(s)	Expected effect	Current recommendations
Gastric acid–reducing agents	• Proton pump inhibitors (pantoprazole, omeprazole) • H2-receptor antagonists (ranitidine) • Antacids	Erlotinib, gefitinib	Decreased TKI exposure	• Erlotinib: Avoid concomitant use with proton pump inhibitors. Take erlotinib 10 hr after H2-receptor antagonists, and leave 2 hr before the next dose of H2-receptor antagonists. Leave several hours between erlotinib and antacids. • Gefitinib: Avoid concomitant use with proton pump inhibitors. Use gefitinib 6 hr before or after H2-receptor antagonists and antacids.
CYP inducers	• Rifampin • Phenytoin • Efavirenz • Tricyclic antidepressants • St. John's wort	Erlotinib, gefitinib, osimertinib	Decreased TKI exposure	• Erlotinib: For concomitant use, increase erlotinib in 50-mg increments at 2-wk intervals as tolerated (maximum 450 mg) • Gefitinib: For concomitant use, increase gefitinib to 500 mg as tolerated. Resume recommended dose after discontinuation of CYP inducer. • Osimertinib: Avoid concomitant use where possible
CYP inhibitors	• Ketoconazole • Itraconazole • Ciprofloxacin • Ritonavir • Telithromycin • Nefazodone • Atazanavir • Clarithromycin • Indinavir • Nelfinavir • Saquinavir • Troleandomycin • Voriconazole • Grapefruit/ grapefruit juice	Erlotinib, gefitinib, osimertinib	Increased TKI exposure	• Erlotinib: Avoid concomitant use where possible. For severe reactions, decrease erlotinib in 50-mg decrements. • Gefitinib: For concomitant use, monitor patients for adverse reactions • Osimertinib: Avoid concomitant use where possible. Monitor patients for adverse reactions when using concomitantly.
P-gp inducers	• Rifampin • Carbamazepine • Phenytoin • Phenobarbital • St. John's wort	Afatinib	Decreased TKI exposure	• Increase afatinib by 10 mg for concomitant use • Resume previous dose 2–3 days after discontinuing P-gp inducer
P-gp inhibitors	• Ritonavir • Cyclosporine A • Ketoconazole • Itraconazole • Erythromycin • Verapamil • Quinidine • Tacrolimus • Nelfinavir • Saquinavir • Amiodarone	Afatinib	Increased TKI exposure	• Reduce afatinib by 10 mg for concomitant use • Resume previous dose following discontinuation of P-gp inhibitor as tolerated

Note. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non–small cell lung cancer; H2 = histamine H2; CYP = cytochrome P450; P-gp = P-glycoprotein; INR = international normalized ratio.
[a]Based on information from AstraZeneca Pharmaceuticals LP (2015a, 2015b); Boehringer Ingelheim Pharmaceuticals, Inc. (2016); Chhun et al. (2009); Deeken et al. (2015); Grenader, Gipps, Shavit, & Gabizon (2007); Hamilton et al. (2006, 2014); Kletzl et al. (2015); O'Malley, King, Conte, Ellingrod, & Ramnath (2014); Onoda et al. (2005); OSI Pharmaceuticals, LLC (2015); Pillai et al. (2013); Rakhit et al. (2008); Ribed, Escudero-Vilaplana, Gonzalez-Haba, & Sanjurjo (2014); Smith et al. (2008); Sohn et al. (2015); Swaisland et al. (2005a); Ter Heine et al. (2010); Thomas, Billingsley, Amarshi, & Nair (2010); Wind et al. (2014).

Table 2. Drug Interactions and Suggested Modifications for Administration of EGFR TKIs in Patients With NSCLC[a] (cont.)

Drug/ interactor class	Examples	Relevant EGFR TKI(s)	Expected effect	Current recommendations
Cigarette smoking		Erlotinib	Decreased TKI exposure	• Increase erlotinib in 50-mg increments at 2-wk intervals as tolerated for concurrent cigarette smoking (maximum 300 mg). Resume recommended dose upon smoking cessation.
Anticoagulants	Warfarin	Erlotinib, gefitinib	Increased INR and bleeding reactions	• Erlotinib/gefitinib: Regularly monitor prothrombin time/INR. No dose modifications are recommended.

Note. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non–small cell lung cancer; H2 = histamine H2; CYP = cytochrome P450; P-gp = P-glycoprotein; INR = international normalized ratio.
[a]Based on information from AstraZeneca Pharmaceuticals LP (2015a, 2015b); Boehringer Ingelheim Pharmaceuticals, Inc. (2016); Chhun et al. (2009); Deeken et al. (2015); Grenader, Gipps, Shavit, & Gabizon (2007); Hamilton et al. (2006, 2014); Kletzl et al. (2015); O'Malley, King, Conte, Ellingrod, & Ramnath (2014); Onoda et al. (2005); OSI Pharmaceuticals, LLC (2015); Pillai et al. (2013); Rakhit et al. (2008); Ribed, Escudero-Vilaplana, Gonzalez-Haba, & Sanjurjo (2014); Smith et al. (2008); Sohn et al. (2015); Swaisland et al. (2005a); Ter Heine et al. (2010); Thomas, Billingsley, Amarshi, & Nair (2010); Wind et al. (2014).

increase erlotinib exposure (Deeken et al., 2015; Pillai et al., 2013; Rakhit et al., 2008). Additionally, grapefruit or grapefruit juice are CYP inhibitors and may increase erlotinib plasma concentrations (Smith et al., 2008). Likewise, patients should avoid concomitant use of erlotinib and CYP inducers, such as rifampin, phenytoin, and St. John's wort, as their use may affect drug exposure (Deeken et al., 2015; Grenader, Gipps, Shavit, & Gabizon, 2007; Hamilton et al., 2014; Pillai et al., 2013). Use of erlotinib with dexamethasone, also a CYP inducer, resulted in a 0.6-fold decrease in erlotinib exposure and may require dose escalation up to the maximum of 450 mg daily (Deeken et al., 2015). For situations where concomitant use of erlotinib with CYP interactors is necessary, erlotinib dose should be decreased (CYP inhibitors) or increased (CYP inducers) in 50-mg decrements/increments at 2-week intervals as tolerated (Table 2).

Drug interactions may also occur between erlotinib and drugs cleared by uridine diphosphate–glucuronosyltransferases, organic cation transporters (OCTs), and organic anion transporters (OATs), potentially affecting exposure to drugs that are substrates of these transporters (e.g., metformin, hydroxyurea, methotrexate, certain statins; Johnston, Rawling, Chan, Zhou, & Murray, 2014; Liu, Ramirez, House, & Ratain, 2010; Minematsu & Giacomini, 2011).

Erlotinib exposure also can be decreased by cigarette smoking (Hamilton et al., 2006; O'Malley,

King, Conte, Ellingrod, & Ramnath, 2014; Sohn et al., 2015). Current smokers, defined as smoking a minimum of 10 cigarettes per day for at least 1 year, required double the dose (300 mg) of erlotinib as nonsmokers (150 mg) to achieve therapeutic concentrations of the drug (Hamilton et al., 2006). Median survival times for patients receiving erlotinib are longest for those who never smoked compared with former smokers and current smokers (O'Malley et al., 2014). Erlotinib dose increases of 50 mg are advised at 2-week intervals to a maximum of 300 mg daily for concurrent cigarette smoking (OSI Pharmaceuticals, LLC, 2015). The interdisciplinary team of health-care providers can be instrumental in smoking cessation education; once cigarette smoking has ceased, the recommended erlotinib dose (100 or 150 mg daily) can be immediately resumed (Table 2).

Adverse interactions between erlotinib and coumarin-based anticoagulants, such as warfarin, have been observed, including increased international normalized ratios (INRs) and bleeding reactions (Thomas, Billingsley, Amarshi, & Nair, 2010). Patients using warfarin should be monitored closely for changes in INR while using erlotinib (Table 2).

Gefitinib
Gefitinib is another reversible inhibitor of wild-type and mutant EGFR (Figure 1) indicated for the first-line treatment of patients with metastatic

NSCLC whose tumors have del19 or L858R *EGFR* mutations (AstraZeneca Pharmaceuticals LP, 2015a). Gefitinib should be taken orally at a dose of 250 mg/day with or without food (AstraZeneca Pharmaceuticals LP, 2015a). The PK profile of gefitinib is similar to that of erlotinib, but gefitinib has a longer half-life of 48 hours (Ranson et al., 2002; Table 1); gefitinib availability is not significantly influenced by food (Swaisland et al., 2005a). Patient age, weight, gender, or ethnicity do not have any apparent effect on gefitinib PK (AstraZeneca Pharmaceuticals LP, 2015a; Li et al., 2006). Gefitinib PK were shown to be impacted by hepatic impairment due to cirrhosis but not liver metastases (Horak et al., 2011), and patients with moderate to severe hepatic impairment should be monitored for an increased risk of adverse reactions (AstraZeneca Pharmaceuticals LP, 2015a). Dose modifications are recommended based on results of periodic liver testing: for grade 2 or higher transaminase elevations, gefitinib should be withheld, and for severe hepatic impairment, treatment should be discontinued. No studies have been conducted to evaluate gefitinib PK in patients with renal impairment.

Due to their similar structure and PK profile, gefitinib and erlotinib share similar drug-interaction potential. Like erlotinib, gefitinib metabolism occurs mainly through CYP enzymes in the liver, including CYP3A4 and CYP2D6 (Li, Zhao, He, Hidalgo, & Baker, 2007). CYP inhibitors (e.g., itraconazole) may increase gefitinib plasma levels, and patients taking gefitinib with CYP inhibitors should be monitored closely (Swaisland et al., 2005b). For concomitant use with strong CYP inducers, such as phenytoin and rifampin, which can decrease gefitinib levels (Chhun et al., 2009; Swaisland et al., 2005b), gefitinib daily dose can be increased from 250 mg to 500 mg. Patients should resume the recommended dose of 250 mg after discontinuation of the CYP inducer (AstraZeneca Pharmaceuticals LP, 2015a). Gefitinib can inhibit the activity of drug transporters, such as OCTs (metformin, oxaliplatin) and OATs (montelukast, certain statins, sulfated estrogens, thyroxine), potentially altering the exposure of coadministered medications that are substrates for these transporters (Johnston et al., 2014; Minematsu & Giacomini, 2011).

Like erlotinib, acid-reducing medications may decrease gefitinib exposure. Gefitinib should not be used with proton pump inhibitors and, when concomitant use is necessary, dosing of gefitinib and the proton pump inhibitor should be spaced by 12 hours (AstraZeneca Pharmaceuticals LP, 2015a). When treatment with antacids or H2 antagonists is required, gefitinib should be taken 6 hours before or after the acid-reducing agent (AstraZeneca Pharmaceuticals LP, 2015a). Similar to erlotinib, gefitinib use has been linked to adverse reactions, including hemorrhage and INR elevations, in patients using warfarin or other coumarin derivatives (Onoda et al., 2005; Ribed, Escudero-Vilaplana, Gonzalez-Haba, & Sanjurjo, 2014), and therefore these patients should be monitored closely for potential reactions.

Afatinib

Afatinib is an oral, irreversible ErbB family blocker that targets mutant and wild-type EGFR/ErbB1, human epidermal growth factor receptor (HER) 2/ErbB2, and HER4/ErbB4, which results in the inhibition of HER3/ErbB3 phosphorylation (Li et al., 2008; Solca et al., 2012; Figure 1). It is currently indicated for the first-line treatment of patients with metastatic NSCLC whose tumors harbor del19 or L858R *EGFR* mutations and for metastatic squamous NSCLC progressing after platinum therapy (Boehringer Ingelheim Pharmaceuticals, 2016). The recommended afatinib dose is 40 mg once daily, taken ≥ 1 hour before or 2 hours after a meal (Boehringer Ingelheim Pharmaceuticals, 2016).

The PK profile of afatinib is presented in Table 1 (Wind, Schmid, Erhardt, Goeldner, & Stopfer, 2013). Weight, age, gender, race, and mild or moderate hepatic impairment do not have a significant effect on afatinib PK (Freiwald et al., 2014; Schnell et al., 2014). Severe renal impairment has been shown to increase afatinib exposure; thus, according to the US prescribing information, these patients should receive a starting dose of 30 mg afatinib (Boehringer Ingelheim Pharmaceuticals, 2016). Afatinib is minimally metabolized by hepatic enzymes (Shibata & Chiba, 2015; Stopfer et al., 2012); therefore, CYP-interacting agents are unlikely to impact afatinib PK. No dose modifications are recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic im-

pairment (Boehringer Ingelheim Pharmaceuticals, 2016). No studies have examined the effects of afatinib on patients with severe hepatic impairment (Child-Pugh C), although these patients should be closely monitored and have their dose adjusted for tolerability (Boehringer Ingelheim Pharmaceuticals, 2016). If periodic liver testing shows worsening of liver function, gefitinib should be withheld; for those who develop severe hepatic impairment, treatment should be discontinued.

Afatinib is a substrate and inhibitor of the P-glycoprotein (P-gp) drug transporter, and inhibitors and enhancers of P-gp activity may impact afatinib exposure. One study demonstrated that concomitant administration of afatinib with ritonavir, a P-gp inhibitor, increased afatinib exposure, although this increase was minimized by spacing out the medications by 6 hours (Wind et al., 2014). When concomitant use of afatinib with P-gp inhibitors is required, the afatinib dose should be reduced by 10 mg, as tolerated (Boehringer Ingelheim Pharmaceuticals, 2016; Table 2). Additionally, coadministration of afatinib with the P-gp inducer rifampin decreased afatinib plasma concentrations (Wind et al., 2014). Patients taking afatinib with a P-gp inducer should increase their afatinib dose by 10 mg (Boehringer Ingelheim Pharmaceuticals, 2016; Table 2). There is also evidence for an inhibitory effect of afatinib on OATs, although this effect is less potent than that observed with erlotinib or gefitinib (Johnston et al., 2014).

Osimertinib

Osimertinib was approved for metastatic NSCLC patients whose tumors harbor the T790M *EGFR* mutation following progression on EGFR-TKI therapy in 2015 (AstraZeneca Pharmaceuticals LP, 2015b; Kuiper et al., 2014). Osimertinib inhibits mutant forms of EGFR, including T790M, del19, and L858R, with minimal inhibition of wild-type EGFR protein (Cross et al., 2014; Figure 1). The recommended osimertinib dose is 80 mg once daily, taken orally with or without food (AstraZeneca Pharmaceuticals LP, 2015b).

There are limited PK and drug interaction data available for osimertinib, as its approval was recent and studies are ongoing. Pharmacokinetic data suggest a long half-life and relatively longer time to maximum plasma concentration com-

pared with other approved EGFR TKIs (AstraZeneca Pharmaceuticals LP, 2015b; Janne et al., 2015; Table 1). Based on its metabolism by CYP3A enzymes, osimertinib exposure may be impacted by CYP enzyme inducers or inhibitors, although extensive studies have not yet been performed (AstraZeneca Pharmaceuticals LP, 2015b). Patients taking osimertinib should avoid concomitant use of strong CYP inhibitors or inducers, and patients should be closely monitored when coadministration is necessary (AstraZeneca Pharmaceuticals LP, 2015b; Table 2).

SAFETY CONSIDERATIONS WITH EGFR-TKI THERAPY

EGFR TKIs have been associated with specific AEs, including diarrhea, mucositis, rash, and paronychia (Melosky & Hirsh, 2014). Because the incidence of these AEs can be high with EGFR-TKI use, dose optimization (where applicable) can mitigate their effects. Advanced practitioners can help anticipate and effectively manage these AEs so that patients can remain on therapy and maximize the clinical benefits of EGFR TKIs.

Diarrhea

Diarrhea is one of the most commonly observed AEs with EGFR TKIs (Melosky & Hirsh, 2014) and is graded from 1 to 5 based on frequency and severity (U.S. Department of Health and Human Services, National Institutes of Health, & National Cancer Institute, 2010). Grade 1 is defined as an increase of less than 4 stools per day over baseline, grade 2 as 4 to 6 stools per day over baseline, grade 3 as more than 7 stools per day over baseline or incontinence, grade 4 includes life-threatening consequences, and grade 5 is death (Cancer.net, 2017). In clinical trials supporting the approval of EGFR TKIs, incidence of any grade diarrhea ranged from 30.8% with gefitinib to 95.2% with afatinib (Douillard et al., 2014; Janne et al., 2015; Rosell et al., 2012; Sequist et al., 2013). The incidence of grade ≥ 3 diarrhea was ≤ 5% for erlotinib, gefitinib, and osimertinib and ranged from 5.4% to 14.4% with afatinib when starting at 40 mg (Douillard et al., 2014; Janne et al., 2015; Rosell et al., 2012; Sequist et al., 2013; Wu et al., 2014). Management strategies for diarrhea include dietary modifications such as avoiding foods that are difficult

to digest (e.g., broccoli, cabbage) and following the bananas, rice, applesauce, and toast (BRAT) diet until symptoms begin to resolve (Melosky & Hirsh, 2014). Loperamide can also be used to treat diarrhea; 4 mg should be given after the first episode of diarrhea, and 2 mg can be administered every 2 to 4 hours until diarrhea stops, typically not exceeding 16 mg/day for prescription use (Drugs. com, 2016; Hirsh, 2011; Melosky & Hirsh, 2014; Sipples, Andan, & Eaby-Sandy, 2015). For more severe diarrhea, diphenoxylate and atropine or octreotide can be considered. The EGFR TKI should be discontinued until severe diarrhea resolves, at which point the EGFR TKI can often be reintroduced (Hirsh, 2011; Melosky & Hirsh, 2014).

Rash

Dermatologic AEs, such as rash and acne, are also commonly observed with EGFR TKIs, and patient education should be provided at the initiation of therapy (Figure 2). Reported rates for these AEs in clinical trials were between 40.0% and 89.1% for rash of any grade and up to 16.2% for grade ≥ 3 rash (Douillard et al., 2014; Janne et al., 2015; Rosell et al., 2012; Sequist et al., 2013). Rashes typically present in stages, with early erythema and edema observed in weeks 1 to 2 of treatment. In week 2, papulopustular eruptions can occur in skin with a high density of sebaceous glands, followed by crusting of the skin in week 4 (Lacouture et al., 2011). Over the next 4
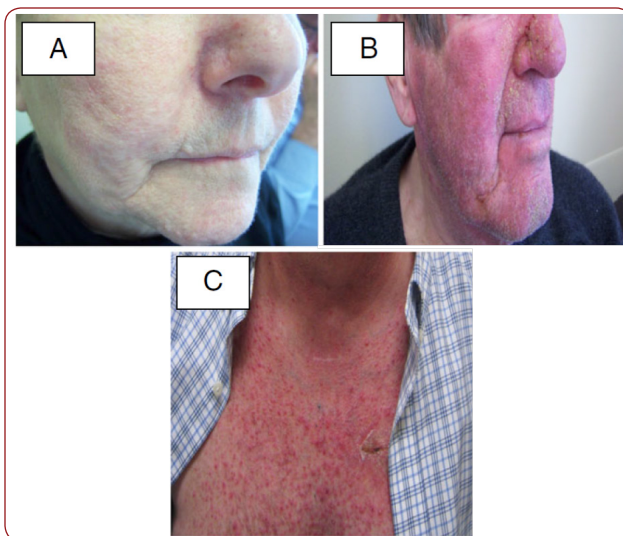
Figure 2. Mild papulopustular (acneiform) rash (A), and papulopustular (acneiform) rash (B and C).

to 6 weeks, patients can experience dry skin and erythema (Lacouture & Melosky, 2007). Based on data from randomized controlled trials, preventive therapy is recommended using 1% hydrocortisone, alcohol-free emollient creams, sunscreen, and doxycycline 100 mg twice daily (Hirsh, 2011; Lacouture et al., 2011; Melosky & Hirsh, 2014). Additional treatments for EGFR-TKI–associated rash include medium- to high-potency topical corticosteroids and isotretinoin at doses lower than those used for acne (Lacouture et al., 2011). EGFR-TKI treatment should be discontinued for severe reactions and can often be reintroduced at a modified dose upon resolution of the rash (Hirsh, 2011; Melosky & Hirsh, 2014).

Stomatitis/Mucositis

Stomatitis (inflammation of the mouth) and mucositis (inflammation of the gastrointestinal tract) have been observed with EGFR-TKIs (Melosky & Hirsh, 2014; Soria et al., 2015). In the LUX-Lung 3 trial, stomatitis/mucositis was seen in 72.1% of patients receiving afatinib, with 8.7% experiencing grade ≥ 3 stomatitis/mucositis (Sequist et al., 2013). Grades 1 and 2 mucosal inflammation were also reported in 12% of patients receiving osimertinib, 18% receiving erlotinib (1% grade ≥ 3), and 7% receiving gefitinib (0.3% grade ≥ 3) (AstraZeneca Pharmaceuticals LP, 2015a; Janne et al., 2015; OSI Pharmaceuticals, LLC, 2015).

Suggested management strategies for stomatitis/mucositis include maintaining good oral hygiene with alcohol-free products, triamcinolone acetonide, clobetasol, erythromycin, viscous lidocaine, and magic mouthwash (Melosky & Hirsh, 2014; Sipples et al., 2015). Analgesics may also be temporarily required for pain management associated with stomatitis/mucositis (Harris, 2006). As with other EGFR-TKI–associated AEs, it is suggested that treatment with the EGFR TKI be paused until severe cases of stomatitis/mucositis are resolved or improved. Following improvement of the AE, the EGFR TKI can be reintroduced at a lower dose (Melosky & Hirsh, 2014).

Paronychia

Another AE seen more frequently with afatinib and osimertinib is paronychia, an infection of the tissue where the skin meets the nail, which

can often be tender and painful. Paronychia was reported in 56.8% of patients receiving afatinib, with grade ≥ 3 paronychia observed in 11.4% (Sequist et al., 2013). Paronychia was reported in 17% of patients taking osimertinib, with less than 0.5% of cases reported as grade ≥ 3 (Janne et al., 2015). Recommended strategies for managing paronychia include the use of topical clobetasol or antibiotics/antiseptics, vinegar soaks, silver nitrate, and nail avulsion for severe cases (Melosky & Hirsh, 2014; Sipples et al., 2015).

Dose-Modification Protocols for Adverse Events

Dose modifications are recommended for patients taking EGFR TKIs who experience grade ≥ 3 AEs, particularly diarrhea and rash. These modifications generally involve withholding the TKI until AE improvement, at which time the TKI can be reintroduced at a lower dose (AstraZeneca Pharmaceuticals LP, 2015a, 2015b; OSI Pharmaceuticals, LLC, 2015). A dose-optimization scheme has been recommended for patients taking afatinib who experience drug-related grade 3 and certain prolonged grade 2 AEs (diarrhea persisting 2 or more consecutive days despite antidiarrheal medication, cutaneous reactions lasting more than 7 days or that is intolerable, and renal impairment; Sequist et al., 2013; Sipples et al., 2015; Yang et al., 2016). Patients should discontinue afatinib temporarily, and appropriate supportive care measures should be implemented. Upon AE improvement, afatinib can be reintroduced at a dose 10 mg lower than the previous dose. Importantly, progression-free survival was similar for patients who dose-reduced on afatinib vs. those who did not reduce their dose, suggesting that dose modification can allow patients to manage AEs without compromising afatinib efficacy (Yang et al., 2016).

DISCUSSION AND HEALTH-CARE TEAM PERSPECTIVES

EGFR TKIs are a key component of the NSCLC treatment landscape, and familiarity with these agents is critical for achieving maximum treatment benefits for patients. Health-care team members are responsible for understanding the drug profile of medications they are prescribing or administering, are key informants to patients, and are crucial to ensuring patient safety and adherence. Comprehensive assessment of patients taking EGFR TKIs helps to identify and quantify adverse reactions and contributes to increased medication compliance. Furthermore, advanced practitioners are pivotal to the interdisciplinary team, help to quantify the impact of cancer treatments on patients' quality of life, and modify treatment care plans as necessary to meet the needs of their patients and their treatment outcomes.

The health-care team provides patient education about EGFR TKIs and can encourage open communication with patients about concurrent medication use and onset of side effects. Providing education can help keep patients out of the hospital due to uncontrolled AEs and can reduce health-care spending by preventing avoidable hospitalizations (Brooks et al., 2014; Newcomer, 2014). Effective counseling and education empowers the patient to deal with EGFR-TKI–associated side effects, and advanced practitioners are an important resource to patients and families on how to manage and mitigate EGFR-TKI–associated toxicities. Continued understanding of the anticipated drug-interaction and side-effect profiles of targeted therapies is the key to keeping patients on the proper doses of these medications to maximize benefit. ●

References

AstraZeneca Pharmaceuticals LP. (2015a). Iressa (gefitinib) tablets for oral use package insert. Retrieved from http://www.azpicentral.com/pi.html?product=iressa&country=us&popup=no

AstraZeneca Pharmaceuticals LP. (2015b). Tagrisso (osimertinib) tablet for oral use package insert. Retrieved from http://www.azpicentral.com/pi.html?product=tagrisso&country=us&popup=no

Boehringer Ingelheim Pharmaceuticals, Inc. (2016). Gilotrif (afatinib) package insert. Retrieved from http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Gilotrif/Gilotrif.pdf?DMW_FORMAT=pdf

Brooks, G. A., Abrams, T. A., Meyerhardt, J. A., Enzinger, P. C., Sommer, K., Dalby, C. K.,…Schrag, D. (2014). Identification of potentially avoidable hospitalizations in patients with GI cancer. *Journal of Clinical Oncology, 32*(6), 496–503. https://doi.org/10.1200/JCO.2013.52.4330

Cancer.net. (2017). Diarrhea. Retrieved from http://www.cancer.net/navigating-cancer-care/side-effects/diarrhea

Chhun, S., Verstuyft, C., Rizzo-Padoin, N., Simoneau, G., Becquemont, L., Peretti, I.,…Mouly, S. (2009). Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. *British Journal of Clinical Pharmacology, 68*(2), 226–237. https://doi.org/10.1111/j.1365-2125.2009.03438.x

Chu, M. P., Ghosh, S., Chambers, C. R., Basappa, N., Butts, C. A., Chu, Q.,…Sawyer, M. B. (2015). Gastric acid suppression is associated with decreased erlotinib efficacy in non-small-cell lung cancer. *Clinical Lung Cancer, 16*(1), 33–39. https://doi.org/10.1016/j.cllc.2014.07.005

Cross, D. A., Ashton, S. E., Ghiorghiu, S., Eberlein, C., Nebhan, C. A., Spitzler, P. J.,…Pao, W. (2014). AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discovery, 4*(9), 1046–1061. https://doi.org/10.1158/2159-8290.CD-14-0337

Deeken, J. F., Beumer, J. H., Anders, N. M., Wanjiku, T., Rusnak, M., & Rudek, M. A. (2015). Preclinical assessment of the interactions between the antiretroviral drugs, ritonavir and efavirenz, and the tyrosine kinase inhibitor erlotinib. *Cancer Chemotherapy and Pharmacology, 76*(4), 813–819. https://doi.org/10.1007/s00280-015-2856-y

Douillard, J. Y., Ostoros, G., Cobo, M., Ciuleanu, T., McCormack, R., Webster, A., & Milenkova, T. (2014). First-line gefitinib in Caucasian *EGFR* mutation-positive NSCLC patients: A phase-IV, open-label, single-arm study. *British Journal of Cancer, 110*(1), 55–62. https://doi.org/10.1038/bjc.2013.721

Drugs.com (2016). Loperamide (loperamide hydrochloride) package insert. Retrieved from https://www.drugs.com/pro/loperamide.html

Freiwald, M., Schmid, U., Fleury, A., Wind, S., Stopfer, P., & Staab, A. (2014). Population pharmacokinetics of afatinib, an irreversible ErbB family blocker, in patients with various solid tumors. *Cancer Chemotherapy and Pharmacology, 73*(4), 759–770. https://doi.org/10.1007/s00280-014-2403-2

Grenader, T., Gipps, M., Shavit, L., & Gabizon, A. (2007). Significant drug interaction: Phenytoin toxicity due to erlotinib. *Lung Cancer, 57*(3), 404–406. https://doi.org/10.1016/j.lungcan.2007.02.011

Gridelli, C., Maione, P., Galetta, D., & Rossi, A. (2007). Safety profile of erlotinib in patients with advanced non-small cell lung cancer with chronic renal failure. *Journal of Thoracic Oncology, 2*(1), 96–98. https://doi.org/10.1097/JTO.0b013e31802bffb0

Hamilton, M., Wolf, J. L., Drolet, D. W., Fettner, S. H., Rakhit, A. K., Witt, K., & Lum, B. L. (2014). The effect of rifampicin, a prototypical CYP3A4 inducer, on erlotinib pharmacokinetics in healthy subjects. *Cancer Chemotherapy and Pharmacology, 73*(3), 613–621. https://doi.org/10.1007/s00280-014-2390-3

Hamilton, M., Wolf, J. L., Rusk, J., Beard, S. E., Clark, G. M., Witt, K., & Cagnoni, P. J. (2006). Effects of smoking on the pharmacokinetics of erlotinib. *Clinical Cancer Research, 12*(7 Pt 1), 2166–2171. https://doi.org/10.1158/1078-0432.CCR-05-2235

Harris, D. J. (2006). Cancer treatment-induced mucositis pain: Strategies for assessment and management. *Therapeutic and Clinical Risk Management, 2*(3), 251–258. https://doi.org/10.2147/tcrm.2006.2.3.251

Hirsh, V. (2011). Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Current Oncology, 18*(3), 126–138. https://doi.org/10.3747/co.v18i3.877

Horak, J., White, J., Harris, A. L., Verrill, M., Carmichael, J., Holt, A.,…Twelves, C. (2011). The effect of different etiologies of hepatic impairment on the pharmacokinetics of gefitinib. *Cancer Chemotherapy and Pharmacology, 68*(6), 1485–1495. https://doi.org/10.1007/s00280-011-1611-2

Janne, P. A., Yang, J. C., Kim, D. W., Planchard, D., Ohe, Y., Ramalingam, S. S.,…Ranson, M. (2015). AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *New England Journal of Medicine, 372*(18), 1689–1699. https://doi.org/10.1056/NEJMoa1411817

Johnston, R. A., Rawling, T., Chan, T., Zhou, F., & Murray, M. (2014). Selective inhibition of human solute carrier transporters by multikinase inhibitors. *Drug Metabolism and Disposition, 42*(11), 1851–1857. https://doi.org/10.1124/dmd.114.059097

Katsuya, Y., Fujiwara, Y., Sunami, K., Utsumi, H., Goto, Y., Kanda, S.,…Hamada, A. (2015). Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. *Cancer Chemotherapy and Pharmacology, 76*(1), 125–132. https://doi.org/10.1007/s00280-015-2778-8

Kletzl, H., Giraudon, M., Ducray, P. S., Abt, M., Hamilton, M., & Lum, B. L. (2015). Effect of gastric pH on erlotinib pharmacokinetics in healthy individuals: Omeprazole and ranitidine. *Anti-cancer Drugs, 26*(5), 565–572. https://doi.org/10.1097/CAD.0000000000000212

Kuiper, J. L., Heideman, D. A., Thunnissen, E., Paul, M. A., van Wijk, A. W., Postmus, P. E., & Smit, E. F. (2014). Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. *Lung Cancer, 85*(1), 19–24. https://doi.org/10.1016/j.lungcan.2014.03.016

Lacouture, M. E., Anadkat, M. J., Bensadoun, R. J., Bryce, J., Chan, A., Epstein, J. B.,…Murphy, B. A. (2011). Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Supportive Care Cancer, 19*(8), 1079–1095. https://doi.org/10.1007/s00520-011-1197-6

Lacouture, M. E., & Melosky, B. L. (2007). Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: A dermatology-oncology perspective. *Skin Therapy Letter, 12*(6), 1–5. Retrieved from https://www.

ncbi.nlm.nih.gov/pubmed/17762902

Li, D., Ambrogio, L., Shimamura, T., Kubo, S., Takahashi, M., Chirieac, L. R.,...Wong, K. K. (2008). BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene, 27*(34), 4702–4711. https://doi.org/10.1038/onc.2008.109

Li, J., Karlsson, M. O., Brahmer, J., Spitz, A., Zhao, M., Hidalgo, M., & Baker, S. D. (2006). CYP3A phenotyping approach to predict systemic exposure to EGFR tyrosine kinase inhibitors. *Journal of the National Cancer Institute, 98*(23), 1714–1723. https://doi.org/10.1093/jnci/djj466

Li, J., Zhao, M., He, P., Hidalgo, M., & Baker, S. D. (2007). Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. *Clinical Cancer Research, 13*(12), 3731–3737. https://doi.org/10.1158/1078-0432.CCR-07-0088

Liu, Y., Ramirez, J., House, L., & Ratain, M. J. (2010). Comparison of the drug-drug interactions potential of erlotinib and gefitinib via inhibition of UDP-glucuronosyltransferases. *Drug Metabolism and Disposition, 38*(1), 32–39. https://doi.org/10.1124/dmd.109.029660

Lu, J. F., Eppler, S. M., Wolf, J., Hamilton, M., Rakhit, A., Bruno, R., & Lum, B. L. (2006). Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clinical Pharmacology and Therapeutics, 80*(2), 136–145. https://doi.org/10.1016/j.clpt.2006.04.007

Melosky, B., & Hirsh, V. (2014). Management of common toxicities in metastatic NSCLC related to anti-lung cancer therapies with EGFR-TKIs. *Frontiers in Oncology, 4*, 238. https://doi.org/10.3389/fonc.2014.00238

Minematsu, T., & Giacomini, K. M. (2011). Interactions of tyrosine kinase inhibitors with organic cation transporters and multidrug and toxic compound extrusion proteins. *Molecular Cancer Therapeutics, 10*(3), 531–539. https://doi.org/10.1158/1535-7163.MCT-10-0731

Newcomer, L. N. (2014). Innovative payment models and measurement for cancer therapy. *Journal of Oncology Practice, 10*(3), 187–189. https://doi.org/10.1200/JOP.2014.001378

O'Bryant, C. L., Haluska, P., Rosen, L., Ramanathan, R. K., Venugopal, B., Leong, S.,...Ramalingam, S. (2012). An open-label study to describe pharmacokinetic parameters of erlotinib in patients with advanced solid tumors with adequate and moderately impaired hepatic function. *Cancer Chemotherapy and Pharmacology, 69*(3), 605–612. https://doi.org/10.1007/s00280-011-1733-6

O'Malley, M., King, A. N., Conte, M., Ellingrod, V. L., & Ramnath, N. (2014). Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. *Journal of Thoracic Oncology, 9*(7), 917–926. https://doi.org/10.1097/JTO.0000000000000191

Onoda, S., Mitsufuji, H., Yanase, N., Ryuge, S., Kato, E., Wada, M.,...Masuda, N. (2005). Drug interaction between gefitinib and warfarin. *Japanese Journal of Clinical Oncology, 35*(8), 478–482. https://doi.org/10.1093/jjco/hyi122

OSI Pharmaceuticals, LLC. (2015). Tarceva (erlotinib) tablets for oral use package insert. Retrieved from http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf

Phelps, M. A., Stinchcombe, T. E., Blachly, J. S., Zhao, W., Schaaf, L. J., Starrett, S. L.,...Villalona-Calero, M. A. (2014). Erlotinib in African Americans with advanced non-small cell lung cancer: A prospective randomized study with genetic and pharmacokinetic analyses. *Clinical Pharmacology and Therapeutics, 96*(2), 182–191. https://doi.org/10.1038/clpt.2014.93

Pillai, V. C., Venkataramanan, R., Parise, R. A., Christner, S. M., Gramignoli, R., Strom, S. C.,...Beumer, J. H. (2013). Ritonavir and efavirenz significantly alter the metabolism of erlotinib—an observation in primary cultures of human hepatocytes that is relevant to HIV patients with cancer. *Drug Metabolism and Disposition, 41*(10), 1843–1851. https://doi.org/10.1124/dmd.113.052100

Rakhit, A., Pantze, M. P., Fettner, S., Jones, H. M., Charoin, J. E., Riek, M.,...Hamilton, M. (2008). The effects of CYP3A4 inhibition on erlotinib pharmacokinetics: Computer-based simulation (SimCYP) predicts in vivo metabolic inhibition. *European Journal of Clinical Pharmacology, 64*(1), 31–41. https://doi.org/10.1007/s00228-007-0396-z

Ranson, M., Hammond, L. A., Ferry, D., Kris, M., Tullo, A., Murray, P. I.,...Rowinsky, E. K. (2002). 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. *Journal of Clinical Oncology, 20*(9), 2240–2250. https://doi.org/10.1200/JCO.2002.10.112

Ribed, A., Escudero-Vilaplana, V., Gonzalez-Haba, E., & Sanjurjo, M. (2014). Increased INR after gefitinib and acenocoumarol co-administration. *European Review for Medical and Pharmacological Sciences, 18*(12), 1720–1722. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24992614

Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E.,...Paz-Ares, L. (2012). 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 Oncology, 13*(3), 239–246. https://doi.org/10.1016/S1470-2045(11)70393-X

Rosell, R., Moran, T., Carcereny, E., Quiroga, V., Molina, M. A., Costa, C.,...Taron, M. (2010). Non-small-cell lung cancer harbouring mutations in the EGFR kinase domain. *Clinical and Translational Oncology, 12*(2), 75–80. https://doi.org/10.1007/S12094-010-0473-0

Scheffler, M., Di Gion, P., Doroshyenko, O., Wolf, J., & Fuhr, U. (2011). Clinical pharmacokinetics of tyrosine kinase inhibitors. *Clinical Pharmacokinetics, 50*(6), 371–403. https://doi.org/10.2165/11587020-000000000-00000

Schnell, D., Buschke, S., Fuchs, H., Gansser, D., Goeldner, R. G., Uttenreuther-Fischer, M.,...Koenen, R. (2014). Pharmacokinetics of afatinib in subjects with mild or moderate hepatic impairment. *Cancer Chemotherapy and Pharmacology, 74*(2), 267–275. https://doi.org/10.1007/s00280-014-2484-y

Sequist, L. V., Yang, J. C., Yamamoto, N., O'Byrne, K., Hirsh, V., Mok, T.,...Schuler, M. (2013). Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology, 31*(27), 3327–3334. https://doi.org/10.1200/JCO.2012.44.2806

Shibata, Y., & Chiba, M. (2015). The role of extrahepatic metabolism in the pharmacokinetics of the targeted covalent inhibitors afatinib, ibrutinib, and neratinib. *Drug Metabolism and Disposition, 43*(3), 375–384. https://doi.org/10.1124/dmd.114.061424

Sipples, R., Andan, C., & Eaby-Sandy, B. (2015). Practical management of adverse events associated with afatinib. *On-*

cology Nursing Forum, 42(2).

Smith, N. F., Baker, S. D., Gonzalez, F. J., Harris, J. W., Figg, W. D., & Sparreboom, A. (2008). Modulation of erlotinib pharmacokinetics in mice by a novel cytochrome P450 3A4 inhibitor, BAS 100. *British Journal of Cancer, 98*(10), 1630–1632. https://doi.org/10.1038/sj.bjc.6604353

Sohn, H. S., Kim, H., Song, I. S., Lim, E., Kwon, M., Ha, J. H., & Kwon, J. W. (2015). Evidence supporting the need for considering the effects of smoking on drug disposition and effectiveness in medication practices: A systematic narrative review. *International Journal of Clinical Pharmacology and Therapeutics, 53*(8), 621–634. https://doi.org/10.5414/CP202260

Solca, F., Dahl, G., Zoephel, A., Bader, G., Sanderson, M., Klein, C.,...Adolf, G. R. (2012). Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *Journal of Pharmacology and Experimental Therapeutics, 343*, 342–350. https://doi.org/10.1124/jpet.112.197756

Soria, J. C., Felip, E., Cobo, M., Lu, S., Syrigos, K., Lee, K. H.,...Goss, G. D. (2015). Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): An open-label randomised controlled phase 3 trial. *Lancet Oncology, 16*(8), 897–907. https://doi.org/10.1016/S1470-2045(15)00006-6

Stopfer, P., Marzin, K., Narjes, H., Gansser, D., Shahidi, M., Uttereuther-Fischer, M., & Ebner, T. (2012). Afatinib pharmacokinetics and metabolism after oral administration to healthy male volunteers. *Cancer Chemotherapy and Pharmacology, 69*(4), 1051–1061. https://doi.org/10.1007/s00280-011-1803-9

Swaisland, H. C., Ranson, M., Smith, R. P., Leadbetter, J., Laight, A., McKillop, D., & Wild, M. J. (2005b). Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clinical Pharmacokinetics, 44*(10), 1067–1081. https://doi.org/10.2165/00003088-200544100-00005

Swaisland, H. C., Smith, R. P., Laight, A., Kerr, D. J., Ranson, M., Wilder-Smith, C. H., & Duvauchelle, T. (2005a). Single-dose clinical pharmacokinetic studies of gefitinib. *Clinical Pharmacokinetics, 44*(11), 1165–1177. https://doi.org/10.2165/00003088-200544110-00004

Ter Heine, R., Fanggiday, J. C., Lankheet, N. A., Beijnen, J. H., Van Der Westerlaken, M. M., Staaks, G. H., & Malingre, M. M. (2010). Erlotinib and pantoprazole: a relevant interaction or not? *British Journal of Clinical Pharmacology, 70*(6), 908–911. https://doi.org/10.1111/j.1365-2125.2010.03748.x

Thomas, K. S., Billingsley, A., Amarshi, N., & Nair, B. A. (2010). Elevated international normalized ratio associated with concomitant warfarin and erlotinib. *American Journal of Health-System Pharmacy, 67*(17), 1426–1429. https://doi.org/10.2146/ajhp090202

U.S. Department of Health and Human Services, National Institutes of Health, & National Cancer Institute. (2010). Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. Retrieved from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

van Erp, N. P., Gelderblom, H., & Guchelaar, H. J. (2009). Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treatment Reviews, 35*(8), 692–706. https://doi.org/10.1016/j.ctrv.2009.08.004

Wind, S., Giessmann, T., Jungnik, A., Brand, T., Marzin, K., Bertulis, J.,...Stopfer, P. (2014). Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. *Clinical Drug Investigation, 34*(3), 173–182. https://doi.org/10.1007/s40261-013-0161-2

Wind, S., Schmid, M., Erhardt, J., Goeldner, R. G., & Stopfer, P. (2013). Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clinical Pharmacokinetics, 52*(12), 1101–1109. https://doi.org/10.1007/s40262-013-0091-4

Wu, Y. L., Zhou, C., Hu, C. P., Feng, J., Lu, S., Huang, Y.,...Geater, S. L. (2014). 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 Oncology, 15*(2), 213–222. https://doi.org/10.1016/S1470-2045(13)70604-1

Yang, J. C., Sequist, L. V., Zhou, C., Schuler, M., Geater, S. L., Mok, T.,...Wu, Y. L. (2016). Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: Post hoc analyses of the randomized LUX-Lung 3 and 6 trials. *Annals of Oncology, 27*(11), 2103–2110. https://doi.org/10.1093/annonc/mdw322