Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Advanced Non-Small Cell Lung Cancer

A paradigm shift in stage IV non-small cell lung cancer treatment

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Abstract

Epidermal growth factor receptor (*EGFR*) mutations act as oncogenic drivers in the cellular signal transduction pathway and induce downstream activation of several key cellular events involved in cellular proliferation and survival. This review is aimed at summarizing the existing knowledge on the role of EGFR in cellular signal transduction, how *EGFR* mutations act as oncogenic drivers in advanced non-small cell lung cancer (NSCLC), current clinical studies of approved EGFR tyrosine kinase inhibitors (TKIs) in the treatment of advanced NSCLC, the development of EGFR TKIs resistance and its management, and future directions in the field.

Key words: EGFR, TKIs, NSCLC, lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death in both men and women in the United States, and the median 5-year survival rate for lung cancer is 5% worldwide.[1] Lung cancer is divided into 2 major categories based on histological features: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which constitute 15% and 85% of lung cancer cases, respectively. Most patients with NSCLC are diagnosed with advanced and unresectable disease (stage IIIB or IV). If left untreated, these patients have a median survival of less than 6 months. The initial standard treatment regimen usually includes a doublet of platinum agents and a taxane. In a landmark study of 1207 patients with advanced NSCLC, treatment with any of 4 doublets resulted in similar outcomes in radiological response (19%) and overall survival (OS; 7.9 months).[2] One promising strategy to improve survival in these patients involves targeting the epidermal growth factor receptor (EGFR) in advanced NSCLC.

In 1986, Stanley Cohen won the Nobel Prize for his discovery of the epidermal growth factor.[3] Its receptor was isolated in 1988 when Mendelsohn and colleagues first suggested EGFR as an anticancer target.[4] It was not until May 2004 that 2 pivotal studies showed the correlation between somatic mutations in the kinase domain of EGFR and the strong response of advanced NSCLC to EGFR tyrosine kinase inhibitors (TKIs).[5,6] These landmark studies opened a new chapter of targeted therapy and a new treatment paradigm in the management of advanced NSCLC.

The Biology of *EGFR* Mutations and Their Role in Intracellular Signaling

EGFR, also referred to as ErbB1, is 1 of 4 receptors collectively described as the receptor tyrosine kinases (RTKs) of the ErbB family. Other members of this family of receptors include ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). All have a common structural architecture comprising an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity for signal transduction. The binding of its ligand to EGFR initiates a cascade of intracellular signaling that ultimately leads to the expression of the cellular effects in the form of cell proliferation and survival.

EGFR mutations as a major and potent oncogenic driver of advanced NSCLC were first described independently by Lynch et al[5] and Paez et al[6] when gefitinib, one of the first EGFR TKIs designed to target the intracellular tyrosine kinase domain of EGFR, was demonstrated to cause dramatic tumor reduction in selected patients with *EGFR* mutations.

The 2 most common *EGFR* mutations in NSCLC are the L858R mutation in exon 21 and the exon 19 deletions. Both are drug-sensitizing mutations and together represent 85% to 90% of *EGFR* mutations in lung cancer. Exons 18 to 21 encode a portion of the tyrosine kinase domain of EGFR, and the most common alteration occurs as a T to G mutation at nucleotide 2,573 in exon 21, leading to substitution of arginine for leucine at position 858 (L858R). In the exon 19 deletants, there is a deletion of 4 amino acids (LREA).[5]

The biochemical mechanism of EGFR kinase domain mutation activation results from an increased and sustained duration of receptor activation (gain-of-function) by the ligands compared with wild-type *EGFR*.[5] Kinetic analysis of the purified intracellular domain of *EGFR* L858R and a representative deletion mutant showed that both mutants displayed a higher Michaelis con-

stant (Km) (substrate concentration at which the reaction rate is half of V_{max}) for ATP and a lower dissociation constant (Ki; the measure of ligand binding affinity) for erlotinib relative to the wild-type receptor, leading to a 100-fold difference in sensitivity to EGFR TKIs.[7,8] Mutations in the EGFR tyrosine kinase are observed in approximately 15% of NSCLC adenocarcinomas in the United States and occur more frequently in women and nonsmokers.[9] The incidence in East Asian populations is 22% to 62%.[10]

EGFR mutations with del 19 and L585R are referred to as gain-of-function mutations because they cause activation of the EGFR signaling pathway in the mutant *EGFR*-positive oncogenic cells, and some of these mutations also lead to greater sensitivity to EGFR TKIs compared with cases with wild-type EGFR. Resistance mutations also occur either de novo or following prolonged exposure to EGFR TKIs. Examples of the primary resistance *EGFR* mutations include the *KRAS, PTEN,* and *BRAF* mutations, all of which confer resistance to EGFR TKIs in NSCLC tumors with these mutations**.** The T790M mutation in the *EGFR* gene can be either primary or acquired, while *MET* amplification and epithelial-mesenchymal transition (*EMT*) are both acquired mutations conferring resistance to EGFR TKIs.

Other mutations in advanced NSCLC tumors are collectively described as uncommon *EGFR* mutations of unknown clinical significance; their number is small compared with the well-described *EGFR* mutations of clinical significance. These mutations in the *EGFR* involve amino acid substitution in E709, G719, S768, L861, and others. Their association to the effectiveness of the EGFR TKI is currently not well understood.[11,12] However, a recent study by Wu et al[13] showed that mutation on G719 and L861 comprised a major part (28 of 62) of the uncommon mutations and were associated with a favorable effectiveness of EGFR TKIs, while mutations other than these 2 led to a worse response to EGFR TKIs. This study concluded that uncommon *EGFR* mutations constitute a distinct part of the whole group of *EGFR* mutations, that their composition was heterogeneous, and that their association with EGFR TKIs differed.[13]

Diagnostic Testing in *EGFR* Mutation–Positive NSCLC

Since the discovery of *EGFR* mutations and other clinically significant molecular aberrations in NSCLC, a number of diagnostic tests have been developed to assay for these genomic alterations. As advancement in this field had culminated in the development of multiple highly sophisticated genomic sequencing technologies, it is imperative to have a firm understanding of the various options and the institutional guidelines available in selecting the appropriate test in the office practice. In an October 2014 press release, the American Society of Clinical Oncology (ASCO) announced its endorsement of the clinical practice guideline on molecular testing for selection of patients with lung cancer for therapies targeting EGFR and anaplastic lymphoma kinase (ALK), developed by the joint College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP).

The guidelines recommend that testing should be offered at the time of diagnosis for patients with advanced NSCLC or recurrence regardless of tumor size or patient characteristics, such as gender, race, and smoking status. Although the guideline did not identify a specific testing platform, it recommends against assays that utilize immunohistochemistry (IHC) for *EGFR* and *EGFR* copy number and mutation analysis, except for samples that are insufficient for molecular analysis. It also advises laboratories to set a minimal cellularity requirement during assay validation for EGFR testing and recommends that the exact method chosen should be able to identify *EGFR* mutations in samples with more than 10% tumor cells. For the detection of acquired resistance *EGFR* mutations such as T790M, the testing should be adequately sensitive in samples with more than 5% tumor cells. There was also stipulation placed on the operationalization for the testing laboratories to ensure that results are made available within 5 to 10 workdays, with transportation times of 3 days for external facilities and 24 hours for institution-based laboratories.[14] The guidelines also recommend molecular testing for *ALK*-rearrangement in all patients with advanced NSCLC to ensure that all patients who are candidates for ALK-targeting therapies, such as crizotinib and certinib, are identified.[14] The currently available range of molecular testing platforms for EGFR testing in laboratories include Sanger sequencing, IHC, multiplex hotspot mutation testing, multiplex sizing assays, and next-generation sequencing.[15]

EGFR TKIs in the Treatment of NSCLC

Clinical oncologists have traditionally made treatment decisions based on the histology of lung tumors, distinguishing NSCLC from SCLC. In 2003, gefitinib, a first-generation EGFR TKI, received accelerated approval from the FDA as a second-line treatment for advanced NSCLC after two phase 2 trials (IDEAL-1 and -2) in chemotherapy-refractory patients demonstrated a response rate (RR) of 10% in Caucasian cohorts and 28% in Japanese cohorts.[16,17] Overall survival was 6 to 8 months in unselected patients.

Erlotinib was approved in 2004 after a phase 3 trial (BR.21) demonstrated that erlotinib monotherapy conferred a 2-month survival benefit over best supportive care (BSC) in patients with chemotherapy-refractory advanced NSCLC, with a RR of 9% in the erlotinib arm and less than 1% in the placebo arm.[18] Following the work of Lynch et al[5] and Paez et al,[6] who independently demonstrated *EGFR* mutations in some of the gefitinib responders, the apparently low RR in these studies was demonstrated to be related to the low incidence of *EGFR* mutations in the unselected patient populations. These studies demonstrated that the target of EGFR TKIs is *EGFR* with either a deletion

in exon 19 or a point mutation in exon 21, not in the wild-type receptor. Multiple phase 2 studies have confirmed the efficacy of the EGFR TKIs as second- and third-line therapy for *EGFR* mutation–positive NSCLC, and tumor response rates were shown to be consistently well over 60% independent of age, gender, and ethnicity.[19-21] A number of other phase 3 studies have validated the use of EGFR TKIs as first-line therapy in advanced NSCLC.[22-28]

EGFR TKIs as First-Line Therapy

The role of EGFR TKIs as first-line therapy in patients with *EGFR*-mutated advanced NSCLC was confirmed by the results of the randomized phase 3 IPASS (Iressa Pan-Asia) study.[23] In this trial, patients were enrolled based on clinical features to ensure good representation of the patient population with activating *EGFR* mutations, and tumor samples were analyzed retrospectively for presence or absence of *EGFR* mutations. *EGFR* mutation was confirmed as a predictive biomarker for response to EGFR TKIs by the results of this trial. Tumor RRs in patients with *EGFR* activating mutations were 71.2% in the gefitinib group compared with 47.3% in the chemotherapy arm, and were statistically significant (P <.001). The primary end point of progression-free survival (PFS) was significantly prolonged in the gefitinib treatment group (9.8 vs 6.4 months; hazard ratio [HR] = 0.48; P <.0001). An OS benefit could not be accounted for in the study because the majority of patients treated with first-line chemotherapy were crossed over to the gefitinib group at the time of progression.

The superiority of EGFR TKIs over standard platinum-based doublet chemotherapy was further supported by subsequent multiple trials that enrolled only patients with activating *EGFR* mutations and randomized them to either an EGFR TKI or chemotherapy (**Table**). Significantly higher RRs and prolonged PFS occurred consistently across all of the randomized studies, offering further support to the efficacy of EGFR TKIs as a standard treatment for patients with advanced NSCLC with *EGFR* mutations.

Afanitib, a second-generation TKI approved by the FDA in July 2013, is an irreversible EGFR TKI and is used as a first-line treatment option for patients with advanced NSCLC with *EGFR*

TABLE. Treatment Outcomes in EGFR-Mutated NSCLC: EGFR TKIs or Chemotherapy

Authors	Study	Arm	# of Patients	Tumor RR (%)	Median PFS (months)
Mok et al[23]	IPASS	Gefitinib vs Carbo/Paclitaxel	261	71.2 vs 47.3	9.8 vs 6.4
Han et al[27]	First-SIGNAL	Iressa vs Gem/Cis	42	84.6 vs 37.5	8.4 vs 6.7
Maemondo et al[73]	NEJ02	Gefitinib vs chemotherapy	114	73.7 vs 30.7	10.8 vs 5.4
Mitsudomi et al[28]	WJTOG 3405	Gefitinib vs Cis/Docetaxel	86	62.1 vs 32.2	9.2 vs 6.3
Zhou et al[20]	OPTIMAL	Erlotinib vs chemotherapy	154	83.0 vs 36.0	13.1 vs 4.6
Rosell et al[21]	EURTAC	Erlotinib vs chemotherapy	175	54.5 vs 10.5	9.4 vs 5.2
Sequist et al[24]	LUX-Lung 3	Afatinib vs Cis/Pemetrexed	345	56 vs 23	11.1 vs 6.9
Wu et al[25]	LUX-Lung 6	Afatinib vs Gem/Cis	364	66.9 vs 23	11.0 vs 5.6

Cis indicates cisplatin; Carbo, carboplatin; Gem, gemcitabine; EURTAC, Erlotinib versus Standard Chemotherapy as First-line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer; FIRST-SIGNAL, First-line Single Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; IPASS, Iressa Pan-Asia Study; LUX-Lung 3, Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations; LUX-Lung 6, a Randomized, Open Label, Phase III Study of Afatinib Versus Gemcitabine/Cisplatin as First-line Treatment for Asian Patients With EGFR Mutation-Positive Advanced Adenocarcinoma of the Lung; NEJ, North East Japan; OPTIMAL, Randomised Phase III Study Comparing First-line Erlotinib versus Carboplatin Plus Gemcitabine in Chinese Advanced Non-Small-Cell Lung Cancer Patients with EGFR Activating Mutations; PFS, progression-free survival; RR, response rate; WJTOG, West Japan Thoracic Oncology Group.

mutations. It covalently bonds with the ATP binding sites of the tyrosine kinases, causing permanent inhibition to the site, and also has inhibitory effect on the HER2 receptor.

In a combined report of the phase 3 randomized LUX-Lung 3 and LUX-Lung 6 trials presented recently at the 2014 Multidisciplinary Symposium in Thoracic Oncology in Chicago by Sequist et al,[29] first-line afatinib was shown to improve OS in patients with advanced NSCLC with *EGFR* exon 19 deletion. In these trials, both of which shared the same design and methodology, patients with stage IIIB and IV NSCLC *EGFR*-positive mutations were randomized 2:1 to receive oral afatinib at a daily dosage of 40 mg or up to 6 cycles of pemetrexed/cisplatin in the LUX-Lung 3 trial and gemcitabine/cisplatin in the LUX-Lung 6 study. Randomization was stratified for both studies based on the mutation type (Del19/L858R/other), with 89% of patients in each trial possessing either del19 or L858R and 11% of patients having uncommon mutations. The patient population (N = 345) in the LUX-Lung 3 trial was stratified by race (Asian/non-Asian), with the non-Asians recruited from Europe, South America, and Australia. For the LUX-Lung 6 trial, the patient population (N = 364) was predominantly Chinese. The primary end point for both trials was PFS, which previously reported data showed was met by both trials.[24, 25] Secondary end points include OS, disease control rate (DCR), patient-reported outcome, and objective response rate (ORR). Median follow-up for OS was 40.9 months and 33.7 months for the LUX-Lung 3 and LUX-Lung 6 trials, respectively. The HR for OS was 0.78 (95% CI, 0.58-1.06; *P* =.109) versus pemetrexed/cisplatin and 0.83 (95% CI, 0.63-1.09; *P* = .176) versus gemcitabine/cisplatin. Results within the mutation subgroup were consistent between both trials. In the analysis of common mutation, OS improved in patients with *EGFR* del19 regardless of their race.

Data from LUX-Lung 3, comprising a global population, show a median OS of 33.3 months with afatinib versus 21.1 months with chemotherapy (HR = 0.54; 95% CI, 0.36-0.79). In LUX-Lung 6, comprising a primarily Asian population, the median OS was 31.4 months with afatinib compared with 18.4 months in the chemotherapy arm (HR = 0.64; 95% CI, 0.44-0.94). In LUX-Lung 3, the non-Asian population had a median OS of 33.6 months with afatinib compared with 20.0 months in the chemotherapy group (HR = 0.45; 95% CI, 0.21-0.95; *P* = .03). No significant difference in OS was seen in patients with L858R mutations between the afatinib and chemotherapy arms. However, the study authors concluded that despite the lack of clear differentiating factors between the regimens, afatinib remains a treatment option with *EGFR* L858R mutations, and that going forward, patients with these 2 mutations can no longer be grouped together in the same study because patients with del19 and L858R mutations behave quite differently.[29]

In an effort to determine which of the 3 currently available EGFR TKIs are best for treatment of advanced NSCLC with positive *EGFR* mutations, a phase 2 randomized study, LUX-Lung 7, is currently ongoing comparing afatinib with gefitinib as first-line therapy for patients with either exon 19 deletion or L858R mutations. Accrual for the study is completed, and results are pending.

EGFR TKIs as Second-Line Therapy

Prospective data comparing first- and second-line EGFR TKIs in patients with advanced NSCLC with activating *EGFR* mutations are limited and are usually based on single-arm studies. The largest of these prospective studies is the Spanish Lung Cancer Study Group, which reported on 113 chemotherapy-naïve and 104 chemotherapy-refractory patients.[17] In this trial, the tumor RR was 73.5% in the chemotherapy-naïve group and 67.4% in the chemotherapy-refractory arm, and the PFS was nearly the same between the groups (14 vs 13 months).

Another small prospective single-arm study from Japan, which evaluated the efficacy of first- and second-line EGFR TKIs, reported a RR of 77.8% in chemotherapy-naïve and 50% in chemotherapy-refractory patients.[30] Other data supporting the use of EGFR TKIs as second-line treatment came from a subgroup analysis of large randomized trials. For example, both the ISEL (Iressa Survival Evaluation in Lung Cancer) study and BR.21 (National Cancer Institute of Canada bronchogenic carcinoma study number 21) were conducted in unselected patient populations after progression on 1 or 2 lines of therapy. Patients were randomized to either an EGFR TKI or BSC.[18,31] In the ISEL study, only 26 patients with mutant *EGFR* received gefitinib, and the RR was 37.5%, while in the BR.21 study, 40 patients with the *EGFR* mutation treated with erlotinib showed a RR of 27%.

A recent study, the TAILOR trial (Tarceva Italian Lung Optimization Trial), compared the efficacy of erlotinib in patients with wild-type *EGFR* with that of docetaxel as a second-line therapy.[32] In this trial, patients with wild-type *EGFR* NSCLC at progression and who were previously treated with a first-line platinum-based regimen, were randomized to receive either erlotinib or docetaxel until disease progression or unacceptable toxicity occurred. Of the 222 patients evaluated (112 for erlotinib vs 110 for docetaxel), the median OS was 8.2 months (95% CI, 5.8-10.9) with docetaxel versus 5.4 months (range, 4.5-6.8 months) with erlotinib (adjusted HR = 0.73; 95% CI, 0.53-1.0; *P* = .05). PFS was significantly better with docetaxel than with erlotinib: median PFS was 2.9 months (95% CI, 2.4-3.8) with docetaxel versus 2.4 months (range, 2.1-2.6 months) with erlotinib (adjusted HR = 0.71; 95% CI, 0.53-0.95; *P* = .02). The study concluded that chemotherapy as a second-line therapy is more effective than erlotinib in previously treated patients with advanced wild-type *EGFR* NSCLC.

EGFR TKIs in Combination With Chemotherapy

Initial attempts to employ EGFR TKIs in combination with

FIGURE. EGFR Signaling Pathway

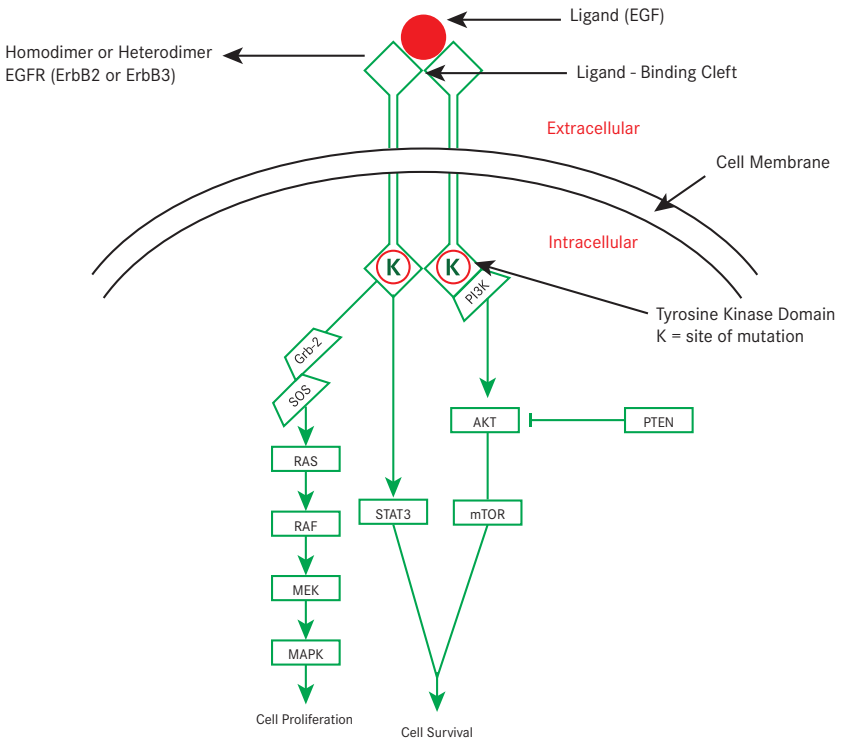

Figure showing the signaling pathway. TKIs block signaling at the tyrosine kinase domain (k). Resistance to TKIs occur when activating mutations occur downstream in KRAS or BRAF.

chemotherapy resulted in poor outcomes; multiple randomized studies that compared the combination of a platinum-based regimen plus an EGFR TKI with chemotherapy alone demonstrated a lack of benefit in the combination therapy group in unselected patient populations.[33-35] Due to the absence of detailed biomarker analysis from these studies, it was not clear whether the absence of benefit was related to the enrollment of a large number of patients with *EGFR* wild-type NSCLC who would derive minimal benefit from EGFR TKIs.

Preclinical studies were carried out to explore the possibility of a negative interaction between EGFR TKIs and chemotherapy when given concurrently. It was revealed in one of the studies that in NSCLC cell lines with activating mutant *EGFR* L858R, gefinitib caused apoptosis, while it only induced G1 cell cycle arrest in the wild-type *EGFR* cell lines.[36] The investigators speculated that this was due to the protective effect conferred on the accumulated tumor cell lines in the G1 phase by the EGFR TKIs, protecting them from the action of chemotherapy, which specifically targets cells in the S or G2 and M phases of the cell cycle. Other preclinical studies in NSCLC cell lines have shown the need for sequential administration of EGFR TKIs and chemotherapy by demonstrating that concurrent administration of erlotinib and an M phase–specific taxane results in lower levels and a sustained shorter duration of apoptosis when compared with the sequence of taxane followed by erlotinib.[37, 38]

In a retrospective analysis in the TRIBUTE trial (a phase 3 study of erlotinib combined with paclitaxel and carboplatin), patients with wild-type *EGFR* tumors who received combination erlotinib and chemotherapy had higher rates of progressive disease and inferior survival compared with patients who received chemotherapy alone.[39] This was also true for patients with activating *EGFR* mutations who received combination therapy or chemotherapy alone.

Based on the results of TRIBUTE, 2 studies were launched in Asia to investigate the role of intercalated chemotherapy with erlotinib. The first was FASTACT (First-line Asian Sequential Tarceva and Chemotherapy Trial), a multicenter randomized, placebo-controlled, phase 2 trial comparing the intercalated combination of chemotherapy (gemcitabine 1250 mg/m^2 on days 1 and 8) and erlotinib (days 15-28) with chemotherapy alone in unselected patient populations with advanced NSCLC.[40] Results from the study showed a significantly improved PFS (HR = 0.57; log-rank P = .018). FASTACT 2, a phase 3 trial, was based on the result of FASTACT with the same study design (N = 451).[41] Approximately 85% of patients in the placebo group received second-line erlotinib on progression; this ensured that the *EGFR* mutation–positive subgroup had adequate exposure to an EGFR-TKI. Results from this trial showed the median PFS was 7.6 months in the combination group compared with 6.0 months in the chemotherapy alone group (HR 0.57; 95% CI, 0.47- 0.69; P ≤.0001). The median OS was 18.3 months versus 15.2 months (HR 0.79; 95% CI, 0.64- 0.99; P = .042), also favoring the combination group. Biomarkers analysis was done in 240 patients, and 97 (40%) had EGFR mutations. The survival benefit for the intercalated combination following subgroup

analysis was restricted to patients with activating EGFR mutations, but not patients with wild-type EGFR tumors. There was a remarkable improvement in the *EGFR* mutation–positive subgroup, with over 10 months of improvement in the median PFS and OS. These results will need further confirmation before the approach can be recommended outside of a formal clinical trial.

Resistance to EGFR TKIs

Primary resistance to EGFR TKIs occurs when tumors do not undergo significant shrinkage in response to gefitinib and erlotinib in EGFR TKI-naïve patients on first exposure. Multiple mechanisms are believed to be involved. One of these was demonstrated by Greulich et al[42] in a preclinical study and later reported by Wu et al[43] in retrospective clinical data, both demonstrating that tumors with exon 20 insertions are generally insensitive to EGFR TKIs. This occurs in less than 5% of patients with NSCLC. In about 20% of NSCLC cases, primary resistance is mediated by mutation in the KRAS signaling protein.[44] An *EGFR* mutation is more common in never-smokers, while the *KRAS* mutation is prevalent in former and current smokers; their occurrences are mutually exclusive. Other implicated but rare mutations in primary resistance to EGFR TKIs include *PTEN, MEK,* and *ALK*-fusion.[45-47]

Acquired resistance eventually develops in all patients with *EGFR* mutation–positive advanced NSCLC treated with gefitinib and erlotinib despite their substantial efficacies. Disease progression usually appears after about 1 year of treatment with either drug.[48,49] The most common acquired resistance results from the T790M mutation, in which a C to T change occurs at the nucleotide 2,369 in exon 20 leading to substitution of methionine for threonine at position 790. The T790M residue lies within the drug-binding cleft of the EGFR and is thought to impair binding of the TKIs to the ATP binding site.[50] As an alternative mechanism, Yun et al[51] suggested that the amino acids change could alter the relative affinity of ATP versus drug. The EGFR exon 20 T790M mutations constitute 50% to 65% of acquired resistance to EGFR TKIs, and overlapping mechanisms are rare.[52-54]

Another well-defined separate mechanism of acquired resistance to EGFR TKIs is the amplification of *MET*, the gene encoding a different membrane-bound RTK.[55] *MET* amplification occurs regardless of the T790M status, and its amplification in cells originally dependent upon mutant *EGFR* illustrates a phenomenon that can be described as "kinase switch," in which surviving *EGFR* mutation–positive oncogenic cells exposed to prolonged action of EGFR kinase inhibition develop resistance by becoming dependent on another kinase, such as MET. Analysis of tumor samples and follow-up studies from multiple independent patients with *EGFR* mutation–positive NSCLC suggests that the prevalence of *MET* amplification may be closer to 10%.[56]

Other rarer forms of acquired resistance that have been described but not completely understood include activating *PIK-3CA* mutation,[57] transformations to SCLC,[58] activation of insulin-like growth factor receptor pathway,[59] and epithelial-mesenchymal transition (EMT).[60] The exact frequencies of these mechanisms have not been completely established.

Management of NSCLC With Acquired Resistance to EGFR TKIs

One modality of treatment in acquired resistance to EGFR TKIs is the use of local therapies, including radiotherapy, local ablation, and surgery if the sites of progression are limited. In a study by Yu et al,[52] local therapy was offered to 18 patients who progressed on an EGFR TKI; they reported a median time to systemic therapy of 22 months and a median OS of 41 months. Another retrospective study of 65 patients with 4 or fewer sites of progression (so-called "oligoprogression") while on an EGFR TKI or ALK inhibitor showed that local therapy could allow continuation of the TKI for more than 6 additional months.[61] A prospective comparative study will be required, however, before a local therapy can be considered as standard treatment. For now, it serves as an option for selective patients.

For systemic progression, platinum-based doublet chemotherapy is the standard option for treatment in patients with EGFR TKI-resistant advanced NSCLC who are chemotherapy-naïve. When there is metastasis to the brain, radiotherapy is the standard therapy. In a retrospective study of patients who had exposure to both chemotherapy and TKIs after the development of resistance, there was improvement in tumor RR: 41% versus 18% in favor of the doublet chemotherapy compared with the TKI group, but no significant differences in PFS or OS.[62] Patients who received platinum-based chemotherapy and erlotinib had a tumor RR of 63% compared with 23% in patients treated with doublet chemotherapy alone. Another small, single-arm, prospective study from Japan in patients treated with pemetrexed in combination with erlotinib or gefitinib after development of acquired TKI resistance showed a tumor RR of 26% and a median PFS of 7 months.[63]

However, results of The IMPRESS study (IRESSA Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone),[64] a phase 3 randomized trial comparing combination pemetrexed/carboplatin and gefitinib with chemotherapy alone in *EGFR* mutation–positive patients who progressed on gefitinib, recently presented at the 2014 European Society for Medical Oncology (ESMO) Congress in Madrid, Spain, demonstrated no significant difference in RR and PFS (primary end point) between the treatment arms. The result showed an ORR of 31.6% for gefitinib versus 34.1% for chemotherapy alone. The disease control rate was 84.2% versus 78.2% respectively, and the median PFS was the same for both groups at 5.4 months.

The OS data are currently immature, with only 33% of required events; however, a preliminary report at the 2014 ESMO Congress was not encouraging either, with survival from time of randomization of 14.8 months with gefitinib versus 17.2 months with chemotherapy. The HR was 1.62, and the difference is potentially significant according to the report. No significant difference was observed between the treatments arms in rates of adverse events (AEs), serious AEs, and events leading to death. The report concluded that gefitinib should not be continued after disease progression by RECIST in patients with *EGFR* mutation–positive NSCLC on first-line gefitinib. A phase 2 study with a similar design is also currently in progress in the United States.

Another recently described EGFR TKI is AZD9291, a selective, third-generation EGFR TKI effective against EGFR TKI sensitizing and resistance T790M mutations in preclinical models. A phase 1 study presented at the 2014 ASCO Annual Meeting appears to show an encouraging outcome.[65] In this study, 199 patients with *EGFR* mutation–positive NSCLC with acquired resistance to EGFR TKIs were enrolled in a multicenter trial into dose escalation and expansion cohorts. Results as of January 16, 2014, in all evaluable patients, show a confirmed plus unconfirmed ORR (c+uORR) of 51%; RECIST responses were observed at all dosage levels and in brain metastasis. Among the 132 patients with centrally confirmed T790M mutation, the c+uORR in the 89 *EGFR* T790M-positive patients was 64% (95% CI, 53%-74%), and in the 43 *EGFR* T790M-negative patients, 23% (95% CI, 12%-39%). The overall DCR in T790M-positive patients was 96%. Among the 60 patients with confirmed response, 97% were ongoing at data cutoff and the longest duration of response as of the time of this report was more than 8 months. The conclusion from the report was that AZG9291 has an impressive efficacy and is well tolerated in patients with *EGFR* mutation–positive NSCLC with acquired resistance to EGFR TKIs. More trials on this agent, as well as trials of another T790M-targeting TKI (rociletinib, also known as CO-1686),[66] are currently ongoing. These third-generation TKIs may provide new options for acquired resistance to EGFR TKIs.

One other way of circumventing the effect of acquired resistance to EGFR TKIs currently under development is to indirectly target mutant *EGFR* by HSP90 inhibitors. HSP90 is a heat shock protein, which is required for stability and functioning of multiple signaling proteins that promote the growth and/or survival of cancer cells such as EGFR, MET, hepatocyte growth factor, and EML4/ALK. Analysis of the interaction between HSP90 and mutant *EGFR* has revealed that the mutant *EGFR* proteins are more dependent than their wild-type counterparts on HSP90 to fold properly; consequently, mutant *EGFR* is more sensitive to degradation following HSP90 inhibition with geldanamycins.[67] Further analysis of this mechanism has shown that HSP90 inhibitors induce stabilization or regression of T790M+ *EGFR* tumors by enhancing the degradation of the mutant receptor and sensitize *EGFR*-mutant tumors to paclitaxel.[68-70] So far, clinical data have been disappointing for HSP90 inhibitor IPI-504,[71] but many more agents are currently under various stages of clinical trials, for which preliminary reports are forthcoming.

Dual targeting of EGFR kinase domain in patients with an acquired resistance to EGFR TKIs is also being explored. One example is a recently reported result of a phase 1 dose escalation and expansion trial involving dual therapy with anti-EGFR monoclonal antibody cetuximab and afatinib.[72] In this study, an ORR of approximately 30% was reported; however, this optimistic result was tempered by the continued presence of toxicities, with as many as 69% and 77% of patients experiencing diarrhea and rash of any grade, respectively.

Future Directions and Conclusion

The past decade has seen an exciting paradigm shift in the management of advanced NSCLC with the development of gefitinib and erlotinib, the approval of a second-generation TKI, and third-generation TKIs currently undergoing various levels of clinical trials. The discovery of *EGFR* mutation as an important determinant of NSCLC response to TKIs has yielded a better outcome in patients with advanced NSCLC with *EGFR* mutations. This development has enabled clinicians to stratify patients according to the type of genetic mutations expressed by their NSCLC cells instead of their histological types alone, and this has made the prospect of personalized medicine more of a reality. With additional research in the study of tumor cell genomics and genetic abnormalities driving the growth of cancer cells, in the near future we hope to be able to characterize more patients according to the genetic expression driving the growth of their tumors and tailor their management by exploiting these mutations for therapeutic benefit in many more cancer types. Above all, there is an optimistic expectation that advanced-stage *EGFR*-positive NSCLC—even though it is incurable—may be managed as a chronic disease in the future.

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