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Choosing the Best EGFR TKI in the Era of Precision Medicine

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Abstract

The treatment of metastatic Non-small Cell Lung Cancer (mNSCLC) has evolved from traditional doublet chemotherapy to a model for precision medicine. Over the past fifteen years, the discovery of Epidermal Growth Factor Receptor (EGFR) mutations as key players in the pathogenesis of mNSCLC has transformed the care of patients with mNSCLC. EGFR Tyrosine Kinase Inhibitors (TKIs) have prolonged both progression free survival and overall survival in patients who harbor EGFR mutations. Most recently, the third generation EGFR TKI osimertinib has shown superior progression free survival compared to earlier TKIs. Osimertinib has also shown excellent penetration into the CNS, less CNS tumor progression, and even leptomeningeal disease response. The efficacy of EGFR TKIs in the CNS may allow clinicians to avoid or defer radiation therapy for CNS disease in select mNSCLC patients with EGFR mutations. The advent of circulating tumor DNA (ctDNA) has shown excellent diagnostic concordance with tumor biopsy in detecting EGFR mutations. While not the most sensitive tests, ctDNA is highly specific in uncovering EGFR mutations. In the future, ctDNA will likely avoid many unnecessary tissue biopsies in suspected lung cancer. As a marker of disease burden, ctDNA load will also play a key complementary role in determining response to therapy, disease resistance, and associated prognosis in EGFR mutated mNSCLC. In light of these remarkable advances, testing for mutations in EGFR, in addition to mutations in *ALK, ROS-1, BRAF* and *PD-L1*, is now more than ever the standard of care for mNSCLC, and critical to precision medicine.

Keywords: Metastatic Non-small Cell Lung Cancer (mNSCLC); Circulating tumor DNA (ctDNA); Precision medicine; Epidermal Growth Factor Receptor (EGFR) mutations

Introduction

Implications for Practice

The third-generation EGFR TKI osimertinib is now first-line therapy for EGFR mutated metastatic Non-small Cell Lung Cancer (mNSCLC). Osimertinib is critical to the practice of precision medicine in lung cancer. It has revolutionized our approach to EGFR mutated mNSCLC, particularly with CNS metastases, with excellent CNS penetration that may in some cases obviate the need for radiation. Newly emerging patterns of resistance to the latest EGFR TKIs will present a clinical challenge going forward. Circulating tumor (ctDNA) is increasingly more important in clinical practice, not just in diagnosis of mNSCLC but in assessing disease response to therapy and guiding prognosis.

The treatment of metastatic Non-small Cell Lung Cancer (mNSCLC) has transformed from doublet chemotherapy to a model for precision medicine. Numerous molecular targets have been identified for personalized treatment replacing cytotoxic chemotherapy, most notably mutations in the Epidermal Growth Factor Receptor (EGFR) tyrosine kinase domain.

In preparing this review, we performed an exhaustive review of the major basic science and clinical studies on EGFR TKIs from the early 2000's onward. Early studies examined the potential benefits of EGFR Tyrosine Kinase Inhibitors (TKIs) compared to placebo in patients with mNSCLC who failed systemic chemotherapy [1,2]. Gefitinib was approved in 2003 and erlotinib in 2004 by the FDA in the second line setting for all-comers with mNSCLC who had progressed on chemotherapy, not specific to those with EGFR mutations. The benefits however were modest.

History of EGFR TKIs

EGFR mutations were first described in the early 2000s as mechanisms that activate survival signaling pathways in mNSCLC. Shortly thereafter, a 2004 study established activating EGFR mutations as drivers for malignancy and predictors of response to EGFR TKIs in mNSCLC [3]. The most common sensitizing EGFR mutations, exon 19 deletion and L858R substitution on exon 21, are the two mutations generally referenced as the EGFR-mutated population. Between 2004 and 2014, multiple studies, including a meta-analysis of six randomized controlled trials, showed EGFR TKIs improved PFS by approximately five months compared to standard chemotherapy in untreated mNSCLC patients harboring EGFR mutations [4-9]. In the IPASS study, the benefits of EGFR TKIs were especially great in the non-smoking Asian population, a group with a high prevalence of EGFR mutations, where 12 month PFS was 24.9% with gefitinib *vs.* 6.7% with carboplatin-paclitaxel [10]. While the benefits of the EGFR TKIs for all-comers in the second-line setting had been modest at best, the benefits of these drugs when used selectively in the EGFR-mutated population were striking. Importantly, while PFS with gefitinib was significantly longer than with chemotherapy for those with EGFR mutations, it was significantly shorter with gefitinib than with

chemotherapy for those who were EGFR-mutation negative (Table 1). Erlotinib and afatinib received FDA approval as first-line therapy for patients with EGFR TKI-sensitizing, mutation-positive mNSCLC in 2013, while gefitinib earned FDA approval for this indication in 2015 [11]. Each of these EGFR TKIs has delivered impressive results in the population with either an exon 19 deletion or *L858R* substitution. A 2014 phase II Japanese study did show improved PFS with erlotinib plus bevacizumab compared to erlotinib alone (median PFS=16.0 *vs.* 9.7 months, HR=0.54, 95% CI=0.36-0.79; p=0.0015) in the first-line setting in patients with EGFR-mutated, non-squamous mNSCLC [12]. Yet to date, bevacizumab has not gained FDA approval as an adjunct to EGFR TKIs in this setting. Multiple trials continue to assess combination treatment of EGFR TKI and VEGF antibodies to enhance outcomes based on possible synergistic responses.

Generation EGFR TKI	Drug	Current FDA Approvals
1st	erlotinib	mNSCLC with exon 19 deletion or exon 21 *L858R* substitution
	gefitinib	mNSCLC with exon 19 deletion or exon 21 *L858R* substitution
2nd	afatinib	mNSCLC with non-resistant EGFR mutations in first-line treatment
		mNSCLC of squamous histology progressing after platinum-based chemotherapy
	dacomitinib	granted priority review designation
3rd	osimertinib	mNSCLC with exon 19 deletion or exon 21 *L858R* substitution in first-line treatment
		mNSCLC with T790M mutation progressing on or after EGFR TKI treatment
	rociletinib	clinical development stopped after new drug application not approved

Table 1: Different generation EGFR TKIs and their Current FDA approvals.

Discussion

The LUX-3 and LUX-6 data showed similar PFS benefits with afatinib as with first generation TKIs when compared to standard chemotherapy in the first-line treatment of advanced NSCLC harboring EGFR mutations [13,14]. Although exon 19 deletion and *L858R* substitutions are more common and known to be sensitizing to the EGFR TKIs, uncommon mutations such as EGFR exon 21 *(L861Q), G719X,* or *S768I* substitution represent less than 10% of those EGFR mutations found in NSCLC patients. Within the LUX-Lung-2, -3, and -6 trials, however, 75 patients treated with afatinib were noted to have uncommon mutations. A post-hoc analysis revealed improvements in response rate, mPFS and mOS in patients with EGFR exon 21 *(L861Q), G719X,* or *S768I* substitutions when treated with afatinib [15] Although no study has shown superiority of afatinib to other EGFR TKIs with these rare mutations, due to these findings, afatinib was FDA approved for the first-line treatment of patients with mNSCLC harboring non-resistant EGFR mutations.

Overall, the first- and second-generation EGFR TKIs have demonstrated similar efficacy [16]. However, within the studied patient populations, the EGFR TKIs have varying responses based on distinct mutation patterns. For example, EGFR TKIs demonstrate generally better outcomes in those tumors harboring exon 19 deletions versus those with *L858R* substitutions. Afatinib has specifically shown better overall survival in patients with deletion 19 mutations. The first- and second-generation EGFR TKIs have not identified significant responses in those with the *T790M* mutation. Additionally, the exon 20 insertion is a mutation resistant to these targeted agents and thus tumors containing EGFR exon 20 insertion should not be treated with the current FDA approved EGFR TKIs.

Many patients who have disease progression on these agents develop an EGFR *T790M* mutation on exon 20, accounting for roughly 60% of cases of resistance to EGFR TKIs [17]. Although well-recognized as the most common mechanism of resistance to first- and second-generation EGFR TKIs, it is associated with slower progression and favorable prognosis relative to other mutations [18]. Osimertinib, a third generation irreversible EGFR TKI, is selective for both the sensitizing mutations and the T790M mutation.

Third generation TKIs and potential clinical benefits

A Phase I study of AZD9291 (osimertinib), examined patients with radiographic progression after being previously treated with first or second-generation EGFR TKIs. Eligible patients either had a known EGFR TKI-sensitizing mutation or had prior clinical benefit from an EGFR TKI, even in absence of a documented mutation. In the dose expansion cohorts, pre-study tumor biopsies were obtained for central determination of EGFR T790M status. The study showed increased Overall Response Rate (ORR) in those whose tumors harbored the EGFR T790M mutation compared to those whose did not (ORR=61%, 95% CI=52-70, *vs.* 21%, 95% CI=12-34, respectively). Median PFS with osimertinib in the T790M positive population was significantly longer than in the T790M negative population (9.6 months, 95% CI=8.3 to not reached, 30% maturity, *vs.* 2.8 months, 95% CI=2.1-4.3, 71% maturity). This study established T790M as a key predictor of response to osimertinib [19].

The phase III AURA3 study compared osimertinib to platinum-pemetrexed in patients with *T790M* resistance mutations who had progressed on first-line EGFR TKI therapy. Duration of PFS was 10.1 months in the osimertinib group *vs.* 4.4 months in the chemotherapy group [20]. Osimertinib quickly gained FDA approval for patients with mNSCLC harboring the T790M mutation after progressing on or after EGFR TKI treatment.

After demonstrating benefit post initial EGFR TKI treatment and recognizing that osimertinib targeted the sensitizing mutations as well as *T790M*, osimertinib was tested in the first-line setting. FLAURA was a double blind, phase 3 trial that enrolled 556 previously untreated patients with exon 19 deletion or L858R substitution EGFR-mutation

positive mNSCLC (irrespective of *T790M* status), and randomized patients to receive either osimertinib 80 mg orally once daily or a standard EGFR TKI (either gefitinib or erlotinib). Results revealed significant improvement in PFS in the first-line setting: 18.9 months in the osimertinib arm versus 10.2 months (HR=0.46, 95% CI=0.37-0.57, p<0.001) in the standard EGFR TKI group. While the overall response rates and disease-control rates were similar between the two groups, the median duration of response was significantly longer in the osimertinib group (17.2 months, 95% CI=13.8-22.0, *vs.* 8.5 months, 95% CI=7.3-9.8). The superiority of osimertinib with respect to PFS was seen across all assessed subgroups, including race (non-Asian *vs.* Asian) and mutation (exon 19 deletion *vs.* L858R substitution) [21]. As a result, osimertinib is now FDA approved as first-line treatment for patients with exon 19 deletion or exon 21 L858R substitution EGFR-mutated mNSCLC.

CNS activity of Osimertinib

Early studies in mouse models demonstrated superior penetration of the Blood Brain Barrier (BBB) and higher brain: plasma concentration ratios with osimertinib than with gefitinib, afatinib, and rociletinib [22]. Thus not surprisingly, osimertinib demonstrated improved PFS in patients with CNS metastases in FLAURA. The number of CNS progression events was significantly lower in the osimertinib arm than in the gefitinib/erlotinib arm (17 (6%) *vs.* 42 (15%) patients, respectively). Median CNS progression free survival was not reached in the osimertinib arm (95% CI=16.5 to not reached) *vs.* 13.9 months (95% CI=8.3 to not reached) with erlotinib or gefitinib. This was regardless of whether patients had known CNS metastases at baseline. Subanalysis of those in the FLAURA trial with CNS disease also showed a durable CNS response rate with osimertinib that was superior to erlotinib or gefitinib [23]. This trial included both patients who were treated with radiation for their CNS disease and those who were not. Given that both groups were included in the same statistical analysis, the degree to which patients with non-radiated CNS metastases benefitted from osimertinib is not clear.

In the phase I BLOOM study (NCT02228369), investigators gathered a cohort of 32 patients with EGFR-mutation positive mNSCLC and leptomeningeal disease, confirmed by positive Cerebrospinal Fluid (CSF) cytology. All patients had progressed on prior EGFR TKI therapy, and were treated with osimertinib 160 mg daily. While only 23 of the 32 patients had follow up brain imaging at 12 weeks, 10 had radiographic improvement, with an ORR in leptomeningeal disease of 43.5%. Of the same 23 patients, 8 had abnormal neurologic status at baseline; of this population, 7 patients (87.5%) had neurologic improvement with osimertinib [24]. The mean decrease from pre-treatment to post-cycle 1 EGFR mutant DNA in the CSF was 57% [25] Though the cohorts were small, the BLOOM data suggests that osimertinib penetrates the blood brain barrier effectively [26]. The response rate of osimertinib in leptomeningeal metastases, a disease notoriously difficult to treat, is promising [27].

More recently, investigators examined the subset of 116 patients who had measurable and/or nonmeasurable CNS lesions on baseline brain scans in the AURA3 study. 46 patients in the study had 1 or more measurable CNS lesions (defined as greater than or equal to 10 mm in longest diameter), and thus were included in the CNS evaluable for response (cEFR) group. Within this smaller group, the CNS Objective Response Rate (ORR) was 70% with osimertinib versus 31% in the platinum/pemetrexed arm (odds ratio=5.13; 95% CI=1.44 to 20.64, p=0.015). For the 116 patients, with measurable and/or nonmeasurable CNS lesions, median CNS progression-free survival was 11.7 months with osimertinib versus 5.6 months with platinum/pemetrexed (hazard ratio=0.32; 95% CI=0.15-0.69, p=0.004). It should be noted that across this group of 116 patients with CNS disease in AURA3, fewer in the osimertinib arm had received prior brain radiotherapy than in the platinum/pemetrexed arm (37% of patients in the osimertinib arm, 49% of patients in the platinum/pemetrexed arm) [28]. Certainly this may confound interpretation of CNS response to osimertinib, as there have been mixed reports on whether recent radiotherapy increases BBB permeability to EGFR TKI therapy [29,30]. In a pooled analysis of phase II studies for *T790M*-positive mNSCLC, 50 patients treated with osimertinib had a confirmed CNS objective response rate and confirmed CNS disease control rate of 54% and 92%, respectively. At a median follow-up of 11 months, median CNS PFS was not yet reached. This CNS response was seen regardless of whether patients had received prior radiation or not [31]. Currently there is a new EGFR TKI designed specifically to penetrate the BBB, AZD3529. An ongoing Phase I trial within BLOOM has not only demonstrated excellent penetration of the BBB with AZD3529, but also has shown CNS tumor regression [32].

The efficacy of osimertinib in the CNS has numerous implications for management of patients with mNSCLC and CNS disease. Due to efficacy and minimal toxicity, Stereotactic Radiosurgery (SRS) will likely remain part of first-line care for locoregional control in those who are symptomatic from oligometastatic disease. Yet Osimertinib has emerged as an intervention that may allow for deferral of brain-specific treatment in the setting of asymptomatic CNS involvement, or for those with multiple metastases not amenable to SRS. It may be reasonable to use the drug as initial therapy for mNSCLC with CNS disease, reserving whole brain radiation for either CNS progression on EGFR TKI or high CNS disease burden, given its multiple neurocognitive effects [33].

Acquired resistance to Osimertinib

The EGFR *C797S* mutation is a common mechanism of acquired resistance to second-line osimertinib [34]. Studies of ctDNA showed that of fifteen advanced NSCLC patients initially positive for *T790M* who were treated with second-line osimertinib, six (40%) acquired the *C797S* mutation. All of these patients with *C797S* mutation maintained a detectable *T790M* mutation. The *C797S* mutation has clinical significance, as quinazoline-based EGFR inhibitors such as gefitinib have been proven to inhibit *C797S* whenever the *T790M* mutation is absent [35]. For those on trial who had ctDNA at disease progression, nearly half had mutations previously reported as mechanisms of resistance to second line osimertinib: amplifications in MET, KRAS, and EGFR, acquired RET fusions, and activating mutations in *BRAF, KRAS*, and *PIK3CA* [30]. Other mutations were uncovered even after no EGFR mutations were found in the plasma, such as HER2 exon 20 insertion, which activates signaling pathways parallel to EGFR [30]. Investigators are currently working to see whether osimertinib combined with the RET inhibitor *BLU-667* or with the MET inhibitor savolitinib may overcome osimertinib resistance [36]. One small study found significant radiographic response when two patients with both EGFR mutations and RET fusion mediated resistance to osimertinib were given both osimertinib and *BLU-667* [37]. Case reports have examined the role of continuing to treat with osimertinib for patients with CNS disease, which often has fewer resistance mutations than extracranial disease, even as chemotherapy is added for osimertinib resistant systemic disease. One cited a patient with osimertinib resistance whose extracranial disease responded well to chemotherapy,

but who developed leptomeningeal disease only after osimertinib was switched to the chemotherapy. Once the osimertinib was given in addition to chemotherapy, the number of CSF tumor cells declined significantly [38]. Mechanisms of resistance to osimertinib are far from fully understood. Relying on tissue and plasma-based analyses to uncover new mechanisms of resistance to osimertinib, will only become more crucial.

Safety

In addition to increased PFS, osimertinib has demonstrated better tolerability in the first line than its predecessors. Osimertinib had a similar safety profile and was associated with fewer Grade 3 or higher adverse events than its earlier counterparts (34% *vs.* 45%, respectively). These Grade 3 events mainly included rash, diarrhea, and prolonged QT interval in the osimertinib group [39]. Finally, while the interim analysis at 25% maturity was not powered to detect a statistically significant benefit in OS with osimertinib, it suggested a 37% reduced risk of death compared with gefitinib or erlotinib (HR of 0.63) [21].

The role of other third generation TKIs and ctDNA tests

Additional second-generation EGFR TKIs have sought to prove superiority to previous TKIs in the first line setting. In 2017, the ARCHER 1050 study showed a mPFS benefit with dacomitinib compared to gefitinib in first line for patients with advanced, stage IIIB/IV NSCLC harboring an exon 19 deletion or *L858R* substitution (14.7 *vs.* 9.2 months, respectively, HR=0.59, 95% CI=0.47-0.74, p<0.0001) [40]. Just recently, at the 2018 ASCO Annual Meeting, the mature OS results of the study were presented, showing a median OS of 34.1 months with dacomitinib (95% CI=29.5-37.7) versus 26.8 months with gefitinib (95% CI=23.7-32.1) in patients with untreated mNSCLC. Notably, patients with CNS metastases were excluded from this trial [41]. Investigators pointed out this was the first study comparing these EGFR TKIs head to head to show an OS benefit of one over the other. In April 2018, the FDA granted priority review designation for dacomitinib in the first-line treatment of patients with EGFR mutated advanced or mNSCLC. While the OS data with dacomitinib is indeed impressive, dacomitinib appeared to have a higher rate of Grade 3 adverse events including diarrhea, rash, and paronychia. Unlike osimertinib, its efficacy in the CNS is unknown. For these reasons, it is unclear what role dacomitinib will play in the osimertinib era [42].

Circulating tumor DNA (ctDNA) tests have become key diagnostic tools for EGFR mutated mNSCLC, as well as helpful markers of disease severity, molecular transformation during therapy, resistance to therapy, and prognosis [43]. Multiple studies have examined the concordance of ctDNA with tissue biopsies in detecting EGFR mutations at diagnosis. One study showed a concordance rate as high as 96.96% between tissue and ctDNA for mutations in exons 19 and 21 of the EGFR gene [44]. Yet a Spanish study found that while the specificity of ctDNA in identifying EGFR mutations was 96.7%, the sensitivity was only 45.5% [45]. This highlights that while ctDNA tests generally are not the most sensitive, positive results have a high probability of being real, and can potentially avoid an unnecessary tissue biopsy. The new ARMS-Plus technology tests ctDNA for EGFR mutations by detecting mutant plasmid DNA. Preclinical studies found the sensitivity, specificity, and concordance of the ARMS-Plus test for EGFR mutations was 60.7%, 94.6%, and 80.0% compared to tumor tissue as the standard [46]. Another study using droplet digital Polymerase Chain Reaction (ddPCR) testing to detect ctDNA noted a positive correlation between concentration of mutant EGFR in the plasma and response to EGFR TKI therapy [47]. As obtaining tissue is logistically and technically difficult, tests for ctDNA offer a valuable opportunity to uncover each patient's genotype and guide therapy in a reliable, yet less expensive and less invasive manner. Circulating tumor DNA tests may also be less susceptible to false results based on heterogenous tumor tissue.

Circulating tumor DNA will play a growing role in uncovering new molecular mutations during treatment and in monitoring for treatment response and resistance. In AURA3, patients who had EGFR-mutated ctDNA at baseline prior to starting osimertinib had RECIST-defined progression sooner than those who did not have ctDNA at baseline (PFS=13.1 months, SD=8.0 months, *vs.* 19.6 months, SD=8.9 months, respectively) [34]. This supports findings throughout multiple studies that ctDNA portends more aggressive disease, poorer performance status, and higher burden of metastases [48]. Studies are currently investigating the routine use of ctDNA to measure minimal residual disease with treatment, and thus further clarify disease severity and prognosis. A study this year demonstrated that the EGFR mutation load uncovered in ctDNA during treatment with EGFR TKIs reliably predicts response and progression well in advance of radiographic findings. It also showed increased PFS for patients in whom ctDNA was undetectable during treatment compared to patients in whom ctDNA remained detectable (295 vs. 55 days, HR=17.1, p<0.001) [49]. With these advances, ctDNA will become widely accepted not as a replacement for traditional tissue biopsy, but as a complementary tool in NSCLC diagnostics. There are currently two FDA approved tests to detect plasma ctDNA in patients with EGFR-mutated mNSCLC, the Cobas EGFR mutation test for common activating EGFR mutations, and the Cobas EGFR mutation test v2, which detects the T790M mutation.

Obstacles to targeted therapy and final thoughts about precision medicine

It is troubling that in spite of all these clinical advances in the treatment of EGFR-mutated mNSCLC, 20% of patients with advanced NSCLC still do not undergo EGFR mutation testing. Some of this is due to insufficient tissue in biopsies. Thus, educating providers on the importance of adequate tissue for biomarker testing is critical. Studies have shown that cytology using endobronchial ultrasound coupled with transbronchial fine needle aspiration (EBUS-TBNA) can provide sufficient tissue for molecular testing. Adequate samples are optimized when the endoscopist performs multiple passes (three to eight per site) and uses Rapid On-site Evaluation (ROSE) of the tissue obtained [50,51]. If it is truly not feasible to obtain adequate tissue for EGFR mutation testing, then plasma testing for mutant DNA is an acceptable alternative. These tests are highly specific and thus reliable if positive. Yet as they are less sensitive, a negative plasma test does not rule out the presence of an EGFR-sensitizing mutation. The lack of education surrounding proper diagnosis of EGFR mutations highlights the importance of a multidisciplinary approach to caring for these patients.

Another challenge is logistics. Of those who are tested and found to be EGFR-mutation positive, still 20% receive chemotherapy rather than an EGFR TKI as first-line therapy. The main reasons for this appear to be long turn-around time for testing and an urgency to start treatment. Clinicians argue that treating severely symptomatic patients with chemotherapy while awaiting EGFR results is at least alleviating symptoms. Yet the studies mentioned have shown that for the EGFR-

mutated population, EGFR TKIs are superior to chemotherapy across the board, regardless of when they are given. Thus, they should be offered to these patients as early as possible in their disease course. As medical providers, our goal must be to create better models of responsive, multi-disciplinary care which will foster more efficient diagnostics. This in turn will expedite the delivery of targeted therapy.

Conclusion

With the discovery of increasingly more targeted therapies, lung cancer is now enjoying its own therapeutic renaissance. It is a biomarker driven disease where we can deliver powerful targeted therapies to achieve remarkable outcomes for patients who are afflicted. These discoveries have transformed lung cancer into a field that demands precision medicine. Routine checking of molecular biomarker status in those with advanced lung cancer, at bare minimum EGFR, ALK, ROS1, BRAF, and PD-L1, is standard of care in these patients. We as researchers and clinicians must stringently uphold this standard for patients to derive maximal benefit. Precision medicine is a reality and needs to be implemented in our daily practice.

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