Targeted Therapies for Non-Small Cell Lung Cancer: An Update on Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Inhibitors

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Background: The development of targeted therapies has revolutionized the treatment of advanced non-small cell lung cancer (NSCLC), with new clinical trials and therapies consistently providing new information. This rapidly changing field mandates ongoing education for nursing professionals whose foremost priority is patient care.

Objectives: This review aims to summarize the history and current status of targeted therapies for NSCLC, focusing on two types of drugs that have had the most impact to date: epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors.

Methods: The safety profiles of first- and second-generation EGFR and ALK inhibitors are described, and strategies for the management of the most commonly experienced adverse events are summarized. Information is also provided to help identify which patients might be eligible for treatment with EGFR or ALK inhibitors in addition to the implications of targeted therapies.

Findings: Therapies designed to target specific molecular features of individual tumor cells are one of the most important developments in treating NSCLC. The safety profiles of targeted therapies differ greatly from chemotherapy and present unique challenges to nurses. Education of nurses and patients on implementation of effective adverse event management and improvement in patient adherence will maximize the benefits of these drugs.

Key words: non-small cell lung cancer; EGFR inhibitors; ALK inhibitors; adverse event management; oncology nursing

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Lung cancer is the most commonly diagnosed cancer worldwide (Ferlay et al., 2010). Non-small cell lung cancer (NSCLC) is its most prevalent form, comprising 85%–90% of newly diagnosed cases in the United States (American Cancer Society [ACS], 2015b). Most patients with NSCLC have a poor prognosis, partially because more than half are diagnosed when the disease is already advanced (Surveillance, Epidemiology, and End Results Program [SEER], 2015). Five-year survival rates for patients diagnosed with stages IIIB and IV lung cancer without regard to molecular subtype are as low as 5% and 1%, respectively (ACS, 2015a). The use of targeted therapies has the potential to increase the survival rate for patients harboring specific mutations.

Because nurses play an essential role in the assessment and management of patients with NSCLC (Walker, 2008), they and other healthcare professionals must remain up to date with developments in the treatment of this challenging and often devastating disease. Epidermal growth factor receptor (EGFR) was identified as a potential anticancer target in the late 1980s (Mendelsohn, 1988; Mok, Lee, & Leung, 2014), but many advances have been made since then. Gefitinib (Iressa®) was approved for use in NSCLC in 2003 (AstraZeneca, 2015), and erlotinib (Tarceva®) was approved in 2004 (Astellas Pharma US, Inc., & Genentech, Inc., 2015). In 2005, restrictions were placed on the use of gefitinib in the United States (U.S. Food and Drug Administration [FDA], 2005). Subsequent to this restriction, the FDA (2015) approved gefitinib for first-line treatment of patients with NSCLC with exon 19 deletion (del19) or exon 21 L858R substitution mutations. Enhanced anaplastic lymphoma kinase (ALK) activity was discovered in NSCLC in 2007. In 2010,
Epidermal Growth Factor Receptor Inhibitors
Rationale and Approved Therapies

EGFR is a transmembrane protein and growth signal receptor that controls cell proliferation and survival (Grünwald & Hidalgo, 2003; Mok et al., 2014). When a ligand binds the extracellular domain of the receptor, the intracellular tyrosine kinase domain is activated, initiating downstream signaling that induces the cell to activate proliferation and inhibit apoptosis (programmed cell death). The potential of EGFR as an anticancer target was first identified in the late 1980s (Mendelsohn, 1988; Mok et al., 2014) and was subsequently supported by preclinical studies that demonstrated its role in oncogenesis and by evidence that EGFR was overexpressed in a variety of human cancers (Grünwald & Hidalgo, 2003). Once EGFR was established as a valid target, drugs were developed that either bind to the extracellular ligand-binding domain of the receptor—as is the case for cetuximab (Erbitux®), a monoclonal antibody used in the treatment of colorectal cancer and head and neck cancer—or that inhibit the tyrosine kinase activity of the intracellular domain (Grünwald & Hidalgo, 2003; Mok et al., 2014). Several mutations have been identified in NSCLC tumors that activate EGFR in the absence of ligand. These activating mutations, including del19 and exon 21 L858R substitution in the tyrosine kinase domain, result in uncontrolled cell proliferation (Eck & Yun, 2010; Kumar, Petri, Halmos, & Boggon, 2008; Yun et al., 2007).

FIGURE 1. EGFR Mutations in Non-Small Cell Lung Cancer

Note. Portions resistant (not sensitive) to EGFR TKIs (gefitinib [Iressa®], erlotinib [Tarceva®], afatinib [Gilotrif®]) include exon 20 insertions and T790M.

EGFR—epidermal growth factor receptor; TKI—tyrosine kinase inhibitor

Note. Portions resistant (not sensitive) to EGFR TKIs (gefitinib [Iressa®], erlotinib [Tarceva®], afatinib [Gilotrif®]) include exon 20 insertions and T790M.
Gefitinib and erlotinib are orally administered, first-generation EGFR tyrosine kinase inhibitors (TKIs) that were approved in the United States in 2003 and 2004, respectively, for use in patients with advanced NSCLC who had failed prior chemotherapy (Astellas Pharma US, Inc., & Genentech, Inc., 2015; AstraZeneca, 2015). Although the introduction of these drugs was a welcomed advance, tumor response rates in unselected patients were low (less than 15% in Western patients treated with gefitinib) (Kris et al., 2003). It was only following the discovery of mutations in the EGFR gene that conferred sensitivity to erlotinib and gefitinib (present in about 10%–12% of non-Asian patients and 30%–40% of Asian patients) that the potential value of these drugs became fully apparent (Ellison et al., 2013; Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004). It turns out that the activating mutations (del19 and exon 21 L858R) result in TKIs, such as erlotinib and gefitinib, having a greater affinity for EGFR when compared to the wild-type receptor (Eck & Yun, 2010) (see Figure 1). Following this discovery, efficacy of first-line gefitinib and erlotinib in patients with EGFR mutation–positive advanced NSCLC was demonstrated in a number of clinical trials. For example, in the EURTAC trial, a phase III randomized, open-label trial of erlotinib versus chemotherapy in patients with mutations in the tyrosine kinase domain of EGFR (NCT00446225), treatment with erlotinib led to a doubling in median progression-free survival (PFS) in patients with the two most common types of EGFR mutations (del19 or L858R) compared with standard chemotherapy (10.4 versus 5.2 months, hazard ratio [HR] = 0.34, p < 0.001) (Astellas Pharma US, Inc., & Genentech, Inc., 2015; Rosell et al., 2012).

Data from EURTAC supported the approval of erlotinib in 2013 as a first-line treatment for metastatic NSCLC harboring del19 or L858R (Astellas Pharma US, Inc., & Genentech, Inc., 2015). Erlotinib is also approved as maintenance treatment in patients with advanced NSCLC whose disease has not progressed after four cycles of platinum-based, first-line chemotherapy (Astellas Pharma US, Inc., & Genentech, Inc., 2015). Since 2005, the use of gefitinib is restricted to patients who are or have benefited from prior treatment with this drug (AstraZeneca, 2015); however, subsequent to this restriction, the FDA (2015) approved gefitinib for the first-line treatment of patients with NSCLC with del19 or exon 21 L858R substitution mutations.

The second-generation EGFR inhibitor afatinib was approved in July 2013 for

### TABLE 1. Safety of EGFR Inhibitors in Patients With NSCLC

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Common AEs or LAs</th>
<th>Any Grade (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td></td>
<td></td>
<td></td>
<td>• Intestinal lung disease</td>
</tr>
<tr>
<td>150 mg orally daily on an empty stomach</td>
<td>Rasha</td>
<td>60–85</td>
<td>9–14</td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td>Diarrheaa</td>
<td>20–62</td>
<td>2–6</td>
<td>• Hepatotoxicity with or without hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>Dyspneaa</td>
<td>41–45b</td>
<td>8–28b</td>
<td>• Gastrointestinal perforation</td>
</tr>
<tr>
<td></td>
<td>Anorexiaa</td>
<td>52c</td>
<td>9c</td>
<td>• Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Fatiguea</td>
<td>52c</td>
<td>18b</td>
<td>• Myocardial infarction or ischemia</td>
</tr>
<tr>
<td></td>
<td>Cougha</td>
<td>48d</td>
<td>1d</td>
<td>• Cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>Nauseaea</td>
<td>33c</td>
<td>3c</td>
<td>• Microangiopathic hemolytic anemia with thrombocytopenia</td>
</tr>
<tr>
<td>Afatinib (Gilotrif®)</td>
<td></td>
<td></td>
<td></td>
<td>• Ocular disorders</td>
</tr>
<tr>
<td>40 mg orally daily on an empty stomach</td>
<td>Diarrheaa</td>
<td>96</td>
<td>15</td>
<td>• Hemorrhage in patients taking warfarin (Coumadin®)</td>
</tr>
<tr>
<td></td>
<td>Rash or dermatitis acneliforma</td>
<td>90</td>
<td>16</td>
<td>• Embryofetal toxicity</td>
</tr>
<tr>
<td></td>
<td>Stomatitisa</td>
<td>71</td>
<td>9</td>
<td>• Combination with vinorelbine in HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td></td>
<td>Paronchiaa</td>
<td>58</td>
<td>11</td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Dry skina</td>
<td>31</td>
<td>–</td>
<td>• Bullous and exfoliative skin disorders</td>
</tr>
<tr>
<td></td>
<td>Elevated ALTb</td>
<td>11</td>
<td>2</td>
<td>• Interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Elevated ASTb</td>
<td>8</td>
<td>2</td>
<td>• Hepatic toxicity</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia (including decreased blood potassium)c</td>
<td>11</td>
<td>4</td>
<td>• Keratitis</td>
</tr>
</tbody>
</table>

*a* AE incidence of 30% or greater with increase of 5% or greater versus comparator group in studies of erlotinib as first-line treatment of patients with metastatic NSCLC harboring EGFR mutations, as maintenance treatment of patients with locally advanced or metastatic NSCLC, or as second- or third-line treatment of locally advanced NSCLC.

*b* First-line and second- or third-line studies only

*c* Second- or third-line study only

*d* First-line study only

*e* AE incidence of 30% or greater in a study of afatinib as treatment of EGFR-TKI–naive patients with metastatic NSCLC harboring EGFR mutations.

*f* LA incidence of 5% or greater in a study of afatinib as treatment of EGFR-TKI–naive patients with metastatic NSCLC harboring EGFR mutations.

AE—adverse event; ALT—alanine transaminase; AST—aspartate transaminase; EGFR—epidermal growth factor receptor; LA—laboratory abnormality; NSCLC—non-small cell lung cancer; TKI—tyrosine kinase inhibitor.

Note. Based on information from Astellas Pharma US, Inc., & Genentech, Inc., 2015; Boehringer Ingelheim Pharmaceuticals, 2015.
first-line treatment of metastatic NSCLC harboring del19 or L858R. This approval was supported by the findings of the LUX-Lung 3 study, a randomized, open-label phase III trial of afatinib versus chemotherapy in patients with EGFR-activating mutations (NCT00949650). In that study, median PFS was 13.6 months in patients with these mutations treated with afatinib and 6.9 months in those on chemotherapy (HR = 0.47, p = 0.001) (Sequist et al., 2013). Unlike gefitinib and erlotinib, which are reversible EGFR inhibitors, afatinib irreversibly inhibits tyrosine kinase activity, a property that may help overcome the drug resistance that often develops during treatment with first-generation inhibitors, but further evidence supporting this hypothesis is required (D’Arcangelo & Hirsch, 2014).

Adverse Events in Patients Treated With Epidermal Growth Factor Receptor Inhibitors

Key information regarding the safety of erlotinib and afatinib in patients with NSCLC is summarized in Table 1. The main AEs observed in patients with NSCLC treated with erlotinib are rash and diarrhea (Kiyohara, Yamazaki, & Kishi, 2013; Reck, Mok, Wolf, Heigener, & Wu, 2011). In EURTAC, the most commonly reported AEs in erlotinib-treated patients were rash, diarrhea, asthenia, cough, dyspnea, and decreased appetite (Astellas Pharma US, Inc., & Genentech, Inc., 2015). Rash and diarrhea occurred as grade 3 or 4 events in 14% and 5% of erlotinib-treated patients in the trial, respectively. Skin toxicities observed with erlotinib include acniform rash, xeroderma, pruritus, and paronychia (Kiyohara et al., 2013). Although most cases are mild and transient, these AEs can significantly reduce patients’ quality of life and lead to treatment interruption or discontinuation. Diarrhea is usually mild or moderate in severity and often can be easily managed with antidiarrheal medications or through dose reduction (Reck et al., 2011). Other rare but potentially serious AEs observed in patients with NSCLC treated with erlotinib include interstitial lung disease (ILD), renal failure, hepatotoxicity, and gastrointestinal perforation (Astellas Pharma US, Inc., & Genentech, Inc., 2015).

The most common AEs following afatinib treatment are gastrointestinal and cutaneous in nature (D’Arcangelo & Hirsch, 2014). Diarrhea, acniform rash, and stomatitis were the most common treatment-related AEs in patients receiving afatinib in the LUX-Lung 3 study (Boehringer Ingelheim Pharmaceuticals,
with diarrhea more common (96% for all grades) and severe (15% for grades 3 and 4) than that observed with first-generation EGFR inhibitors (D’Arcangelo & Hirsch, 2014). No major differences exist in rates of skin rash observed with afatinib versus erlotinib (D’Arcangelo & Hirsch, 2014). ILD, hepatotoxicity, and keratitis are among the other potential AEs that have been observed with afatinib (Boehringer Ingelheim Pharmaceuticals, 2015; Sequist et al., 2013). 

**Anaplastic Lymphoma Kinase Inhibitors**

**Rationale and Approved Therapies**

*ALK* is a member of the insulin receptor superfamily of tyrosine kinases that controls cell proliferation and survival and was first identified in anaplastic large cell lymphoma cell lines in 1994 (Morris et al., 1994; Palmer, Vernersson, Grabbe, & Hallberg, 2009). Chromosomal rearrangements that cause truncation of *ALK* and its fusion with other proteins have been implicated in a number of different cancers (Palmer et al., 2009). The fusion of the *ALK* gene with the gene for echinoderm microtubule-associated protein-like 4 (EML4) and subsequent activation of the *ALK* gene was discovered in NSCLC in 2007 (Palmer et al., 2009; Soda et al., 2007) (see Figure 3). About 4% of all cases of NSCLC involve *ALK* gene rearrangements (Palmer et al., 2009).

Crizotinib is an orally administered TKI originally identified in 2005 as an inhibitor of hepatocyte growth factor receptor and was later shown to inhibit ALK and ROS proto-oncogene 1, receptor tyrosine kinase, another protein implicated in NSCLC (Ou, Bartlett, Mino-Kenudson, Cui, & IafRATE, 2012; Rodig & Shapiro, 2010). Clinical trials of crizotinib in advanced *ALK*-positive NSCLC were started in 2007 following the development of an assay that enabled reliable detection of *ALK* rearrangements (Ou et al., 2012). Crizotinib was approved for use in patients with advanced *ALK*-positive NSCLC in 2011 (Pfizer, Inc., 2015) after two single-arm trials reported objective response rates of 50% and 61% in these patients (Camidge et al., 2012; Ou et al., 2012).

A next-generation oral ALK inhibitor, ceritinib, was approved in April 2014 for treatment of patients with *ALK*-positive NSCLC who have progressed on or are intolerant to crizotinib (Novartis, 2015). Ceritinib is an ALK inhibitor that has shown activity against crizotinib-resistant ALK in the preclinical setting (Friboulet et al., 2014; Shaw et al., 2014). Approval of ceritinib was based on the results of a single-arm trial in *ALK*-positive NSCLC (Novartis, 2015; Shaw et al., 2014). In this trial, investigator-assessed and independently assessed objective response rates (defined as complete response plus partial response, per Response Evaluation Criteria in Solid Tumors, version 1.1) were 55% and 44%, respectively (Novartis, 2015). About half of patients in the ceritinib trial had metastatic brain disease, and objective responses were also seen in untreated metastatic central nervous system tumors (Shaw et al., 2014).

**Adverse Events in Patients Treated With Anaplastic Lymphoma Kinase Inhibitors**

The most common AEs observed in clinical trials of crizotinib were vision disorders, gastrointestinal effects (e.g., diarrhea, nausea, vomiting, constipation), edema, and fatigue (Pfizer, Inc., 2015; Roberts, 2013; Rothenstein & Letarte, 2014), as summarized in Table 2. Visual disturbances associated with crizotinib generally occur with the transition between light and dark and are experienced as transient flashes of...
light in the peripheral vision. These events are usually mild and begin within two weeks of starting therapy, improving over time. Gastrointestinal AEs also tend to occur early and improve with time as treatment continues. The most common grade 3 or 4 events observed with crizotinib include elevated alanine transaminase (ALT) levels and neutropenia (Pfizer, Inc., 2015; Roberts, 2013; Rothenstein & Letarte, 2014). Potentially serious AEs include hepatotoxicity,ILD or pneumonitis, bradycardia, and QT interval prolongation (Roberts, 2013; Rothenstein & Letarte, 2014).

The safety profile of ceritinib is similar, but not identical, to that of crizotinib. The most common AEs in the trial of ceritinib in ALK-positive NSCLC were diarrhea, nausea, vomiting, abdominal pain, fatigue, and decreased appetite (Novartis, 2015). The most common grade 3 or 4 events were increased ALT, increased aspartate transaminase, and increased glucose. Other potentially important, although uncommon, AEs includeILD or pneumonitis, QT interval prolongation, and bradycardia.

Management Strategies for Key Anaplastic Lymphoma Kinase Inhibitor–Associated Adverse Events

Strategies for the management of common ALK inhibitor–associated side effects are summarized in Figure 4. Gastrointestinal AEs are associated with crizotinib and ceritinib, and dose modifications may be necessary for some patients. Diarrhea can be managed as described previously for EGFR inhibitors, but dose adjustments may be required. To help prevent ALK inhibitor–associated nausea, patients should predose with an antiemetic. Ceritinib should be taken at least two hours after and two hours before food to ensure that the stomach is empty, and patients may be advised to take ceritinib at night before bed (Rothenstein & Letarte, 2014). Patients who prefer to take ceritinib at bedtime may consider predosing with loperamide to ameliorate or prevent the occurrence of loose stools or diarrhea overnight. Dicyclomine (Bentyl®), an agent with antispasmodic properties, may be useful for treatment of abdominal pain, a common gastrointestinal AE associated with ceritinib.

In cases where severe gastrointestinal symptoms persist despite antiemetic or anti diarrheal therapy, ceritinib may be withheld and then resumed at a lower dose. Dose reductions must occur in 150 mg increments because that is the only capsule size available.

### TABLE 2. Safety of ALK Inhibitors in Patients With NSCLC

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Common AEs or LAs</th>
<th>Any Grade (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (Xalkori®) 250 mg orally twice daily</td>
<td>Vision disorders&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 –</td>
<td>–</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Diarrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 –</td>
<td>–</td>
<td>• Interstitial lung disease (pneumonitis)</td>
</tr>
<tr>
<td></td>
<td>Nausea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55 1</td>
<td></td>
<td>• QT interval prolongation</td>
</tr>
<tr>
<td></td>
<td>Vomiting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 1</td>
<td></td>
<td>• Gastrointestinal perforation</td>
</tr>
<tr>
<td></td>
<td>Constipation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42 2</td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51 9</td>
<td></td>
<td>• Embryofetal toxicity</td>
</tr>
<tr>
<td></td>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypokalemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceritinib (Zykadia™) 750 mg orally once daily on an empty stomach</td>
<td>Diarrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>86 6</td>
<td></td>
<td>• Severe or persistent gastrointestinal toxicity</td>
</tr>
<tr>
<td></td>
<td>Nausea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 4</td>
<td></td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Vomiting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 4</td>
<td></td>
<td>• Interstitial lung disease (pneumonitis)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54 2</td>
<td></td>
<td>• QT interval prolongation</td>
</tr>
<tr>
<td></td>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 5</td>
<td></td>
<td>• Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34 1</td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Decreased hemoglobin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>84 5</td>
<td></td>
<td>• Embryofetal toxicity</td>
</tr>
<tr>
<td></td>
<td>Elevated ALT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated AST&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated creatinine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated glucose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased phosphate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated lipase&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated total bilirubin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>AEs with an incidence of 30% or greater with increase of 5% or greater for all grades or 2% or greater for grade 3 or 4 versus comparator group in a study of crizotinib in ALK-positive NSCLC

<sup>b</sup>LAs with an incidence of 4% or greater for grade 3 or 4 in a study of crizotinib in ALK-positive NSCLC

<sup>c</sup>AEs with an incidence of 30% or greater in a study of ceritinib in ALK-positive metastatic NSCLC

<sup>d</sup>LAs with an incidence of 10% or greater in a study of ceritinib in ALK-positive metastatic NSCLC

AE—adverse event; ALK—anaplastic lymphoma kinase; ALT—alanine transaminase; AST—aspartate transaminase; LA—laboratory abnormality; NSCLC—non-small cell lung cancer

Note. Based on information from Novartis, 2015; Pfizer, Inc., 2014.
Visual disturbances are common with crizotinib treatment, but symptoms are usually mild. Ophthalmologic assessment is only necessary if mild symptoms worsen in severity or adversely affect normal daily activities. Patients must be advised to avoid or take extra care when driving or operating machinery depending on the severity of their symptoms.

Identifying Candidates for Targeted Therapy and Caring for All Patients

The development of erlotinib, crizotinib, ceritinib, and other targeted therapies has had a major impact on the management of advanced NSCLC. However, because these drugs are targeted toward specific pathways upregulated by genetic mutations or other alterations, limited subpopulations of patients are most likely to benefit from treatment. Identifying patients who might benefit from targeted therapies is of major importance. Available evidence suggests that certain patient and clinical characteristics might increase or decrease the likelihood of an EGFR mutation or ALK rearrangement being detected. EGFR mutations are thought to be more likely to occur in East Asian patients versus non-East Asian patients, women versus men, never smokers versus smokers, and in patients with adenocarcinomas versus those with lung cancers of other histologies (Shigematsu et al., 2005; Tokumo et al., 2005). ALK rearrangements are associated with younger age and a light-smoking history or nonsmoking status (Inamura et al., 2009; Wong et al., 2009). Although knowledge of the characteristics associated with these genetic alterations is useful, the current standard of care is to perform molecular testing whenever clinically indicated for all patients with adenocarcinomas and mixed lung cancers with an adenocarcinoma component regardless of histologic grade or other clinical characteristics (Lindeman et al., 2013).

Considering the impact of targeted therapies and molecular testing from patient perspectives is useful. Before undergoing molecular testing, patients need to be made aware of the relatively low individual likelihood of obtaining a positive result for either an activating EGFR mutation (about 15% of primary lung adenocarcinoma) or ALK rearrangement (2%–6% of patients with NSCLC) (Brega & Brandao, 2014). Patients should be advised that current targeted therapies are not curative and that all of these lung cancers are eventually expected to develop resistance to the treatment. Many EGFR- or ALK-positive patients are younger and at a different stage of life than the historically typical patient with lung cancer; accordingly, they may have different concerns and support needs, particularly with respect to end-of-life considerations (e.g., they may have young children). Another important consideration is cost. Oral targeted therapies are often billed on patients’ pharmacy benefits, unlike chemotherapeutic drug costs, which are commonly paid for via an infusion charge. Patients with high deductibles and co-pays for outpatient prescriptions may find their out-of-pocket costs to be considerable. This fact needs to be made clear to patients along with the availability of pharmaceutical company patient-assistance programs.

Another concern with oral agents in general is that patients are responsible for managing their medication regimen, making adherence an important issue. The World Health Organization (2003) cites the issue of nonadherence with oral chemotherapy as the single most important yet modifiable factor.

### Diarrhea

**Initial assessment**
- Rule out other causes (other medications or dietary factors).
- Order complete blood count and differential to rule out neutropenia, blood tests for renal function, and stool culture for bacterial pathogens.

**Severity assessment**

**Initial treatment strategy**
- BRAT (banana, rice, apple sauce, toast) diet with 3–4 L fluid intake per day.
- Use loperamide (Imodium®) 4 mg then 2 mg every four hours or after each loose stool until 20 mg per day maximum.

**Treatment of grade 1 or 2 diarrhea**
- After the first loose stool, use loperamide 4 mg, then 2 mg every two hours.
- Enact ALK inhibitor dose reduction if symptoms persist.
- Use IV fluids.
- If no resolution, use octreotide (Sandostatin®) (100–150 mcg subcutaneously three times daily).

**Treatment of grade 3 or 4 diarrhea**
- After 12–24 hours, admit to hospital.
- Discontinue or reduce dose of ALK inhibitor.
- Use IV fluids.

ALK—anaplastic lymphoma kinase

*Note.* At the authors’ institution, it is uncommon to use octreotide for treatment of grade 1 or 2 diarrhea.

### Nausea and Vomiting

**General management**
- Predose with antiemetic, such as metoclopramide (Reglan®) or dimenhydrinate (Dramamine®). However, avoid or use cautiously prochlorperazine and 5-HT3 receptor antagonists (e.g., ondansetron [Zofran®]) because of risk of QT prolongation.
- Consider taking ALK inhibitors at night before bed.
- Take ceritinib (Zykadia™) at least two hours after eating.
- Crizotinib (Xalkori®) may be taken with or without food. However, many patients experience less nausea when taken with food.

### Abdominal Pain

**General management**
- Consider use of dicyclomine (Bentyl®) for its antispasmodic properties.

### Visual Impairment

**General management**
- Usually, no ophthalmologic assessments are necessary. However, if visual adverse events worsen, ophthalmologic evaluation is desirable.
- If vision is greatly affected in low-light conditions, driving should be avoided at those times of day. In general, caution should be taken when driving and operating machinery if vision is affected.

**FIGURE 4. Strategies for the Management of Key ALK Inhibitor–Associated Adverse Events**

*Note.* Based on information from Hirsh, 2011; Melosky, 2012; Rothenstein & Letarte, 2014.
that can compromise treatment outcomes and projects that about 50% of patients take their medication as prescribed. Preparing patients for oral therapy regimens is a nursing responsibility. Nurses should instruct patients about the timing of doses, specify whether they can be taken with food or on an empty stomach, and suggest aids that can be used to help patients remember when to take their medications (e.g., phone or computer alarms, a dosing diary). Improved patient–provider communication and education are powerful tools to increase adherence to oral chemotherapeutic agents. The Oncology Nursing Society (2009) provides a toolkit for oral adherence with strategies and resources that nurses can use to improve patient adherence.

**Conclusion**

Possibly, the most critical nursing responsibility is to manage side effects so that patients will not abandon a therapy before a fair trial of its efficacy. Since approval of the first-generation EGFR inhibitors more than 10 years ago, healthcare providers have witnessed a continued evolution of targeted therapy in NSCLC with improving patient outcomes. These changes have presented new clinical challenges to all those involved in the care of patients with NSCLC, including the nursing community. However, via implementation of effective AE management strategies, education to improve patient adherence, and clear communication of this information to patients, maximizing the benefits of these drugs in the clinic is possible.

**References**


Boehringer Ingelheim Pharmaceuticals, Inc. (2015). Gilotrif® (afa 
titinib) [Package insert]. Retrieved from http://docs.boehringer- 
ingelheim.com/Prescribing%20Information/PIs/Gilotrif/Gilotrif.pdf


