Accepted Manuscript

Driven by Mutations: The Predictive Value of Mutation Subtype in *EGFR*-Mutated Non–Small Cell Lung Cancer

Emily Castellanos, MD, Emily Feld, MD, Leora Horn, MD, MSc

PII: S1556-0864(16)33604-8

DOI: 10.1016/j.jtho.2016.12.014

Reference: JTHO 462

To appear in: *Journal of Thoracic Oncology*

Received Date: 22 August 2016

Revised Date: 12 December 2016

Accepted Date: 16 December 2016

Please cite this article as: Castellanos E, Feld E, Horn L, Driven by Mutations: The Predictive Value of Mutation Subtype in *EGFR*-Mutated Non–Small Cell Lung Cancer, *Journal of Thoracic Oncology* (2017), doi: 10.1016/j.jtho.2016.12.014.

Driven by Mutations: The Predictive Value of Mutation Subtype in *EGFR*-Mutated Non–Small Cell Lung Cancer

Short title: Mutation Subtypes in *EGFR*-Mutated NSCLC

Emily Castellanos, MD; Emily Feld, MD; Leora Horn, MD, MSc

Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN

Emily Castellanos, MD

Vanderbilt Ingram Cancer Center

2220 Pierce Avenue

777 Preston Research Building

Nashville, TN 37232

E-mail: Emily.hon@vanderbilt.edu

Fax: (888) 981-4318

Phone: 615-875-7874

Emily Feld, MD

Department of Medicine

1161 21st Avenue South

D-3100 Medical Center North

Nashville, TN 37232

E-mail: emily.feld@vanderbilt.edu

Fax: (615) 343-7550

Phone: (615) 322-3384

Corresponding author:

Leora Horn, MD, MSc

Vanderbilt Ingram Cancer Center

2220 Pierce Avenue

777 Preston Research Building

Nashville, TN 37232

Email: leora.horn@vanderbilt.edu

Fax: 615-343-7602

Phone: 615-322-2120

Sources of Support

Boehringer Ingelheim Pharmaceuticals, Inc.

Conflicts of Interest

EC: No conflicts of interest

EF: No conflicts of interest

LH: Consulted for Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Genentech, Merck, and Xcovery; received honorarium from Biodesix; received research funding from AstraZeneca

Abstract

Epidermal growth factor receptor (EGFR)-mutated non–small cell lung cancer (NSCLC) is a genetically heterogeneous disease that includes over 200 distinct mutations. The implications of mutational subtype for both prognostic and predictive value are being increasingly understood. While the most common *EGFR* mutations—exon 19 deletion or L858R mutations—predict sensitivity to EGFR tyrosine kinase inhibitors (TKIs), it is now being recognized that outcomes may be improved in patients with exon 19 deletions. Additionally, 10% of patients will have an uncommon *EGFR* mutation, and response to EGFR TKI therapy is highly variable depending upon the mutation. Given the growing recognition of the genetic and clinical variation seen in this disease, the development of comprehensive, bioinformatics-driven tools to both analyze response in uncommon mutation subtypes and inform clinical decision making will be increasingly important. Clinical trials of novel EGFR TKIs should prospectively account for the presence of uncommon mutation subtypes in study design.

Key words: lung cancer, targeted therapy, EGFR

Introduction

The advent of targeted therapy has revolutionized treatment for a subset of patients with non–small cell lung cancer (NSCLC), and testing newly diagnosed NSCLC patients for the presence of driver mutations is now considered standard of care.[1] The epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases that include EGFR/ERBB2 receptor tyrosine kinase 1 (ERBB1), HER2/ERBB2, HER3/ERBB3, and HER4/ERBB4.[2] When stimulated, the transmembrane receptors trigger a cascade of intracellular signaling that affects cellular proliferation, angiogenesis, and apoptosis.[2] Sensitizing *EGFR* mutations are the most common actionable driver mutations found in patients with NSCLC, and occur in approximately 10% of Caucasian patients and up to 50% of Asian patients.[3-5]

Mutations occur within the *EGFR* exons 18 to 21, which encode a portion of the EGFR kinase domain. Although approximately 90% of patients with *EGFR*-mutated NSCLC will have either deletions in exon 19 or substitutions of leucine for arginine (L858R) in exon 21 of the *EGFR* gene (the "common mutations"),[6-9] numerous other mutations with varying sensitivity to EGFR tyrosine kinase inhibitors (TKIs) have been identified. With some exception, most mutations involving exons 18, 19, and 21 are considered predictive of sensitivity to EGFR TKI therapy, while mutations in exon 20 are typically resistant.[10-19] This review focuses on the prognostic and predictive implications of *EGFR* mutation subtype.

Development of EGFR TKIs: a brief history

The first EGFR TKIs, erlotinib and gefitinib, were developed prior to the identification of *EGFR* somatic gene mutations, and were first studied in an unselected patient population.[20, 21] Erlotinib

received US Food and Drug Administration (FDA) approval for the treatment of patients with disease progression after initial chemotherapy on the basis of the National Cancer Institute of Canada Clinical Trials Group study BR.21, which demonstrated that erlotinib, compared with placebo, improved overall survival (OS; 6.7 vs 4.7 months, respectively); response rate (8.9% vs <1%, respectively); and tumor-related symptoms of pain, cough, and dyspnea.[20] A similar study in an unselected patient population, ISEL, compared gefitinib to placebo and showed nonstatistically significant trends in improved OS and time to treatment failure (TTF) that favored the gefitinib arm,[21] leading to the approval of gefitinib outside of the United States.

Although these initial trials were performed prior to the development of molecular testing, certain clinical features, including female gender, never or light smoking status, Asian ethnicity, and adenocarcinoma histology, were noted to be associated with increased chance of response and prolonged survival.[20, 21] Based on these data, the IRESSA Pan-Asia Study (IPASS) was designed to compare first-line gefitinib to carboplatin and paclitaxel in a clinically enriched patient population with metastatic NSCLC; tumor samples were retrospectively analyzed for the presence of *EGFR* mutation.[6] IPASS was the first trial to demonstrate an improvement in response rate and median progression-free survival (PFS) in patients with *EGFR* mutation–positive NSCLC treated with an EGFR TKI compared with chemotherapy (71.2% vs 47.3% and 9.5 months vs 6.3 months, respectively, with a hazard ratio [HR] for progression of 0.48).[22] Subsequent studies confirmed the *EGFR* mutation to be the most important predictor of benefit of response to therapy with an EGFR TKI.[22-28]

Options for first-line therapy were expanded with the approval of afatinib, an oral, irreversible ErbB-family blocker for first-line treatment of patients with metastatic NSCLC whose tumors have exon 19 deletion or L858R *EGFR* mutations (as detected by an FDA-approved test),[29] based on the results of 2 randomized phase III studies (LUX-Lung 3 and LUX-Lung 6).[8, 9] More recently, it has also been indicated for patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.[29] Preclinical data demonstrated that afatinib was active against EGFR T790M,[30] an acquired resistance mutation seen in approximately 50% of patients after progression on first-line EGFR TKI therapy.[31] In studies comparing erlotinib, gefitinib, and afatinib to chemotherapy in molecularly selected populations, all 3 of these agents have consistently demonstrated an improvement in PFS (though not OS in the intention-to-treat population), with PFS ranging from 9.2 to 16.4 months; lack of improvement in OS has been attributed to high rates of crossover to an EGFR TKI after progression with chemotherapy.[6-9, 32-35]

Table 1 presents a summary of EGFR TKI trials in patients with exon 19 deletions or L858R mutations; **Table 2** presents a summary of EGFR TKI trials in patients with uncommon mutations.

Major *EGFR* mutations

Multiple studies have confirmed that upwards of 80% to 90% of patients with *EGFR*-mutated NSCLC will have either an exon 19 deletion or an L858R point mutation.[4, 36, 37] Individual trials of erlotinib and gefitinib have been underpowered to detect differences in outcome by mutation subtype. In most clinical trials of EGFR TKIs, patients with uncommon mutations are either

excluded or molecular stratification is simplified into common (exon 19 deletions, exon 21 L858R substitutions) and uncommon mutations.[7, 35, 38] There are, however, data suggesting that patients with exon 19 deletions have improved outcomes when treated with first-generation EGFR TKIs as compared with L858R substitutions, although whether this benefit translates into an OS difference between the 2 mutations has not been proven.[39, 40] Both OPTIMAL and ENSURE, phase III studies of erlotinib compared with platinum doublets, showed a trend towards improved PFS in patients with exon 19 deletions when compared with L858R mutations.[26, 27] An early small prospective study of 36 patients treated with either gefitinib or erlotinib found improved OS among patients with exon 19 deletions as compared with L858R substitutions (38 vs 17 months; $p = 0.04$), as well as trends towards higher response rates (73% vs 50%) and PFS (24 vs 10 months).[39] Similar results were found in a single-institution, retrospective study of patients treated with first-generation EGFR TKIs.[40] Of the 34 evaluable patients with *EGFR* mutations, those with *EGFR* exon 19 deletions had better outcomes than patients with L858R mutations, with PFS of 12 months versus 5 months ($p = 0.01$) and OS of 34 months versus 8 months ($p = 0.01$), respectively. The reasons for this possible clinical benefit are not determined, although kinetic analysis of these 2 mutations found that exon 19 deletions appeared to be more sensitive to erlotinib inhibition than tumors harboring the L858R substitution.[41] Additionally, when outcomes were examined in larger prospective studies, patients with exon 19 deletions demonstrated improvements in OS and PFS compared with those harboring L858R mutations following treatment with first-generation EGFR TKIs.[33, 42]

In contrast to studies of first-generation TKIs, several studies of afatinib have examined outcomes by *EGFR* mutation subtype, and both common and uncommon mutations have been

included in different trials. LUX-Lung 2 was a phase II study of afatinib in a population of 129 EGFR TKI–naïve patients who were treated with 2 different doses of afatinib, with the primary endpoint of response.[43] Ninety-nine patients received a starting dose of 50 mg daily, and 30 patients received a starting dose of 40 mg daily. Forty-seven percent (61/129) of the patients received afatinib as a first-line therapy, and 53% (68/129) patients had received at least 1 prior line of chemotherapy. While the objective response rate (ORR) was 61%, patients with L858R mutations or exon 19 deletions were the most sensitive to afatinib, with 66% of those patients demonstrating a response in comparison to 39% of patients harboring other types of *EGFR* mutations. Additionally, patients with exon 19 deletions or L858R mutations had a median PFS of 13.7 months, whereas patients with uncommon mutations had a shorter PFS of 3.7 months. Two large, randomized, phase III trials, LUX-Lung 3 and LUX-Lung 6, compared afatinib with standard first-line chemotherapy with cisplatin and pemetrexed (LUX-Lung 3) or cisplatin and gemcitabine (LUX-Lung 6) in NSCLC patients with advanced-stage disease, who were positive for the *EGFR* mutations.[8, 9] Both trials reported a significant improvement in PFS, with no significant improvement in OS for the intention-to-treat populations. However, a preplanned analysis of both trials independently demonstrated a significant improvement in OS in patients with exon 19 deletions who were treated with first-line afatinib compared with chemotherapy (LUX-Lung 3: median OS, 33.3 months vs 21.1 months, respectively; HR, 0.54; 95% confidence interval [CI], 0.36-0.79; $p = 0.0015$ and LUX-Lung 6: median OS, 31.4 months vs 18.4 months, respectively; HR, 0.64; 95% CI, 0.44-0.94; $p = 0.023$).[44] This benefit was not seen in patients who were L858R mutation–positive.

A recent meta-analysis using randomized trial data from studies of patients undergoing first-line treatment with first- and second-generation EGFR TKIs examined the impact of mutation subtype and clinical characteristics on PFS outcome.[42] A total of 7 studies involving 1,649 patients treated with gefitinib, erlotinib, or afatinib were included. A total of 950 patients were assigned to EGFR TKIs, and 699 were assigned to chemotherapy. Across all *EGFR* mutation subtypes, treatment with an EGFR TKI showed a 63% reduction in the risk of disease progression or death as compared with treatment with chemotherapy (HR = 0.37; 95% CI, 0.32-0.42; p <0.001). The vast majority of patients harbored common *EGFR* mutations: 872 patients had exon 19 deletions, and 686 patients had exon 21 L858R substitutions. Subgroup analyses demonstrated that patients with exon 19 deletions showed a 50% greater PFS benefit when treated with an EGFR TKI than did patients with exon 21 L858R substitutions (interaction p <0.001).

Rare *EGFR* mutations

Because the majority of patients with *EGFR*-mutated NSCLC harbor either an L858R substitution or an exon 19 deletion, randomized trial data of other uncommon mutations are lacking. However, insight into the behavior and clinical responsiveness of uncommon *EGFR* mutations has been gained from various case series, retrospective studies, and pooled analyses.[10-19, 45] Available information regarding mutation frequency, as well as in vitro sensitivity and response rate to first-, second-, and third-generation EGFR TKIs according to mutation type, is illustrated in **Figure 1**. Generally, mutations involving exons 18 to 21 are considered to be sensitive to EGFR TKIs, with the exception being mutations involving exon 20, including T790M, and exon 20 insertions.

Studies in which patients with uncommon *EGFR* mutations have been analyzed as a single group often find these patients to be less responsive to EGFR TKI therapy than patients with either of the common mutations alone.[10, 11, 46, 47] However, when analyses are performed on individual mutations or smaller, selective subsets, it is clear that significant clinical heterogeneity exists.

Mutations in exon 18 are typically considered to be sensitizing to EGFR TKI therapy. The most commonly detected exon 18 mutation is the G719X mutation, followed by the E709X mutation.[12, 13] The G719X mutation is associated with a 10-fold increase in EGFR activation compared with wild-type EGFR,[48] but in vitro studies have suggested that it is not as sensitive to gefitinib as NSCLC cell lines with L858R mutations.[49] While patients with G719X mutations do respond to EGFR TKI therapy, responses have not always been as prolonged as those seen with the more common mutations. For example, a retrospective analysis of patients treated with afatinib following progression on 1 line of prior EGFR TKI treatment and chemotherapy as part of the Afatinib Compassionate-Use Program included 10 patients with G719X mutations, and median TTF was only 2.6 months.[50] In contrast, patients with E709X (exon 18 indel) mutations had a median TTF of 12.2 months with afatinib therapy. Interestingly, complex mutations within exon 18 may be associated with a better prognosis than point mutations.[10, 13] For example, the L861Q mutation is associated with sensitivity to EGFR TKIs.[51, 52] A post hoc analysis of 838 patients from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 found uncommon *EGFR* mutations in 100 (12%) study patients, 16 of which were L861Q substitutions.[14] The ORR associated with afatinib for patients with L861Q mutations was 56.3%, with median PFS and OS of 8.2 months and 17.1 months, respectively. Additional sensitizing *EGFR* aberrations, occurring at frequencies of <0.5%, include exon 19 insertions, exon 18-25 kinase domain duplications

(*EGFR*-KDD) and gene rearrangements.[53] Clinical responses have been reported with EGFR TKIs in individual patients with exon 19 insertions,[54] and case reports of patients with the *EGFR*-KDD duplication have shown responses to afatinib and gefitinib/erlotinib.[55, 56] Though gene fusions of *EGFR* with the RAD51 recombinase (*EGFR-RAD51*) or with purine-rich element binding protein B (*EGFR-PURB*) have only recently been discovered, antitumor responses have been observed in lung cancer patients harboring these alterations.[57]

EGFR mutations that are associated with resistance to EGFR TKI therapy remain a clinical challenge. Exon 20 mutations exist at a prevalence of approximately 2% among patients with stage IV lung adenocarcinoma.[15] Although it appears that exon 20 mutations are more likely to occur in patients with a similar phenotype to the common *EGFR* mutations (ie, female gender, Asian ethnicity, and never smoker status), multiple studies have confirmed that this mutation confers primary resistance to EGFR TKI therapy, with an ORR of approximately 10% and PFS of approximately 2.5 months.[12, 14, 16-18, 58, 59] Structural and molecular analyses have shown that while these mutations may activate EGFR, unlike the common sensitizing *EGFR* mutations, they activate EGFR without increasing receptor affinity for EGFR TKIs.[58] One exception may be the A763_Y764insFQEA variant, which appears to have sensitivity to EGFR TKIs both in vitro and in vivo, although reported sample sizes are small.[15, 58] Another mutation of note is the S768I mutation, which is associated with poor responses in some studies[19, 60] and did show good clinical outcomes from treatment with afatinib, with median PFS of 14.7 months and median OS not yet reported (95% CI, 3.4 months-not estimable).[14]

The T790M mutation is well characterized as the most common mechanism of acquired resistance to EGFR TKI therapy,[61, 62] and has been identified as a de novo T790M mutation, germline mutation, and in combination with other genetic aberrations. This "gatekeeper" mutation, which involves a threonine-to-methionine substitution in exon 20, increases the affinity of mutant EGFR for adenosine triphosphate (ATP), thereby competitively inhibiting the binding ability of reversible EGFR TKIs.[63] Third-generation EGFR TKIs that are highly selective for mutant *EGFR* have demonstrated efficacy in patients with lung cancer with acquired T790M mutations after progression on an EGFR TKI,[64, 65] with the first approval of a third-generation EGFR TKI (osimertinib) occurring in 2015. T790M germline mutations occur in approximately 1% of patients with NSCLC; however, these patients may also have a second activating *EGFR* mutation.[66-68] Familial studies have found that patients carrying a germline T790M mutation have a high lifetime risk of developing lung cancer, and up to 31% among never-smoking genetic carriers.[66, 69] De novo baseline EGFR T790M mutations occur in <1% of patients with NSCLC; similar to patients with acquired resistance from T790M mutations, this population does not respond to first-generation EGFR TKIs.[70, 71] However, a retrospective analysis of 60 patients with an uncommon *EGFR* mutation who were treated with afatinib following progression on 1 line of prior EGFR TKI treatment and chemotherapy suggested that patients with T790M mutations, as well as exon 20 insertions, may derive benefit from this agent.[50] The median TTF with afatinib for patients with T790M mutation and exon 20 insertions was 4.4 months (range, 0.4-21.8 months) and 6.5 months (range, 3.6-9.1 months), respectively. However, this positive finding may have been related to positive selection, as only patients who had previously responded to EGFR TKI therapy were eligible for the compassionate-use program.

Although the rate of germline and de novo T790M mutations is low, the frequency of T790M with another activating mutation ranges from 0.32%-79%, with variation based on detection method.[72] In a meta-analysis of 3 randomized, controlled trials and 15 observational studies, pretreatment T790M mutations were more likely to be present with L858R mutations than with exon 19 deletions.[72] This association may underlie observations of improved PFS in patients with exon 19 deletions compared with L858R mutations.[39, 40, 44] T790M is most often seen in the *cis* position with a L858R mutation or exon 19 deletion; however, it can occur in the *trans* position as well.[62] Interestingly, in a study of acquired resistance to third-generation EGFR inhibitors, when C797S and T790M mutations were present in *trans*, cells were resistant to third-generation TKIs but sensitive to combined treatment with first- and third-generation inhibitors. When these mutations were in *cis* conformation, no TKIs were able to suppress EGFR activity.[73]

While the EGFR T790M mutation can be a mechanism of acquired resistance, adaptive resistance also plays an important role in response to targeted therapy. Unlike acquired resistance, adaptive resistance is a process whereby tumor cells can rapidly respond to oncogene inhibition by altering signaling pathways to promote cell proliferation and survival.[74] One proposed mechanism of adaptive resistance in NSCLC involves inhibition of mitogen-activated protein kinase kinase (MEK), a downstream signaling molecule of EGFR, leading to activation of signal transducer and activator of transcription 3 (STAT3) and interleukin-6 (IL-6), which promotes cell survival and ultimately resistance.[75] Additional research has demonstrated that therapies targeting EGFR can immediately activate nuclear factor kappa B (NFκB) to induce an anti-apoptotic signaling cascade.[74] These findings suggest that in addition to targeting EGFR,

upfront combined inhibition of NFκB, IL6, and STAT3 may be necessary to subvert mechanisms of adaptive resistance and prevent tumor cell survival.

As the cost and convenience of comprehensive molecular testing improve, it is expected that comprehensive tumor genome profiling will become common practice,[76, 77] increasing the likelihood that oncologists will encounter rare *EGFR* mutations for which little or no trial data are available. For instance, a recent analysis of next-generation sequencing data from a commercial entity identified rare *EGFR* mutations in ~20% of samples,[53] a higher proportion than had been previously estimated.[36, 38] More than 200 known combinations of unique *EGFR* mutations have been identified to date in patients treated with TKIs,[78] and comprehensive data is available only on a select group of these, as described previously. Thus, development of accessible tools to support medical decision-making will be key to making the increasing burden of molecular data clinically useful. One such tool, the DNA-Mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT), is a comprehensive electronic catalog of reported *EGFR* NSCLC mutations paired with clinical outcome.[78] Information was pulled using a retrospective PubMed medical subject heading (MeSH) search to identify patient-level, mutation-specific, drug-response data from different studies in NSCLC with *EGFR*-mutant tumors. At last report, DIRECT catalogued 188 unique *EGFR* mutations that occurred in 207 different combinations, including 149 mutation combinations associated with disease control and 42 associated with disease progression.[78] Electronic queries of DIRECT will result in a customized report of patient-level, mutation-specific, drug-response data. A similar approach was taken in "My Cancer Genome," a searchable database that matches specific tumor mutations to a clinical significance report, including pertinent active clinical trials.[77] These data are continuously

updated for public use. A growing number of genomic profiling services that include pertinent clinical relevance data are becoming available for community use. For example, FoundationOne utilizes massively parallel DNA sequencing to characterize clinically actionable mutations across a wide array of cancer-related genes from routine formalin-fixed and paraffin-embedded tissue specimens.[79] This information is provided in conjunction with an interpretive report that highlights the genomic alterations related to available targeted therapies or clinical trials and has the potential to identify new mutations or genetic fusions not been previously described.[57] Finally, novel biopsy-free techniques such as digital droplet PCR, in which genomic testing can be performed on circulating tumor DNA, may make mutational testing at diagnosis and at progression more convenient, which has the potential to increase use not only at diagnosis but also at progression.[80, 81] As identification of rare or combination mutations becomes routine clinical practice, the use of dynamic, evidence-based databases to guide clinical treatment will likely become an essential component of oncology practice.

Clinical characteristics

While certain clinical characteristics have been associated with *EGFR*-mutated NSCLC, it has also been demonstrated that not all patients with *EGFR* mutations will fit this phenotype.

While patients with *EGFR*-mutated NSCLC and a heavy smoking history do show response to EGFR TKI therapy, outcomes may not be as good as in patients with never or light smoking history.[20, 21] Prior study of the pharmacokinetics of erlotinib found that erlotinib had an increased metabolic clearance in current smokers as compared with never-smokers.[82] A multivariate analysis of data from 4 large trials of first-generation EGFR TKIs found that,

compared with chemotherapy, EGFR TKI treatment demonstrated a 27% greater benefit in women than men (interaction $p = 0.02$), with pooled HR for PFS of 0.33 in women and 0.45 in men.[42] Similar findings were demonstrated when comparing the pooled HR for PFS in never-smokers to smokers. Although both never-smokers and smokers showed significant improvement in PFS with EGFR TKI treatment as compared with chemotherapy (pooled HR for PFS of 0.32 and 0.50, respectively), treatment with an EGFR TKI resulted in a 36% greater benefit to never-smokers than current or former smokers (interaction $p = 0.002$). However, there was no difference in improvement to PFS with EGFR TKI treatment compared with chemotherapy with respect to ethnicity, age, tumor histologic subtype, or performance status in this meta-analysis.

Conclusions

EGFR-mutated NSCLC is a heterogeneous entity, in which response to EGFR TKIs depends on the mutational subtype of the tumor. The vast majority of patients with *EGFR*-mutated NSCLC will have either an exon 19 deletion or L858R substitution. Increasingly, it appears that these 2 mutations may exhibit different biology when treated with EGFR TKI therapy, with improved outcomes in patients harboring exon 19 deletions. Uncommon mutations are a clinically heterogeneous group composing about 10%-20% of *EGFR*-mutated NSCLC. Thus, analyses of EGFR TKI sensitivity in uncommon mutations should be performed on individual mutations or in appropriately selected subgroups so that sensitivity to certain mutations is not masked by resistance in others. Patients with primary resistance, such as those with baseline T790M mutations or exon 20 insertions, remain a therapeutic challenge. As the number of identified mutations continues to grow, the development of comprehensive, dynamic, data-driven tools to

support clinical decision making will become increasingly useful. *EGFR* mutation subtype has important prognostic and predictive implications, and should inform both future drug development and interpretation of clinical trial outcomes.

Conflicts of Interest

EC: No conflicts of interest

EF: No conflicts of interest

LH: Consulted for Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Genentech, Merck, and Xcovery; received honorarium from Biodesix; received research funding from AstraZeneca

Acknowledgments

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript. Fact checking and editorial support were provided by Jason Jung, PhD, of MedErgy, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. V.4.2016. 2016.

2. Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. *Clin Cancer Res*. 2006;12:5268-5272.

3. Hirsch FR, Bunn PA Jr. EGFR testing in lung cancer is ready for prime time. *Lancet Oncol*. 2009;10:432-433.

4. Shi Y, Li J, Zhang S, et al. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology – Mainland China subset analysis of the PIONEER study. *PLoS One*. 2015;10:e0143515.

5. Skov BG, Hogdall E, Clementsen P, et al. The prevalence of EGFR mutations in non-small cell lung cancer in an unselected Caucasian population. *APMIS*. 2015;123:108-115.

6. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.

7. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380-2388.

8. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327-3334.

9. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213-222.

10. Baek JH, Sun JM, Min YJ, et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small cell lung cancer except both exon 19 deletion and exon 21 L858R: a retrospective analysis in Korea. *Lung Cancer*. 2015;87:148-154.

11. Chiu CH, Yang CT, Shih JY, et al. Epidermal growth factor receptor tyrosine kinase inhibitor treatment response in advanced lung adenocarcinomas with G719X/L861Q/S768I mutations. *J Thorac Oncol*. 2015;10:793-799.

12. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol*. 2014;25:126-131.

13. Cheng C, Wang R, Li Y, et al. EGFR exon 18 mutations in East Asian patients with lung adenocarcinomas: a comprehensive investigation of prevalence, clinicopathologic characteristics and prognosis. *Sci Rep*. 2015;5:13959.

14. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16:830-838.

15. Naidoo J, Sima CS, Rodriguez K, et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. *Cancer*. 2015;121:3212-3220.

16. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther*. 2013;12:220-229.

17. Wu JY, Wu SG, Yang CH, et al. Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response. *Clin Cancer Res*. 2008;14:4877-4882.

18. Sasaki H, Endo K, Takada M, et al. EGFR exon 20 insertion mutation in Japanese lung cancer. *Lung Cancer*. 2007;58:324-328.

19. Asahina H, Yamazaki K, Kinoshita I, et al. Non-responsiveness to gefitinib in a patient with lung adenocarcinoma having rare EGFR mutations S768I and V769L. *Lung Cancer*. 2006;54:419-422.

20. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123-132.

21. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005;366:1527-1537.

22. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29:2866-2874.

23. Zhu CQ, da Cunha SG, Ding K, et al. Role of *KRAS* and *EGFR* as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol*. 2008;26:4268-4275.

24. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339-346.

25. Han JY, Park K, Kim SW, et al. First-SIGNAL: First-line single-agent Iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30:1122-1128.

26. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735-742.

27. Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol*. 2015;26:1883-1889.

28. Sebastian M, Schmittel A, Reck M. First-line treatment of EGFR-mutated nonsmall cell lung cancer: critical review on study methodology. *Eur Respir Rev*. 2014;23:92-105.

29. GILOTRIF® (afatinib) tablets, for oral use [package insert]. Ridgefield, CT.; Boehringer Ingelheim Pharm. 2016.

30. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008;27:4702-4711.

31. Suda K, Onozato R, Yatabe Y, et al. EGFR T790M mutation: a double role in lung cancer cell survival? *J Thorac Oncol*. 2009;4:1-4.

32. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor

receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121-128.

33. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009;361:958-967.

34. Haaland B, Tan PS, de Castro G Jr, et al. Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations. *J Thorac Oncol*. 2014;9:805-811.

35. Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol*. 2012;30:2063-2069.

36. Krawczyk P, Reszka K, Ramlau R, et al. Prevalence of rare EGFR gene mutations in non-small cell lung cancer: a multicenter study on 3856 Polish Caucasian patients. *Ann Oncol*. 2015;27:358-359.

37. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239-246.

38. Mitsudomi T, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J*. 2010;277:301-308.

39. Jackman DM, Yeap BY, Sequist LV, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res*. 2006;12:3908-3914.

40. Riely GJ, Pao W, Pham D, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res*. 2006;12:839-844.

41. Carey KD, Garton AJ, Romero MS, et al. Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib. *Cancer Res*. 2006;66:8163-8171.

42. Lee CK, Wu YL, Ding PN, et al. Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: a meta-analysis. *J Clin Oncol*. 2015;33:1958-1965.

43. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol*. 2012;13:539-548.

44. Yang JCH, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. 2015;16:141-151.

45. Yang CH, Yu CJ, Shih JY, et al. Specific *EGFR* mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. *J Clin Oncol*. 2008;26:2745-2753.

46. Arrieta O, Cardona AF, Corrales L, et al. The impact of common and rare EGFR mutations in response to EGFR tyrosine kinase inhibitors and platinum-based chemotherapy in patients with non-small cell lung cancer. *Lung Cancer*. 2015;87:169-175.

47. Watanabe S, Minegishi Y, Yoshizawa H, et al. Effectiveness of gefitinib against non-small-cell lung cancer with the uncommon EGFR mutations G719X and L861Q. *J Thorac Oncol*. 2014;9:189-194.

48. Yun CH, Boggon TJ, Li Y, et al. Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity. *Cancer Cell*. 2007;11:217-227.

49. Kancha RK, von Bubnoff N, Peschel C, et al. Functional analysis of epidermal growth factor receptor (EGFR) mutations and potential implications for EGFR targeted therapy. *Clin Cancer Res*. 2009;15:460-467.

50. Heigener DF, Schumann C, Sebastian M, et al. Afatinib in non-small cell lung cancer harboring uncommon EGFR mutations pretreated with reversible EGFR inhibitors. *Oncologist*. 2015;20:1167-1174.

51. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129-2139.

52. Lohinai Z, Hoda MA, Fabian K, et al. Distinct epidemiology and clinical consequence of classic versus rare EGFR mutations in lung adenocarcinoma. *J Thorac Oncol*. 2015;10:738-746.

53. Costa DB. Kinase inhibitor-responsive genotypes in EGFR mutated lung adenocarcinomas: moving past common point mutations or indels into uncommon kinase domain duplications and rearrangements. *Transl Lung Cancer Res*. 2016;5:331-337.

54. He M, Capelletti M, Nafa K, et al. EGFR exon 19 insertions: a new family of sensitizing EGFR mutations in lung adenocarcinoma. *Clin Cancer Res*. 2012;18:1790-1797.

55. Gallant JN, Sheehan JH, Shaver TM, et al. EGFR kinase domain duplication (EGFR-KDD) is a novel oncogenic driver in lung cancer that is clinically responsive to afatinib. *Cancer Discov*. 2015;5:1155-1163.

56. Baik CS, Wu D, Smith C, et al. Durable response to tyrosine kinase inhibitor therapy in a lung cancer patient harboring epidermal growth factor receptor tandem kinase domain duplication. *J Thorac Oncol*. 2015;10:e97-99.

57. Konduri K, Gallant JN, Chae YK, et al. EGFR fusions as novel therapeutic targets in lung cancer. *Cancer Discov*. 2016;6:601-611.

58. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med*. 2013;5:216ra177.

59. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol*. 2013;8:179-184.

60. Siegelin MD, Borczuk AC. Epidermal growth factor receptor mutations in lung adenocarcinoma. *Lab Invest*. 2014;94:129-137.

61. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2:e73.

62. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352:786-792.

63. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008;105:2070-2075.

64. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689-1699.

65. Sequist LV, Soria JC, Goldman JW, et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. 2015;372:1700-1709.

66. Gazdar A, Robinson L, Oliver D, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol*. 2014;9:456-463.

67. Yu HA, Arcila ME, Harlan FM, et al. Germline EGFR T790M mutation found in multiple members of a familial cohort. *J Thorac Oncol*. 2014;9:554-558.

68. Oxnard GR, Miller VA, Robson ME, et al. Screening for germline EGFR T790M mutations through lung cancer genotyping. *J Thorac Oncol*. 2012;7:1049-1052.

69. Bell DW, Gore I, Okimoto RA, et al. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet*. 2005;37:1315-1316.

70. Yu HA, Arcila ME, Hellmann MD, et al. Poor response to erlotinib in patients with tumors containing baseline EGFR T790M mutations found by routine clinical molecular testing. *Ann Oncol*. 2014;25:423-428.

71. Wu JY, Yu CJ, Chang YC, et al. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res*. 2011;17:3812-3821.

72. Chen LY, Molina-Vila MA, Ruan SY, et al. Coexistence of EGFR T790M mutation and common activating mutations in pretreatment non-small cell lung cancer: A systematic review and meta-analysis. *Lung Cancer*. 2016;94:46-53.

73. Niederst MJ, Hu H, Mulvey HE, et al. The allelic context of the C797S mutation acquired upon treatment with third-generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. *Clin Cancer Res*. 2015;21:3924-3933.

74. Pazarentzos E, Bivona TG. Adaptive stress signaling in targeted cancer therapy resistance. *Oncogene*. 2015;34:5599-5606.

75. Lee HJ, Zhuang G, Cao Y, et al. Drug resistance via feedback activation of Stat3 in oncogene-addicted cancer cells. *Cancer Cell*. 2014;26:207-221.

76. Macconaill LE, Garraway LA. Clinical implications of the cancer genome. *J Clin Oncol*. 2010;28:5219-5228.

77. Levy MA, Lovly CM, Pao W. Translating genomic information into clinical medicine: lung cancer as a paradigm. *Genome Res*. 2012;22:2101-2108.

78. Yeh P, Chen H, Andrews J, et al. DNA-mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT): a catalog of clinically relevant cancer mutations to enable genome-directed anticancer therapy. *Clin Cancer Res*. 2013;19:1894-1901.

79. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31:1023-1031.

80. Alegre E, Fusco JP, Restituto P, et al. Total and mutated EGFR quantification in cell-free DNA from non-small cell lung cancer patients detects tumor heterogeneity and presents prognostic value. *Tumour Biol*. 2016;37:13687-13694.

81. Karachaliou N, Mayo-de las CC, Queralt C, et al. Association of EGFR L858R mutation in circulating free DNA with survival in the EURTAC trial. *JAMA Oncol*. 2015;1:149-157.

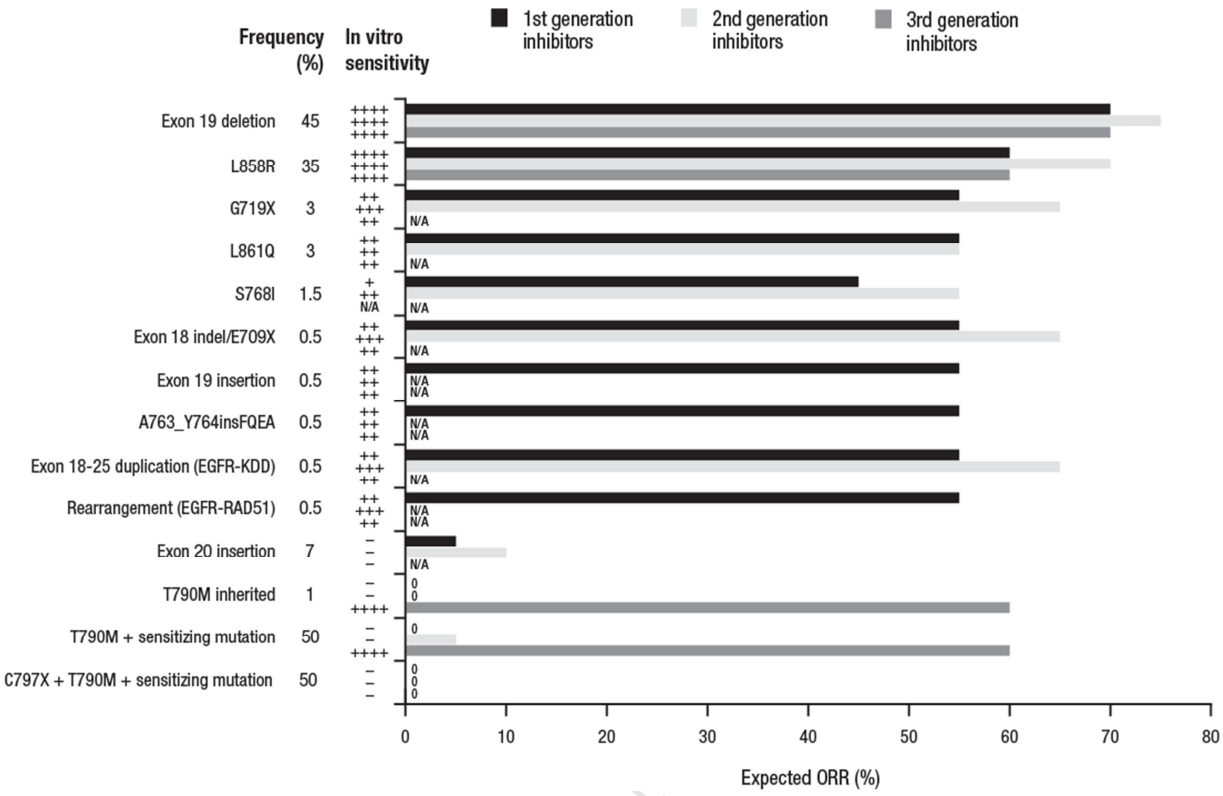
82. Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res*. 2006;12:2166-2171.

83. Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol*. 2013;24:54-59.

84. Yoshioka H, Mitsudomi T, Morita S, et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol*. 2014;32.

85. Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol*. 2015;26:1877-1883.

Figure 1. Frequency of *EGFR* mutations and in vitro sensitivity to EGFR TKIs.[53]



EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; KDD, kinase domain duplication; ORR, objective response rate.

Table 1: EGFR TKI Trials in Patients with Exon 19 Deletions or L858R Mutations

Study	Study Type	Patient Population	ORR (%)	Median PFS (mo)	Median OS (mo)
LUX-Lung 2[43]	Phase II trial	129 *EGFR*-mutation–positive pts treated with afatinib Pts with exon 19 del: 52 Pts with L858R mutation: 54	61 69 (pts with exon 19 del) 63 (pts with L858R mutations)	10.1 13.7 (pts with exon 19 del) 13.7 (pts with L858R mutations)	24.8 38.7 (pts with exon 19 del) 31.5 (pt with L858R mutations)
LUX-Lung 3[8, 44]	Phase III trial	345 *EGFR*-mutation–positive pts treated with afatinib vs cisplatin/pemetrexed Pts with exon 19 del: 170 Pts with L858R mutation: 138	56 vs 23	11.1 vs 6.9 (HR = 0.58; 95% CI, 0.43-0.78; *p* = 0.001) 13.6 vs 6.9 (for exon 19 del and L858R pts only) (HR = 0.47; 95% CI, 0.34-0.65; *p* = 0.001)	28.2 vs 28.2 (HR = 0.88; 95% CI, 0.66-1.17; *p* = 0.39) 33.3 vs 21.1 (exon 19 del) (HR = 0.54; 95% CI, 0.36-0.79; *p* = 0.0015) 27.6 vs 40.3 (L858R mutation) (HR = 1.30; 95% CI, 0.80-2.11; *p* = 0.29)
LUX-Lung 6[9, 44]	Phase III trial	364 *EGFR*-mutation–positive pts treated with afatinib vs cisplatin/gemcitabine Pts with exon 19 del: 186 Pts with L858R mutation: 138	66.9 vs 23 (*p* <0.0001)	11.0 vs 5.6 (HR = 0.28; 95% CI, 0.20-0.39; *p* <0.0001)	23.1 vs 23.5 (HR = 0.93; 95% CI, 0.72-1.22; *p* = 0.61) 31.4 vs 18.4 (exon 19 del) (HR = 0.64; 95% CI, 0.44-0.94; *p* = 0.023) 19.6 vs 24.3 (L858R mutation) (HR = 1.22; 95% CI, 0.81-1.83; *p* = 0.34)
IPASS[6, 22]	Phase III trial	261 *EGFR*-mutation–positive pts treated with gefitinib vs carboplatin/paclitaxel Pts with exon 19 del: 140 Pts with L858R mutation: 111	71.2 vs 47.3 (pts with *EGFR* mutations) (*p* <0.001) 84.8 vs 60.9 (exon 19 del vs L858R mutation)	9.5 vs 6.3 (pts with *EGFR* mutations) (HR = 0.48; 95% CI, 0.36-0.64; *p* <0.001)	21.6 vs 21.9 (pts with *EGFR* mutations) (HR = 1.0; 95% CI, 0.76-1.33; *p* = 0.99)
NEJ002[7, 83]	Phase III trial	230 sensitizing *EGFR*-mutation positive pts treated with gefitinib vs carboplatin/paclitaxel Pts with exon 19 del: 117 Pts with L858R mutation: 97	73.7 vs 30.7 (*p* <0.001) 82.8 vs 67.3 (exon 19 del vs L858R mutation)	10.8 vs 5.4 (HR = 0.30; 95% CI, 0.22-0.41; *p* <0.001) 11.5 vs 10.8 (exon 19 del vs L858R mutation)	27.7 vs 26.6 (HR = 0.89; 95% CI, 0.63-1.24; *p* = 0.48)

WJTOG3405[32, 84]	Phase III trial	172 activating *EGFR*-mutation–positive pts treated with gefitinib vs cisplatin/docetaxel Pts with exon 19 del: 87 Pts with L858R mutation: 85	62.1 vs 32.2 (p <0.0001)	9.2 vs 6.3 (HR = 0.49; 95% CI, 0.34-0.71; p <0.0001) 9.0 vs 9.6 mo (exon 19 del vs L858R mutation) (HR = 1.13; 95% CI, 0.63-2.0; p = 0.68)	34.8 vs 37.3 (HR = 1.25; 95% CI, 0.883-1.78)
EURTAC[37]	Phase III trial	173 activating *EGFR*-mutation–positive pts treated with erlotinib vs cisplatin/docetaxel/gemcitabine Pts with exon 19 del: 115 Pts with L858R mutation: 58	64 vs 18	9.7 vs 5.2 (HR = 0.37; 95% CI, 0.25-0.54; p <0.0001) 11.0 vs 8.4 (exon 19 del vs L858R mutation) 11.0 vs 4.6 (exon 19 del) (HR = 0.30; 95% CI, 0.18-0.50; p <0.0001) 8.4 vs 6.0 (L858R mutation) (HR = 0.55; 95% CI, 0.29-1.02; p = 0.054)	19.3 vs 19.5 (HR = 1.04; 95% CI, 0.65-1.68; p = 0.87)
First-Signal[25]	Phase III trial	42 activating *EGFR*-mutation–positive pts treated with gefitinib vs gemcitabine/cisplatin Pts with exon 19 del: 27 Pts with L858R mutation: 15	84.6 vs 37.5 (p = 0.002)	8.0 vs 6.3 (HR = 0.54; 95% CI, 0.27-1.10; p = 0.086)	27.2 vs 25.6 (HR = 1.04; 95% CI, 0.50-2.18)
OPTIMAL[26, 85]	Phase III trial	154 activating *EGFR*-mutation–positive pts treated with erlotinib vs gemcitabine/carboplatin Pts with exon 19 del: 82 Pts with L858R mutation: 72	83 vs 36 (p <0.0001)	13.1 vs 4.6 (HR = 0.16; 95% CI, 0.10-0.26; p <0.0001)	22.8 vs 27.2 (HR = 1.19; 95% CI, 0.83-1.71; p = 0.27)
ENSURE[27]	Phase III trial	217 activating *EGFR*-mutation–positive pts treated with erlotinib vs gemcitabine/cisplatin Pts with exon 19 del: 118 Pts with L858R mutation: 98	62.7 vs 33.6	11.0 vs 5.6 (HR = 0.42; 95% CI, 0.27-0.66; p = 0.0001) 11.1 vs 8.3 (exon 19 del vs L858R mutation)	26.3 vs 25.5 (HR = 0.91; 95% CI, 0.63-1.31; p = 0.61)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; pts, patients; HR, hazard ratio; CI, confidence interval.

Table 2: EGFR TKI Trials in Patients with Uncommon Mutations

Study	Study Type	Patient Population	ORR (%)	Median PFS (mo)	Median OS (mo)
Yang et al[14]	Post hoc analysis of LUX-Lung 2, 3, 6	75 pts with uncommon *EGFR* mutations receiving afatinib			
		Group 1: point mutations or duplications in exons 18-21 (38 pts)	Group 1: 71.1	Group 1: 10.7	Group 1: 19.4
		Group 2: de novo T790M mutations in exon 20 alone or in combination with other mutations (14 pts)	Group 2: 14.3	Group 2: 2.9	Group 2: 14.9
		Group 3: exon 20 insertions (23 pts)	Group 3: 8.7%	Group 3: 2.7	Group 3: 9.2
Baek et al[10]	Retrospective analysis	54 pts with uncommon *EGFR* mutations treated with gefitinib (35) or erlotinib (19)	20.4	2.6	12.7
Chiu et al[11]	Retrospective analysis	161 pts with uncommon *EGFR* mutations; 478 pts with common *EGFR* mutations	41.6 vs 66.5 (uncommon vs common mutations) (p <0.001)	7.7 vs 11.4 (uncommon vs common mutations) (p <0.001)	24.0 vs 29.7 (uncommon vs common mutations) (p = 0.005)
Arrieta et al[46]	Observational prospective cohort	38 pts with uncommon *EGFR* mutations; 150 pts with common *EGFR* mutations	32.4 vs 63.8 (uncommon vs common mutations) (p <0.001)	3.9 vs 15.5 (uncommon vs common mutations) (p <0.001)	17.4 vs 37.3 (uncommon vs common mutations) (p <0.001)
Watanabe et al[47]	Post hoc analysis of NEJ002 trial	10 pts with uncommon *EGFR* mutations (only G719X and L861Q); 215 pts with common *EGFR* mutations	20 vs 76 (gefitinib group: uncommon vs common mutations) (p = 0.017)	2.2 vs 11.4 (gefitinib group: uncommon vs common mutations) (p <0.001)	11.9 vs 29.3 (gefitinib group: uncommon vs common mutations) (p <0.001)
			20 vs 32 (carboplatin-paclitaxel group: uncommon vs common mutations) (p = 0.34)	5.9 vs 5.4 (carboplatin-paclitaxel group: uncommon vs common mutations) (p = 0.85)	22.8 vs 28.0 (carboplatin-paclitaxel group: uncommon vs common mutations) (p = 0.36)
Lohinai et al[52]	Retrospective analysis	49 pts with uncommon *EGFR* mutations; 42 pts with common *EGFR* mutations	37 vs 71 (uncommon vs common mutations) (p = 0.039)	6.2 vs 12 (uncommon vs common mutations) (p = 0.048)	7.4 vs 20.5 (uncommon vs common mutations)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; pts, patients.