This year marks the tenth anniversary of the approval of the EGFR inhibitor erlotinib for the treatment of non–small-cell lung cancer (NSCLC) and the discovery that activating EGFR mutations predict sensitivity to EGFR inhibitors. Together, these landmark advances in the molecular causation and treatment of NSCLC paved the way for additional targeted drugs with striking clinical activity in specific molecular subsets of NSCLC (e.g., ALK, ROS1, and RET fusions; BRAF mutations)—redefining the disease as a collection of heterogeneous cancers based upon specific molecular alterations. The recently published data from The Cancer Genome Atlas (TCGA) again demonstrate the great diversity in molecular alterations across lung adenocarcinomas. Consistent with previous studies, this analysis highlights that activating EGFR mutations (found in ∼10%–15% of tumors overall) represent the most frequent mutation in nonsmokers following mutations in TP53 (1).

For patients with metastatic nonsquamous NSCLC, testing for EGFR mutations is the standard-of-care used to select the best first-line therapy. The EGFR tyrosine kinase inhibitors (TKI) erlotinib (approved in the United States) and gefitinib (approved in Asia and Europe) have high rates of single-agent activity in EGFR-mutated cancers (∼60%).

More recently, afatinib (previously BIBW-2992), an irreversible ERBB family inhibitor (approved in Asia and Europe) and cetuximab (previously BIBW-2992), an irreversible ERBB family inhibitor (approved in Asia and Europe) have high rates of single-agent activity in EGFR-mutated cancers (∼60%). More recently, afatinib (previously BIBW-2992), an irreversible ERBB family inhibitor (approved in Asia and Europe) and cetuximab (previously BIBW-2992), an irreversible ERBB family inhibitor (approved in Asia and Europe) have high rates of single-agent activity in EGFR-mutated cancers (∼60%).

In this issue of Cancer Discovery, Janjigian and colleagues (5) report the results from the phase Ib clinical trial of afatinib combined with the monoclonal antibody cetuximab in 126 patients with or without T790M mutation after the development of acquired resistance to erlotinib or gefitinib. This study grew out of the authors’ preclinical work described above, and demonstrated that in a significant subset of patients, dual targeting of the EGFR pathway with afatinib plus cetuximab had measurable clinical activity. The results of this study—including an overall response rate of 29%—support the authors’ hypothesis and preclinical observation that a subset of EGFR-mutant cancers with acquired TKI resistance retain dependence on the EGFR pathway.
This phase I study was performed in three phases: (i) an initial dose-finding phase to establish the MTD; (ii) an expansion phase testing the MTD (afatinib 40 mg daily plus cetuximab 500 mg/m² every 2 weeks) in patients with prior erlotinib or gefitinib treatment (reported in this issue); and (iii) a sequential phase testing the addition of cetuximab after progression on first-line afatinib (ongoing). The protocol was amended to add additional patients (target n = 140) to the expansion phase based on early responses observed at the MTD.

Eligible patients included those with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, without untreated or symptomatic brain metastases, and without prior EGFR-targeting antibody therapy. Patients were allowed to continue on their EGFR TKI (erlotinib or gefitinib) up to 3 days before initiation of study drugs to prevent disease flare. All patients were required to have a post-TKI resistance biopsy within 30 days of enrollment, which was used to determine T790M status.

The 126 patients studied in the expansion phase were heavily pretreated. All patients had received and progressed on erlotinib or gefitinib. An additional 79% had at least one prior line of cytotoxic chemotherapy and 52% had received two or more lines of chemotherapy. At the time of enrollment, patients were a median of 2 years from their initial diagnosis (range, 4.5 months to 11 years). This suggests a population of patients with longer than average survival, even among EGFR-mutated NSCLC, and is likely the result of enrichment for T790M patients (57% of the cohort), given its association with more indolent disease progression (6). Consistent with this, the duration of previous erlotinib or gefitinib treatment was twice as long among T790M-positive patients (median of 2 years), as compared with 1 year in the overall population.

Overall response rates (RR) were 29%, with a median progression-free survival (PFS) of 4.7 months and median duration of confirmed overall response of 5.7 months. There were no statistically significant differences in response between T790M-positive (RR, 32%) and T790M-negative (RR, 25%) patients. Responses to the combination of afatinib plus cetuximab were directly correlated with the degree of prior response to EGFR TKI, with 80% of patients who had previously achieved a complete response to erlotinib or gefitinib demonstrating response to the combination.

Given the overlapping toxicities of afatinib and cetuximab (based on their shared target of EGFR), it was not surprising that high rates of toxicity were observed (99% of patients overall). In fact, almost half of the patients experienced grade 3 (44%) or grade 4 (2%) toxicities, and 2 patients died of treatment-related effects (dyspnea and pneumonitis). The most common treatment-related toxicities (all grades) included rash
(90%), diarrhea (71%), nail effects (57%), and stomatitis (56%). However, despite high rates of toxicity, only a minority of patients stopped treatment as a result of these drug-related adverse events. Moreover, 64% of patients were able to receive full-dose therapy, suggesting that the symptoms were relatively manageable, without requiring dose reductions.

The responses observed with the afatinib–cetuximab combination are in contrast with the LUX-1 lung trial that compared afatinib with placebo in a similar patient population. In this trial, RRs to afatinib were only 7%, with a markedly shorter PFS of 3.3 months, supporting the benefit of adding cetuximab to this combination (7). Interestingly, the efficacy of the combination seems to require afatinib—rather than a different EGFR TKI—given prior clinical data (as well as preclinical data) that failed to show a significant benefit of combining erlotinib with cetuximab (8). The activity of afatinib with cetuximab may rely, at least in part, on its inhibition of other HER family members, such as HER2 and HER4, and the authors report that investigation is ongoing into the potential role of HER2 amplification or other alterations that may be associated with patients’ responses in this trial.

There are practical considerations of whether insurance companies will pay for this combination and whether the addition of cetuximab will provide benefit after progression on first-line, single-agent afatinib. However, the afatinib–cetuximab combination will certainly become incorporated into clinical practice alongside other treatments for EGFR TKI–resistant disease. As such, it is important to address two critical questions. First, how do we select the best second-line targeted strategy for an individual patient; and second, what are the anticipated additional resistance mechanisms likely to develop for the afatinib–cetuximab combination?

Multiple strategies have been developed to address EGFR TKI–resistant disease, including the combination reported here (Fig. 1). One of the strategies furthest along in development is the use of third-generation irreversible EGFR TKIs that specifically bind the protein with T790M, which include AZD9291 (AstraZeneca) and CO-1686 (Clovis). Dramatic response rates have been reported for both of these compounds, which are currently in phase II trials for patients with confirmed T790M, along with low rates of the usual toxicities from EGFR inhibitors because of relatively low affinity of the compounds for wild-type EGFR.

Although the current study shows a strong signal of activity, we must keep in mind that a majority of patients (71%) still did not respond to afatinib–cetuximab. As the third-generation TKIs and other drugs materialize as options for the treatment of resistant disease, we will need to develop a biologically based biomarker strategy for selecting which of these treatments is likely to be the most effective for a given patient. On the basis of the current data, for example, we speculate that the third-generation TKIs may be favored for T790M–positive disease (given high RRs and low toxicity), with afatinib–cetuximab favored for non-T790M. Presumably, the pretreatment samples used to assess T790M in the current study will also allow for further scientific exploration of candidate predictive biomarkers, especially because T790M did not help in delineating a more sensitive patient population in this trial. Given the multiple mechanisms of disease resistance, optimal drug selection in EGFR TKI–resistant patients will likely require a multiplexed biomarker approach that incorporates screening for a combination of gatekeeper mutations, potential bypass tracks (e.g., MET amplification), EMT, or immune-escape markers.

This multiplexed approach is especially important for choosing individualized therapy because tumorigenesis and therapeutic resistance are dependent upon the tumor microenvironment and not simply tumor cell–intrinsic changes. Using preclinical models, it was recently demonstrated that tumor cell EGFR signaling produces an immunosuppressive tumor microenvironment (9). In both animal models and human cell lines, the expression of programmed death ligand 1 (PD-L1, B7-H1) was potentiated by EGFR mutation and ligand stimulation. Tumors from genetically engineered mouse models (EGFR exon 19 deletion, T790M/L858R, or T790M/deletion 19 genotypes) displayed increased FOXP3+ CD4+ T regulatory cells and suppression of the effector CD8+ T-cell population. Therapeutic treatment of the different EGFR-mutant model genotypes with anti–PD-1 antibodies reversed the immunosuppressive phenotype, and produced tumor shrinkage and survival benefit to the animals. In this setting, multiple clinical trials have been initiated to take advantage of concurrent or sequential combination therapies with EGFR TKIs and anti–PD-1 or anti–PD-L1 antibodies (e.g., NCT02088112).

In considering the second question (mechanisms of resistance to afatinib–cetuximab), we recognize that every successful targeted drug or drug combination leads, through selective pressure, to acquired resistance. Using the same preclinical models of EGFR-mutant lung cancer and samples of patient tumors treated with the combination, Pirazzoli and colleagues (10) have recently reported that upregulation of mTOR-dependent signaling drives resistance to the combination, whereas inhibition of mTOR signaling resestisntized cells to the combination therapy. The finding that mTOR is a non–EGFR-dependent mechanism of resistance in T790M tumors was confirmed by a second group of investigators (11). Even before the combination treatment has become a standard part of our arsenal, we have already gained insights into its potential weaknesses.

The rapid evolution of our thinking over the past 10 years about EGFR-mutant lung cancer continues to drive the development of new therapeutic options for patients. Importantly, these clinical advances are being driven by solid scientific investigation using preclinical models, analysis of patient tumors in TCGA-type efforts or from clinical trials, along with the testing of these ideas in well-designed clinical protocols. This combined investigative approach has been extended into other oncogenotypes (ALK, ROSI, RET, and KRAS mutations) to explore the basis for new treatment options and therapeutic resistance. Here, the authors demonstrate the potential of translating promising preclinical work rapidly into the clinic, dealing a blow to EGFR-TKI–resistant lung cancer with a “HER 1-2 punch” from afatinib–cetuximab.

Disclosure of Potential Conflicts of Interest

D.L. Gibbons has ownership interest in AstraZeneca. No potential conflicts of interest were disclosed by the other author.
Grant Support

L.A. Byers is supported, in part, by the R. Lee Clark Fellow Award (supported by the Jeane F. Shelby Scholarship Fund), the MDACC Physician Scientist Award, the NCI Cancer Clinical Investigator Team Leadership Award, and the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy’s Khalifa Scholar and Fellows Award. D.L. Gibbons is supported, in part, by the MDACC Physician Scientist Award and NCI K08-CA151651, and is an R. Lee Clark Fellow of The University of Texas MD Anderson Cancer Center, supported by the Jeane F. Shelby Scholarship Fund.

Published online September 2, 2014.

REFERENCES

A HER 1-2 Punch: Dual EGFR Targeting Deals Resistance a Deadly Blow

Don L. Gibbons and Lauren Averett Byers

Cancer Discovery 2014;4:991-994.

Updated version  Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/4/9/991

Cited articles  This article cites 10 articles, 6 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/4/9/991.full#ref-list-1

Citing articles  This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/4/9/991.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.