Targeted Therapy for Non–Small Cell Lung Cancer

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The treatment of advanced non–small cell lung cancer has been with systemic chemotherapy and usually consists of a platinum doublet chemotherapy. The identification of somatic driver mutations has resulted in new drugs that target these mutations. This report discusses the two most important new targeted therapy drugs for the treatment of advanced non–small cell lung cancer that have these driver mutations.

Keywords: lung cancer; erlotinib; crizotinib; targeted therapy; driver mutations

Before 2005, platinum-based doublet chemotherapy was the standard of care for stage IV non–small cell lung cancer (NSCLC) (1, 2). The treatment for all subtypes of NSCLC was the same, and the pathologist's job consisted of differentiating small cell lung cancer from NSCLC. Accordingly, data from the Surveillance Epidemiology and End Results from 2000 to 2006 noted that 25% of NSCLC was typed as "not otherwise specified" (3).

The landscape began to change in 2004 with the discovery of the sensitizing mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain (4–6). This was the first driver mutation identified in lung cancer for which a targeted therapeutic drug was available. Driver mutations are mutations in genes that encode signaling protein crucial for cell proliferation and drive tumor formation. Two sensitizing EGFR mutations (Exon 19 deletion and Exon 21 mutation [L858R]) were identified as the reason some NSCLC had a dramatic response to gefitinib, an EGFR TK inhibitor (TKI). Subsequently, these somatic mutations were identified as occurring predominantly in adenocarcinomas of the lung.

The watershed report of the I-PASS (Iressa Pan Asian Study) trial by Mok and colleagues (7) verified the importance of identifying EGFR-sensitizing mutations before selecting initial treatment with an EGFR-TKI or platinum doublet chemotherapy. Although EGFR mutations were predominantly in adenocarcinomas, there was no way to accurately predict which individuals had EGFR somatic mutation without performing mutational testing of the cancer.

Soda and colleagues first reported the identification of the transforming echinoderm microtubule-associated protein like (EML)4-anaplastic lymphoma kinase (ALK) gene fusion (8). EML-4 is fused with the intracellular kinase domain of ALK and results in a constitutively activated TK, which functions as a driver mutation. Multiple less common fusion partners for ALK have been reported (9, 10). The ALK mutations have also been shown to occur predominantly in lung adenocarcinomas.

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The literature since 2005 has substantiated the necessity of histologically subclassifying NSCLC to identify which tumors should be sent for molecular testing of EGFR mutations and ALK fusions or for the selection of optimal therapy (11, 12). This review is limited to discussing the two most important new drugs for the treatment of NSCLC: the EGFR-TKI erlotinib and the ALK-TKI crizotinib. Gefitinib activity against EGFR-sensitizing mutation is similar to erlotinib, but it was pulled from the United States market by the United States Food and Drug Administration after the ISEL (Iressa Survival Evaluation Lung Cancer) trial failed to demonstrate a statistically significant survival benefit with the use of gefitinib in an unselected NSCLC population (13). Gefitinib is still widely used in the rest of the world, and most oncologists believe that it has similar benefits to those of erlotinib.

The main role of the pulmonologist in the care of the patient with suspected lung cancer is to obtain adequate tissue for histologic diagnosis and molecular testing. Reports have documented that adequate tissue samples can be obtained from bronchoscopic biopsies and from endobronchial ultrasound-guided specimens but will likely require two or three extra needle passes (14). Cell pellets from malignant pleural effusion are often adequate for molecular testing. Pulmonary physicians should not be satisfied with only enough tissue for histology. In such cases, if the patient has stage IV disease, the medical oncologist should send the patient for repeat biopsies before deciding on the best treatment option.

MECHANISM OF ACTION

The somatic sensitizing mutation in the EGFR-TK domain results in a constitutively activated TK that serves as a driver mutation for cell proliferation. Erlotinib is an orally administered small molecule that binds to the intracellular TK domain by competing with ATP and inhibiting receptor autophosphorylation (5, 15) and downstream proliferation (Figure 1). Binding with erlotinib or gefitinib is reversible, but irreversible EGFR-TKI drugs are in clinical trials. All patients with EGFR-TK mutations develop acquired resistance to TKIs. A second mutation in T790M is the most common mechanism of developing resistance to EGFR-TKIs and accounts for resistance in 50 to 60% of cases based on two large series using repeat biopsies at the time of progression after front-line treatment with TKIs (16, 17).

Crizotinib is an oral, small-molecule ATP competitive inhibitor of ALK and c-MET that inhibits phosphorylation of the TK domain, which blocks signaling in a number of cell pathways critical to growth and survival (12, 18, 19). Crizotinib is the first in class ALK-TKI, but additional drugs are in development.

PHARMACOKINETICS

The usual oral dose of erlotinib is 150 mg once a day. Erlotinib is best absorbed on a full stomach (almost 100%). Approximately 60% absorption occurs on an empty stomach. The metabolism is hepatic primarily via cytochrome (CYP)3A4 (erlotinib: Lexicomp drug information) (20, 21). Excretion is mainly in the feces, with less than 10% in the urine. Dose adjustment is usually not necessary with renal impairment if the patient is euvolemic, but clinical judgment should be used. No dose

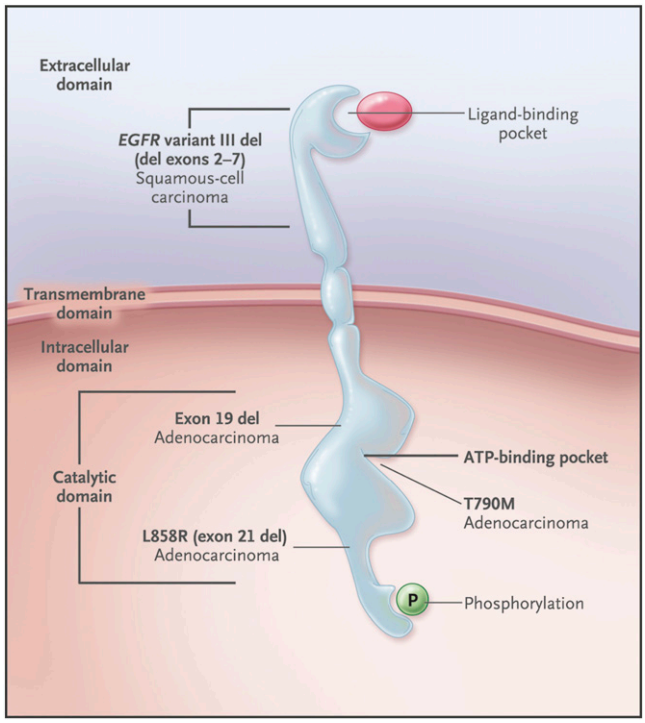

Figure 1. Epidermal growth factor receptor (EGFR) with extracellular domain and intracellular tyrosine kinase domain. Exon 19 deletion and L858R point mutation in exon 21 are the two major sensitizing mutations. These mutations are associated with increased sensitivity to EGFR tyrosine kinase inhibitors gefitinib and erlotinib. Mutations in T790M are associated with acquired resistance to these drugs. EGFR variant III mutant deletions occur in extracellular domain and are associated with squamous cell cancer. Figure reproduced with permission from Reference 59.

adjustment is needed with moderate hepatic impairment (22). For patients with total bilirubin greater than three times the upper limit of normal, its use is not recommended. The cerebral spinal fluid penetration rate of erlotinib with a standard dose of 150 mg in patients with central nervous system (CNS) metastases was 5.1% and exceeded the median inhibitory concentration of erlotinib in intact tumor cells (23); this result indicates that it can be used in the appropriate patient population with CNS metastases. Pharmacokinetic studies in patients with malignant pleural effusions show essentially 100% penetration from plasma to pleural effusions by Day 8 of treatment (24).

The usual oral dose of crizotinib is 250 mg twice daily. It may be taken with or without food. The metabolism is mainly hepatic via CYP3A4/5. It is largely excreted in the feces, with approximately 20% excreted in the urine (crizotinib: Lexicomp drug information) (25). No dosage adjustment is needed for mild to moderate renal impairment, but data are not available on dosage adjustment for patients with creatine clearances less than 30 ml/min. Similarly, data are insufficient on dosage adjustment in patients with hepatic impairment. Cerebral spinal fluid penetration is generally low and therefore precludes treatment of CNS disease with standard doses (26, 27).

PHARMACODYNAMICS

Normal epithelial cells have receptors of the ErbB family, including EGFR (15). EGFR expression has been identified in a number of cancers, especially NSCLC. Skin expresses EGFR, and early studies have suggested that the presence and degree of skin rash could be used as a surrogate marker of clinical benefits for erlotinib and gefitinib (20).

Recent studies have evaluated EGFR expression in tumors by immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and mutational analysis. Sensitizing mutations of EGFR are the most reliable predictor of response to erlotinib or gefitinib (11, 28).

ALK is a transmembrane receptor TK. Human expression in adults occurs in small intestine, testes, and nervous system (28). ALK fusion was first discovered in anaplastic large cell lymphoma. Crizotinib is a multitargeted TKI with the ability to block ALK phosphorylation in ALK fusion–positive NSCLC. Identification of ALK fusion is based on FISH with the ALK break-apart (or split signal) probe. Due to the high cost of the FISH assay, recent investigators have advocated the use of screening for ALK with IHC. If there is any signal based on IHC, then confirmation with FISH is the "gold standard" in the United States (29).

CLINICAL USE

The National Cancer Institute of Canada trial with erlotinib (BR.21) in previously treated stage IV NSCLC reported a 9% response rate and an overall survival of 6.7 versus 4.7 months with placebo alone. Based on this trial, the FDA approved erlotinib for second-line treatment of NSCLC (31). However, this trial was conducted before the discovery of the sensitizing mutations in EGFR and was performed on an unselected patient population. Trials with combining erlotinib and chemotherapy did not demonstrate increased benefit over chemotherapy alone (32, 33).

The I-PASS trial, a practice-changing study, was conducted in Asia by Mok and associates (6). They enrolled light or never smokers with stage IV adenocarcinoma of the lung from the Asian population to enrich for a population with a high frequency of EGFR-sensitizing mutations. Participants were randomized to gefitinib alone or to carboplatin and paclitaxel. In the subgroups of 261 patients with EGFR-sensitizing mutations, the progression-free survival was significantly longer among patients receiving gefitinib than among those receiving chemotherapy (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.36–0.64). In participants whose tumors were negative for EGFR mutations, the progression-free survival was significantly longer in those receiving chemotherapy rather than gefitinib (HR for progression or death with gefitinib, 2.85; 95% CI, 20.05–3.98). This was the first trial demonstrating the importance of determining the EGFR mutational status before initial treatment (7). Subsequently, there have been multiple trials around the world demonstrating superior progression-free survival and quality of life with initial treatment of gefitinib or erlotinib as compared with platinum-based doublet therapy in individuals with sensitizing somatic mutations in EGFR (34–37) (Table 1).

A study from Spain tested over 2,000 patients with advanced-stage NSCLC and identified EGFR mutations in 16.6% (38). The frequency of EGFR mutations in East Asian patients with NSCLC is approximately double that of Caucasian patients. A recently reported European trial randomized participants with advanced-stage NSCLC and EGFR mutations (Exon 19 deletion or L858R mutation in Exon 21) and no prior therapy (37). Treatment was with oral erlotinib 150 mg/d or intravenous chemotherapy with cisplatin 75 mg/m^2 plus docetaxel 75 mg/m^2 both on Day 1 every 3 weeks. Enrollment was halted early at a preplanned interim analysis. The progression-free survival was 9.7 months in the erlotinib group compared with 5.2 months

TABLE 1. RANDOMIZED STUDIES COMPARING EGFR TKI WITH CHEMOTHERAPY IN PATIENTS WITH EGFR MUTATION

Authors	Study	EGFR TKI	Number of Patients	Tumor Response Rate (%)	Median PFS* (mo), HR (95% CI)	Median OS* (mo), HR (95% CI)
Mok *et al.* (7)	IPASS	Gefitinib	261	71.2 vs. 47.3	9.8 vs. 6.4; HR, 0.48 (0.36–0.64; $P < 0.001$)	21.6 vs. 21.9; HR, 1.00 (0.76–1.33; $P = 0.99$)
Mitsudomi *et al.* (34)	WJTOG 3405	Gefitinib	172	62.1 vs. 32.2	9.6 vs. 6.6; HR, 0.52 (0.38–0.72; $P < 0.0001$)	35.5 vs. 38.8; HR, 1.18 (0.77–1.83)
Maemondo *et al.* (35)	NEJ002	Gefitinib	228	73.7 vs. 30.7	10.8 vs. 5.4; HR, 0.32 (0.24–0.44; $P < 0.001$)	27.7 vs. 26.6; HR, 0.88 (0.63–1.24; $P = 0.31$)
Zhou *et al.* (36)	OPTIMAL	Erlotinib	154	83.0 vs. 36.0	13.7 vs. 4.6; HR, 0.16 (0.11–0.26; $P < 0.0001$)	22.7 vs. 28.9; HR, 1.04 (0.69–1.58)
Rosell *et al.* (37)	EURTAC	Erlotinib	173	58.1 vs. 14.9	9.7 vs. 5.2; HR, 0.37 (0.25–0.54; $P < 0.0001$)	19.3 vs. 19.5; HR, 1.04 (0.65–1.68)
Yang *et al.* (56)	LUX-Lung 3	Afatinib	345	56.1 vs. 22.6†	11.1 vs. 6.9; HR, 0.59 (0.43–0.78; $P = 0.0004$)	

Definition of abbreviations: CI = confidence interval; EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; EURTAC = European Tarceva (erlotinib) versus Chemotherapy; First-SIGNAL = First-Line Single Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; HR = hazard ratio; IPASS = Iressa Pan-Asia Study; NEJ = North East Japan; OPTIMAL = randomized phase III study comparing first-line erlotinib versus carboplatin plus gemcitabine in Chinese patients with advanced non–small cell lung cancer with EGFR-activating mutations; OS = overall survival; PFS = progression-free survival; WJTOP = West Japan Thoracic Oncology Group.

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*EGFR TKI vs. chemotherapy.

† LUX-Lung 3; response by independent review.

in the chemotherapy group (HR, 0.37; 95% CI, 0.25–0.54). These results are consistent with those reported by other investigators testing an EGFR-TKI (gefitinib or erlotinib) as initial therapy in patients with a sensitizing EGFR mutation. Current guidelines of the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend that individuals with NSCLC and an EGFR-sensitizing mutation should be treated initially with an EGFR-TKI (11).

Crizotinib is the only currently available ALK-TKI and is approved by the FDA only for use in patients whose NSCLC is FISH positive for ALK fusion. The first report of efficacy was based on an expanded phase I trial by Kwak and colleagues, who treated 82 patients with advanced ALK-positive disease (18). Almost all patients had received prior treatment, and most had received two or more prior therapies. They observed a 57% overall response and 33% with stable disease. At the time of the report, 63 of 82 patients were still on treatment. In an updated report, Camidge and associates detailed 143 ALK-positive patients with NSCLC with advanced-stage disease treated with crizotinib (12). An objective response was observed in 61% (95% CI, 52–69%). The median duration of response was 49 weeks, and the median progression-free survival was 9.7 months. Median overall survival data were not mature, but the 6- and 12-month survival rates were 88 and 75%, respectively. These survival results were similar to those reported by Shaw and colleagues (39). In their retrospective analysis, survival of 56 ALK-positive patients treated with crizotinib was similar (MST not reached [95% CI, 17 mo to not reached]) to 63 ALK-negative, EGFR-positive patients treated with an EGFR-TKI (MST, 24 mo) and superior to ALK-positive control subjects who did not receive crizotinib (MST, 20 mo) (39).

DOSING STRATEGIES

The standard adult dose of erlotinib is 150 mg orally once a day until progression of disease (20, 31). Dose reduction should be made in 50-mg decrements for toxicity. The drug may need to be stopped for a short duration to allow for recovery from toxicity and then restarted at the 100 mg dose. There have been reports of patients with EGFR-sensitizing mutations having a clinical response with doses as low as 50 and 25 mg/d. The main concern about these lower doses is that the CSF concentration of drug would be below the therapeutic level.

Concomitant use of CYP3A4 inhibitors such as azole antifungals, clarithromycin, protease inhibitors, and others may result in increased drug levels of erlotinib and associated toxicity. Conversely, CYP3A4 inducers (phenobarbital, phenytoin, rifamycin, St. John's Wort, etc.) may result in decreased drug levels that are subtherapeutic. Cigarette smoking has been shown to decrease drug levels (erlotinib: Lexicomp drug information).

The standard dose of crizotinib is 250 mg orally twice a day (12, 18). Initial dose reduction, based on toxicity, to 200 mg orally twice a day is recommended, with further reduction to 250 mg orally once daily if necessary. CYP3A4 inhibitors or inducers may have similar effects on drug levels of crizotinib as those described above for erlotinib.

Crizotinib generally has poor CSF penetration even at the current standard dose. A recent case report of high-dose crizotinib (600 mg once daily) plus high-dose pemetrexed (900 mg/m^2) demonstrated reduction in multiple CNS lesions (26). The contributory role of the high-dose crizotinib was not certain.

PHARMACOTHERAPY LUNG CANCER

Cost Effectiveness

An economic analysis was performed by the National Cancer Institute Canada Clinical Trials Group based on the BR.21 trial where patients were randomized to erlotinib or placebo after failing front-line therapy for advanced-stage NSCLC (40). This study was performed before EGFR mutational testing was available for patient selection.

The incremental cost-effectiveness ratio (ICER) was calculated as the ratio of incremental cost (in 2007 Canadian dollars) to incremental effectiveness in life years gained. The ICER for erlotinib treatment was $94,638 per life-year gained (95% CI, $52,359–$429,148). Based on this ICER, the authors concluded that erlotinib treatment for previously treated NSCLC was marginally cost effective (CE).

Investigators from the United Kingdom performed a CE analysis of erlotinib versus docetaxel for second-line treatment of advanced NSCLC (41). Erlotinib was associated with a reduction in total costs and improved outcomes (total quality-adjusted life years [QALYs], 0.24 vs. 0.21) compared with docetaxel. They concluded that, from a health economic perspective for treatment of patients with relapsed advanced-stage NSCLC in the United

Kingdom, erlotinib has advantages over docetaxel. In 2012, the National Institute for Health and Clinical Excellence in the United Kingdom evaluated erlotinib for front-line treatment of EGFR-TK mutation–positive patients with advanced NSCLC and approved it as a front-line treatment option (42).

Crizotinib was approved for use in ALK fusion patients with NSCLC by the FDA in 2011. The European Medicines Agency has also approved crizotinib use in ALK fusion patients. An early health economic modeling of cost per QALY was based on literature review and expert opinion (43). The CE of initial testing with FISH and then treating only those that are positive was estimated to be $106,707/QALY. However, when screening for ALK fusion is performed with IHC testing and then treating, the CE is $57,165/QALY. If one only tested those individuals with adenocarcinoma who were EGFR and KRAS wild type and were never smokers, then the CE for ALK-FISH scre would be $4,756/QALY (43). As more clinical results are reported with crizotinib, further CE analysis is anticipated. A decision by NICE on crizotinib for previously treated NSCLC with ALK fusion is scheduled for July 2013 (44). The average wholesale price for crizotinib in the United States is $12,400 per month.

Combination Therapy

Two large phase III trials have evaluated the addition of erlotinib to a platinum-based doublet chemotherapy in unselected patients with NSCLC (32, 33). The addition of erlotinib to chemotherapy did not prolong survival. Numerous randomized trials of single-agent EGFR-TKI (erlotinib or gefitinib) versus platinum-based doublet chemotherapy in patients with sensitizing mutations in EGFR have reported superior progression-free survival and response rates with single-agent TKI (7, 34–37) (Table 1). The phase III trial (TORCH) evaluated front-line erlotinib followed by second-line cisplatin and gemcitabine versus the same chemotherapy first line followed by second-line erlotinib. The patients had unselected NSCLC. The regimen of first-line erlotinib followed by chemotherapy was significantly inferior in terms of overall survival (45). No studies have shown that adding an EGFR-TKI to chemotherapy in patients with or without sensitizing EGFR mutation results in superior survival rates (Table 1).

Crizotinib is approved for use only as a single agent in patients with somatic ALK fusion. It has not been tested in combination with other chemotherapeutic agents. Based on the experience with EGFR-TKI, it is doubtful that crizotinib will be combined with standard chemotherapy. Trials combining it with other targeted agents are likely.

Measuring Effects and Outcomes

The standard measurements for lung cancer clinical trials are tumor response by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, progression-free survival, and overall survival (46). The RECIST criteria of response are dependent on measurement of tumor size, and methods of performing these measurements may vary among clinicians. In recent years, waterfall plots to measure individual patient tumor change from baseline have been increasingly used to assess responses for noncytotoxic agents (12, 47).

Progression-free survival has been shown to correlate with overall survival better than response rates in lung cancer trials. Progression-free survival is the primary endpoint of most randomized phase II or III trials. Response rates and survival are usually secondary endpoints (48).

A large percentage of patients with NSCLC survive long enough to receive second-line or third-line therapy, and a number of agents have been approved for second-line therapy in NSCLC (docetaxel, pemetrexed, and erlotinib). Accordingly, survival has proven to be a difficult endpoint in front-line chemotherapy trials for NSCLC due to crossover in subsequent lines of therapy. Quite often in phase III trials, participants receive second-line therapy with the agents in the comparator arm especially if the drugs are clinically available. This was true of many of the phase III trials comparing an EGFR-TKI with doublet chemotherapy.

Adverse events in clinical trials in oncology are recorded according to the common terminology criteria for adverse events. Version 4.0 is in use for all cancer treatment evaluation program protocols approved since October 2009 (49).

Adverse Effects

The toxicities with the EGFR-TKIs erlotinib and gefitinib are similar. The main toxicities are dermatologic and gastrointestinal. Gefitinib 250 mg/d was given to over 600 participants in the I-PASS trial (7). Skin toxicities were rash (66%), dry skin (24%), puritus (19%), and paronychia (14%). Most of these toxicities were mild or moderate (grade 1 and 2). Adverse events lending to death occurred in 3.8% of the patients. Gastrointestinal toxicity included diarrhea (47%), stomatitis (17%), nausea (17%), vomiting (13%), and constipation (12%). Most of the toxicities were mild to moderate. Four percent of diarrhea events were classified as severe or greater (Grade 3–5). Severe or greater neutropenia occurred in less than 4% of participants. Interstitial lung disease (ILD) events occurred in 16 patients (2.6%), of whom three died. Adverse events leading to discontinuation of gefitinib occurred in 6.9% and adverse events leading to death occurred in 3.8% of patients on gefitinib treatment.

In the EURTAC trial, erlotinib (150 mg/d) was administered to 84 patients with EGFR-sensitizing mutations (37). Rash (67%) and diarrhea (52%) were the most common toxicities. Grade 3 (severe) rash was observed in 13%, and grade 3 diarrhea was observed in 5%. A grade 3 elevation in aminotransferase occurred in two patients (3%). One patient had severe pneumonitis. No severe hematologic toxicity was noted. Eleven (13%) patients on erlotinib withdrew from treatment due to adverse events, and one patient died of treatment-related toxicity (hepatotoxicity). In the OPTIMAL trial in China, patients ($n = 83$) received erlotinib 150 mg/d, and increased alanine aminotransferase levels were the most common drug-related toxicity that led to adverse reduction ($n = 3$). and grade 3 toxicity occurred in two patients (36). No pulmonary toxicity was observed, and there were no treatment-related deaths.

ILD related to EGFR-TKIs has been well documented (49, 50). The FDA performed a detailed analysis of 50,000 patients treated with gefitinib, and the worldwide incidence of ILD was 1% (2% in Japan and 0.3% in the United States) (51). Patients with underlying pretreatment ILD are at greater risk of pulmonary toxicity with treatment (52). Erlotinib has also been associated with ILD in about 0.8% of patients (53).

In the largest review of crizotinib therapy, 149 patients were treated. A total of 144 (97%) patients experienced treatment-related toxicity, but most ($n = 108$) were reported to be grade 1 or 2 (12). The most frequent treatment-related adverse events were visual effects (64%), nausea (56%), diarrhea (50%), vomiting (39%), and/or constipation (28%). Rash was reported in 11% of subjects. Visual effects were Grade 1 (no grade 3 or greater) and consisted of light trails, flashes, or brief image persistence. These occurred at the edges of the visual fields. There were no permanent visual effects, and the drug did not need to be discontinued. Twenty-four percent ($n = 36$) of patients experienced grade 3 or grade 4 events that included neutropenia ($n = 9$), raised liver enzymes ($n = 6$), and pneumonitis ($n = 3$). Three

patients discontinued treatment due to adverse events. There were no treatment-related deaths.

Guidelines

- Therapy for patients with advanced NSCLC should be based on results of histology and molecular testing, preferably performed before treatment. Molecular testing should at least include testing for EGFR mutations and ALK fusions (11).
- Previously untreated patients with metastatic NSCLC and a sensitizing EGFR mutation should be treated front line with an EGFR-TKI (erlotinib or gefitinib) alone.
- Previously untreated patients with metastatic NSCLC and an ALK fusion should be treated front line with single-agent crizotinib.
- For patients initially treated with chemotherapy and subsequently discovered to contain a sensitizing EGFR mutation or ALK fusion, consideration should be given to subsequent treatment with erlotinib/gefitinib (EGFR mutation) or crizotinib (ALK fusion). The timing of the switch to a TKI is an area of uncertainty but should occur if the patient develops progressive disease (54).
- ILD is a toxicity of treatment with TKI in a small percentage of cases. Underlying ILD is a predisposing factor for pulmonary toxicity and is a relative contraindication to usage of a TKI.

Future Developments

Multiple irreversible EGFR-TKIs are undergoing clinical trials. Perhaps the furthest in development is afatanib (55, 56). It has demonstrated activity in front-line therapy of patients with sensitizing EGFR mutations, but it is uncertain if it is more active and/or less toxic than erlotinib or gefitinib. Those trials are underway. At least two other irreversible inhibitors, dacomitinib and neratinib, are in phase III trial testing. A large number of other EGFR-targeted biologic therapies are in various phases of clinical trials (55). ROS1 receptor TK chromosomal rearrangements have recently been shown to respond to crizotinib treatment (57). Similarly, there are at least four small-molecule ALK inhibitors that are in phase I/II testing. It is too early to predict if any of these will challenge the current status of crizotinib in ALK fusion–positive NSCLC (55, 58).

Author disclosures are available with the text of this article at www.atsjournals.org.

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