Review Article on Mechanisms of Resistance to EGFR-targeted Therapy

Advances in targeting acquired resistance mechanisms to epidermal growth factor receptor tyrosine kinase inhibitors

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Abstract: Next-generation sequencing (NGS) of tumor samples and circulating tumor DNA has revolutionized diagnostic and therapeutic strategies in lung cancer. The identification of the epidermal growth factor receptor (EGFR) oncogenic driver has translated into successful therapy of advanced lung cancer using EGFR tyrosine kinase inhibitors (TKI). Unfortunately, responses are limited by acquired mechanisms of resistance. We review herein the current landscape of acquired resistance mechanisms to EGFR-TKI therapy and recent advances in therapeutic strategies to overcome acquired resistance.

Keywords: Lung neoplasms; receptor, epidermal growth factor; drug resistance; protein kinase inhibitors; carcinoma; non-small cell lung

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Introduction

Lung cancer remains the most common and deadliest malignancy worldwide. Incidence in 2018 has been reported to be 2.1 million new cases and mortality rates represent the highest for cancer-related disease at nearly 20% (1). The identification of epidermal growth factor receptor (EGFR) as an oncogenic driver and the subsequent development of EGFR-targeted therapy represent a revolutionary change in treatment for advanced non-small cell lung cancer (NSCLC).

Lung cancer was traditionally characterized as small cell or NSCLC with non-small cell histology further stratified into squamous, adenocarcinoma, and others (including large cell and neuroendocrine) representing 34%, 55%, and 11% of NSCLC, respectively (2). The distinction between squamous and adenocarcinoma has had predictive therapeutic implications, as pemetrexed has been shown to be preferentially effective in non-squamous histology (3). Application of histological subtype to predict therapeutic response was therefore an early indicator of "personalized" therapy. Now, the revolution and availability of sequencing technology has ushered in a new era of further sub-categorization of NSCLCs and targeted therapy against specific oncogenic driver mutations, with *EGFR* mutants serving as a successful model for drug development against a molecular target (2).

EGFR

EGFR mutations account for approximately 15% of all NSCLC cases. In Caucasian populations, this represents 10–20% of NSCLC compared to 30–40% in Eastern Asian populations (2,4,5). Prevalence is also significantly higher in females, non-smokers, and in adenocarcinoma histology (4).

EGFR is a membrane-bound receptor tyrosine kinase of the ErbB family. Activation causes downstream effects via several signaling pathways including RAS/MAPK, JAK/STAT, and PI3K/AKT/mTOR. Downstream effects include

proliferation, migration, and survival (6,7). Activation of EGFR, therefore, is considered an oncogenic driver. *EGFR* mutants can be categorized as either activating mutations or resistance mutations.

EGFR activating mutations cause constituent activation of EGFR through ligand-independent dimerization and downstream signaling activation. Mutations of exons 18–21 are the most common, with nearly 90% due to deletions in exon 19 or a point mutation in exon 21 (L858R) (8). These mutants lend higher sensitivity to EGFR tyrosine kinase inhibitors (TKIs) owing to an open ATP-binding pocket and lower affinity for ATP itself, thus allowing a competing compound to bind instead (9,10). Other less common activating mutations include exon 20 insertions and mutations at G719X, L861Q, S768I, as well as compound heterozygous mutations in *EGFR* (8,11-13).

EGFR exon 20 insertions account for 5–12% of *EGFR* mutations in NSCLC (9,14). Although they are activating mutations, the mechanism of constituent activation of the tyrosine kinase is unique to that of deletion 19 or L858R. While exon 19 deletions and L858R are considered sensitizing mutations to TKI therapy, insertions of exon 20 are typically resistant to approved EGFR-TKIs with the uncommon exception of the proximal A763_Y764insFQEA mutant (15-18). Exon 20 insertion resistance to EGFR-TKI has been attributed to a conformational change resulting in steric hindrance in the ATP-binding pocket (9,19). Additional means of resistance include the conformational change that induces constituent activation without reducing ATP affinity or increasing affinity for 1st generation EGFR-TKIs (17).

In rare cases, germline mutations in *EGFR* have been reported that increase the risk of developing lung cancer, including the rarely reported *de novo* T790M mutation (20,21). This germline mutation itself can lead to *EGFR*-mutant NSCLC; however, the development of malignancy frequently co-occurs with a second *EGFR* mutation (20). Similar to T790M that arises as an acquired resistance mechanism, germline T790M may be sensitive to 3rd generation TKI (22).

Current guidelines for treatment of advanced non-small cell lung cancers (NSCLC) now include identification of *EGFR* mutations at baseline (23); however, most patients on therapy will develop resistance via acquired mutations. In addition to bypass tracts such as *MET* and *HER2* amplification, secondary on-target resistance mutations while on therapy using EGFR-TKIs can develop. This includes on-target mutations to first-generation EGFR-TKI such as T790M or to third generation EGFR-TKI such as C797S. Multiple clinical trials are underway to evaluate safety and preliminary efficacy of therapeutic strategies to target and overcome *EGFR*-mutant NSCLC that has developed acquired resistance to currently approved EGFR-TKIs (*Table 1*).

First-generation TKIs

First-generation, reversible tyrosine kinase inhibitors (TKI) include gefitinib and erlotinib which exert their effect by competing against ATP at an ATP-binding site (24). Clinical trials examining first-line gefitinib compared to standard chemotherapy has demonstrated significantly improved progression-free survival (PFS) and overall response rates (ORR) (25-27). Gefitinib versus chemotherapy in both NEJ002 and IPASS resulted in similar overall survival between treatment arms, although this was attributed to high crossover to gefitinib therapy in chemotherapy groups (28,29). First-line erlotinib has been examined compared to chemotherapy in the OPTIMAL, EURTAC, and ENSURE trials with findings of improved PFS and ORR, with equivalent overall survival (OS), again suggesting cross-over effect (30-33). Although response rates for first-generation TKIs are up to 70%, inevitably patients will progress after approximately 12 months (34,35).

Second-generation TKIs

Second generation TKIs include afatinib and dacomitinib which are irreversible EGFR-TKIs that covalently bond to C773 and C797 of EGFR, respectively (36,37). Afatinib additionally covalently binds to C805 of HER2 and has been suggested to have activity against T790M in pre-clinical studies (37), although this has not been demonstrated in clinical studies thus far because of its inability to achieve serum concentrations to effectively inhibit T790M in patients without substantial toxicity.

Afatinib in *EGFR*-mutated adenocarcinoma has been compared against chemotherapy in the LUX-Lung clinical trials. In both LUX-Lung 3 and 6, median PFS (mPFS) for afatinib was near 11 months compared to 6.9 months for cisplatin/pemetrexed and 5.6 months for gemcitabine/cisplatin (38,39). Follow-up OS analyses showed no difference between the afatinib and cisplatin-based chemotherapy regimens in all comers; however, a subset of patients with exon 19 deletions showed improved OS in pooled analysis of LUX-Lung 3 and 6. In exon 19 deletion

Table 1 Ongoing selected clinical trials in epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC)

Title	NCT Number	Phase	Target	EGFR TKI	Addition	Mechanism
A phase I trial of AZD9291 and necitumumab in EGFR-mutant non-small cell lung cancer after progression on a previous EGFR tyrosine kinase inhibitor	NCT02496663	I	EGFR	Osimertinib	Necitumumab	EGFR antibody
An open-label, multicenter, phase 1 study with expansion cohorts of ramucirumab or necitumumab in combination with osimertinib in patients with advanced T790M-positive EGFR-mutant non-small cell lung cancer after progression on First-Line EGFR TKI therapy	NCT02789345	I	EGFR T790M	Osimertinib	Necitumumab or ramicirumab	EGFR antibody
A multi-arm, phase Ib, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of AZD9291 in combination with ascending doses of novel therapeutics in patients with EGFRm+ advanced NSCLC who have progressed following therapy with an EGFR TKI	NCT02143466 (TATTON)	I	EGFR, MET, MEK	Osimertinib	Savolitinib, selumetinib, durvalumab	VEGFR2 antibody
A pilot study of dacomitinib for patients with metastatic EGFR mutant lung cancers with disease progression on osimertinib	NCT03755102	I	EGFR C797S	Dacomitinib		
A phase 1/2 study of osimertinib in combination with gefitinib in EGFR inhibitor naïve advanced EGFR mutant lung cancer	NCT03122717	I	EGFR	Osimertinib	Gefitinib	Dual EGFR
A multicenter, open-label phase 1 study of DS-1205c in combination with osimertinib in subjects with metastatic or unresectable EGFR-mutant non-small cell lung cancer	NCT03255083	I	EGFR	Osimertinib	DS-1205c	AXL inhibition
A phase 1B study of AZD9291 in combination with navitoclax in EGFR-mutant non-small cell lung cancer following resistance to initial EGFR kinase inhibitor	NCT02520778	I	EGFR	Osimertinib	Navitoclax	Bcl-2 inhibition
A phase 1 trial of MLN0128 (TAK-228) in combination with osimertinib (AZD9291) in advanced EGFR mutation positive non-small cell lung cancer (NSCLC) after progression on a previous EGFR tyrosine kinase inhibitor	NCT02503722	I	EGFR, T790M negative	Osimertinib	Sapanisertib	mTOR inhibition
A phase 1/2 study of the safety, pharmacokinetics, and anti-tumor activity of the oral EGFR/HER2 inhibitor TAK-788 (AP32788) in non-small cell lung cancer	NCT02716116	I/II	Exon 20 (EGFR and HER2)	TAK-788		
An open-label phase 1/2 study of itacitinib in combination with osimertinib in subjects with locally advanced or metastatic non-small cell lung cancer	NCT02917993	I/II	EGFR	Osimertinib	Itacitinib	JAK1 inhibition
A phase II, single arm study assessing efficacy of osimertinib with savolitinib in patients with EGFRm+ MET+, locally advanced or metastatic non-small cell lung cancer who have progressed following osimertinib treatment	NCT03778229 (SAVANNAH)	II	EGFR, MET	Osimertinib	Savolitinib	MET inhibition

Table 1 (*continued*)

Table 1 (*continued*)

Title	NCT Number	Phase	Target	EGFR TKI	Addition	Mechanism
A phase II study of poziotinib in EGFR in exon 20 mutant advanced non-small cell lung cancer	NCT03066206	II	Exon 20 (EGFR and HER2)	Poziotinib		
A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb–IVb NSCLC with confirmed EGFRm and T790M	NCT03133546	II	EGFR T790M	Osimertinib	Bevacizumab	VEGF-A antibody
Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation	NCT03414814	II	Exon 20 (EGFR)	Osimertinib		
A phase II trial of AZD9291 (osimertinib) with or without bevacizumab in patients With EGFR mutation positive NSCLC and brain metastases	NCT02971501	II	EGFR T790M, brain mets	Osimertinib	Bevacizumab	VEGF-A antibody

patients, median OS for LUX-Lung 3 was 33.3 months in the afatinib group compared to 21.1 months in the chemotherapy group (HR 0.54, P=0.0015). Similar findings were seen in LUX-Lung 6, with median OS 31.4 months in the afatinib group compared to 18.4 months in the chemotherapy group (HR 0.64, P=0.023). This effect was not seen in L858R mutants (40). Afatinib has also been examined against placebo in patients that failed chemotherapy and first-generation TKIs. This demonstrated a median PFS benefit of 2 months but no OS benefit (41). LUX-Lung 7 compared afatinib to gefitinib, with a mild improvement in time to treatment failure of 2 months but with more toxicity, predominantly diarrhea and rash. Follow-up analyses demonstrated higher responses with afatinib (72.5% *vs.* 56.0%) but similar OS including exon 19 deletion and L858R subgroups (42).

Afatinib with cetuximab, a monoclonal antibody against EGFR that reduces the EGFR burden in tumors, has been examined in the setting of erlotinib and gefitinib resistance. Combination afatinib and cetuximab was studied in a phase Ib trial of patients with advanced *EGFR*-mutated NSCLC resistant to 1st generation TKIs (43). Response rates of 29% and median PFS of 4.7 months were similar regardless of acquired T790M status. The afatinib and cetuximab combination was furthermore examined in a sequential treatment strategy. Patients who progressed on 1st generation TKI, then progressed on afatinib were additionally given cetuximab (44). Overall response rate was 11% with median PFS 2.9 months. Results favored the T790M-positive tumors, as all responders were in this group and median PFS was 4.8 *vs.* 1.8 months for T790M-negative tumors. SWOG 1403 examined front-line afatinib with or without cetuximab in *EGFR* exon 19 deletion or L858R mutants; however, accrual was halted early owing to interim analysis demonstrating futility in PFS, OS, and time to treatment discontinuation (45). For *EGFR* exon 20 insertion patients, a small study of afatinib and cetuximab showed promise, as partial responses were seen in 3 out of 4 patients with median PFS of 5.4 months (46).

Dacomitinib has been less well-studied than afatinib but has also been evaluated in the phase III ARCHER 1050 trial, which lead to FDA approval in front-line therapy. Compared to gefitinib, dacomitinib resulted in higher median PFS (14.7 *vs.* 9.2 months), higher duration of response (14.8 *vs.* 8.3 months), but also higher rates of grade 3 and higher adverse events (63% *vs.* 41%) including diarrhea, paronychia, and rashes (47).

Uncommon EGFR mutations

Of the *EGFR*-mutated NSCLCs, exon 19 deletion and L858R accounts for the vast majority. Other less common mutants include exon 20 insertion, G719X, L861Q, S768I, and compound heterozygous mutations in *EGFR*. These represent 5–10% of *EGFR* mutants with exon 20 insertion being the most frequent of the uncommon mutations (12,13). Afatinib has demonstrated efficacy against G719X, L861Q, and S768I and is FDA approved for these mutations, although only 75 out of 600 patients in the study had uncommon *EGFR* mutations (48). A phase II trial of osimertinib in 35 patients with *EGFR* mutations other than exon 19 deletion, L858R, and exon 20 insertions has also suggested preliminary efficacy but this is not yet conclusive (49).

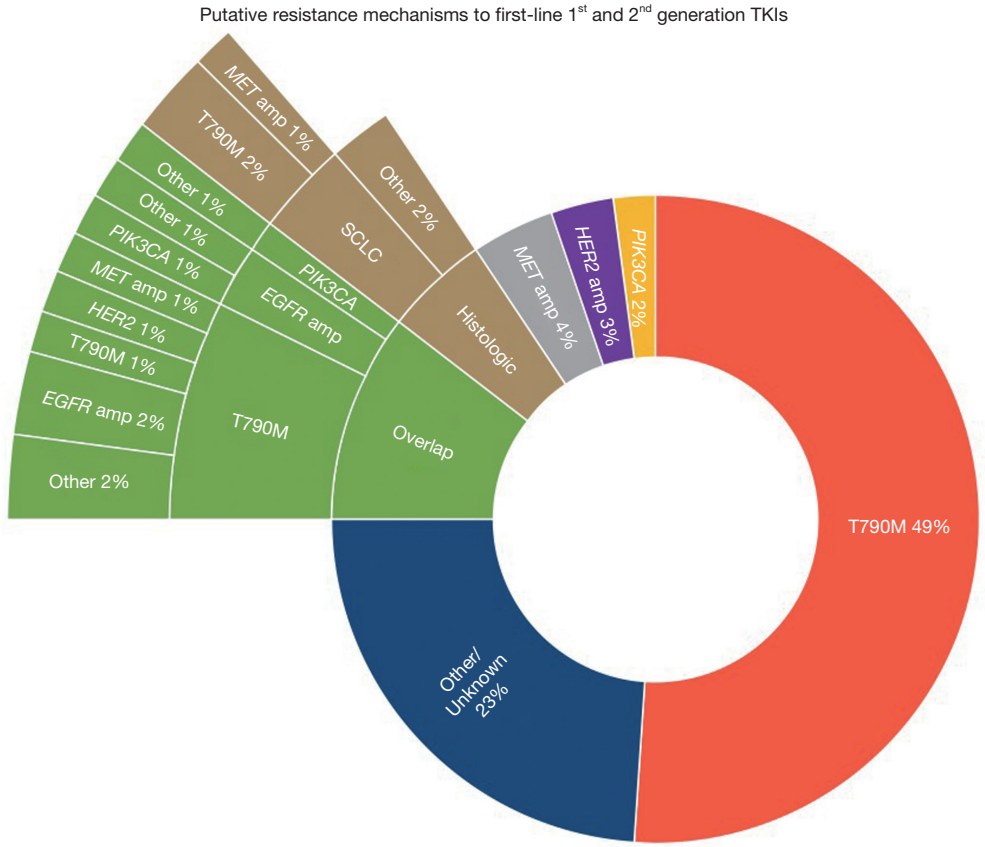

Figure 1 Approximate frequencies of acquired resistance mechanisms to first-line 1st and 2nd generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) amongst selected studies that evaluated pre- and post-progression genomic data (55,59-62). Amp, amplification; SCLC, small cell lung cancer.

T790M

Invariably, patients develop resistance and progress on EGFR-TKI treatment. Identification of mechanisms of resistance to first- and second-generation EGFR-TKI were initially examined in case reports and small retrospective studies with a common finding of a secondary *de novo EGFR* mutation of exon 20 with methionine to threonine substitution at position 790 (T790M) (50-53). Threonine 790 has been considered a "gatekeeper" given its location in the ATP binding cleft (24,54). Therefore, one proposed mechanism of resistance for T790M has been steric hindrance (24) but further examination has shown that the mechanism is likely due to increasing ATP affinity, thus superseding the ATP-competing effects of first-generation TKIs (54).

Subsequent larger retrospective studies, prospective studies, and meta-analyses have shown approximately 50–60% of patients treated with first- or second-generation EGFR-TKI develop T790M mutation, with other less frequent mechanisms including secondary mutations bypassing the EGFR pathway (e.g., *BRAF*, *PIK3CA*, *KRAS*, *MET* amplification, *HER2* or *ERBB2* amplification), histologic transformation (e.g., small cell transformation), and other *EGFR* mutations (35,55-59). Amongst reports studies of paired pre- and post-progression tumor genetics that have analyzed T790M, *HER2* amplification, *MET* amplification, or *PIK3CA*, overlap of multiple oncogenic drivers are commonly reported as a means of acquired resistance (*Figure 1*) (55,59-62).

Although afatinib was promising against T790M in pre-clinical studies, subsequent clinical studies have shown rates of acquired T790M mutations comparable to first-generation TKIs (35,58,63). Dacomitinib long-term response is similarly limited by T790M and additionally C797S mutations (64).

Third-generation TKIs

Osimertinib is a third-generation EGFR-TKI that irreversibly binds to the EGFR-TKD and is able to overcome resistance mediated by *EGFR*-T790M. The mechanism of action is via covalent binding to the C797 residue of the ATP-binding domain of EGFR (65,66). Its effects are mechanistically unique from first and second-generation TKIs with additional activity against T790M mutants in addition to activity against canonical *EGFR*-sensitizing mutations (exon 19 deletion and L858R) while sparing wild-type *EGFR* more than previous generation EGFR-TKIs (66).

Osimertinib was examined in patients with *EGFR*-mutated NSCLC that failed first-generation TKIs with promising results (67). Sixty two percent of the enrolled patients in this study had T790M, with approximately three-fold higher response rates and median PFS compared to non-T790M cases (T790M positive—ORR 61%, mPFS 9.6 months; T790M negative—ORR 21%, mPFS 2.8 months). The phase I AURA trial initially demonstrated promising results with response rates over 70% and median PFS of 20 months (68). AURA3 furthermore examined osimertinib compared to platinum/pemetrexed chemotherapy in patients with progression after first-generation TKIs and T790M mutation (69). Osimertinib had higher response rates and median PFS compared to platinum-based chemotherapy (ORR 71% *vs.* 31%; mPFS 10.1 *vs.* 4.4 months; HR 0.30; 95% CI, 0.23–0.41; P<0.001). Median PFS benefit was also seen in patients with brain metastases (8.5 *vs.* 4.2 months; HR 0.32; 95% CI, 0.21–0.49; P value not reported).

The pivotal FLAURA trial examined front-line osimertinib against first-generation TKIs in *EGFR*-mutated patients with either exon 19 deletion or L858R (70). Compared to first-generation TKIs, osimertinib demonstrated comparable response rates but with significantly higher median PFS (18.9 *vs.* 10.2 months; HR 0.46; 95% CI, 0.37–0.57; P<0.001) and median duration of response (17.2 *vs.* 8.5 months). A trend towards improved OS was shown (18-month survival: 83% *vs.* 71%; HR 0.63; 95% CI, 0.45–0.88), though has not reached sufficient accrual yet to determine statistical significance. Toxicity profile also favored osimertinib. In patients with CNS metastases, the progression-free survival and response rates were similar to the overall population with progression-free survival still favoring osimertinib.

Rociletinib is a 3rd generation EGFR-TKI that covalently binds the C797 residue and at first showed promise in a phase I/II clinical trial TIGER-X of 130 patients (later enrolling over 600 patients) in the second-line setting (71,72). Median follow-up time was only 10.5 weeks and unconfirmed responses were included in analysis. ORRs were initially reported as 59% amongst T790M-patients. Updated results however showed ORRs of 45% (73). Side effects notably included QT prolongation (grade 3, 5%) and hyperglycemia (grade 3, 22%), the latter owing to a rociletinib metabolite inhibiting insulin growth factor receptor 1. Unfortunately, due to less-than-expected ORRs, side effects, and a better tolerated alternative in osimertinib, the FDA declined to grant rociletinib accelerated approval and its development was subsequently halted (72).

Similar to earlier generation TKIs, a similar problem of eventual progression and development of acquired resistance exists with 3rd generation TKIs. Examination of patients who progressed on previous generation *EGFR*-targeted therapy and then progression on osimertinib initially revealed three patterns of resistance: loss of T790M, maintenance of T790M with or without the *EGFR* C797S mutation (74). These findings have been confirmed in larger patient cohorts with the C797S mutation (75,76). Interestingly, loss of T790M may portend a worse prognosis as it has been associated with significantly shorter time to discontinuation of therapy (6.1 *vs.* 15.2 months) (75). Other resistance pathways have included *EGFR* L718 and L792 mutants and small cell transformation (74,75,77,78).

Putative resistance mechanisms of 1st line osimertinib

The phase I AURA trial examined osimertinib in sixty *EGFR*-mutated, NSCLC, treatment-naïve patients. Nineteen patients with progression underwent next-generation sequencing analysis of peripheral blood for identification of putative resistance mechanisms. In contrast to earlier generation EGFR-TKIs, acquired T790M was not identified as a resistance mechanism. Of these cases, other resistance mutations included C797S, *MET* amplification, and *KRAS*, *PIK3CA*, *HER2*, and *JAK2* mutations (68).

Preliminary data from the FLAURA trial has resulted in unique resistance patterns for front-line osimertinib use compared to second-line osimertinib use (*Figure 2*). Resistance mechanisms included *MET* amplification (15%), C797S mutation (7%), and less commonly *HER2* amplification, *PIK3CA* mutation, and *RAS* mutations (79). T790M was not detected as a secondary mutation as it

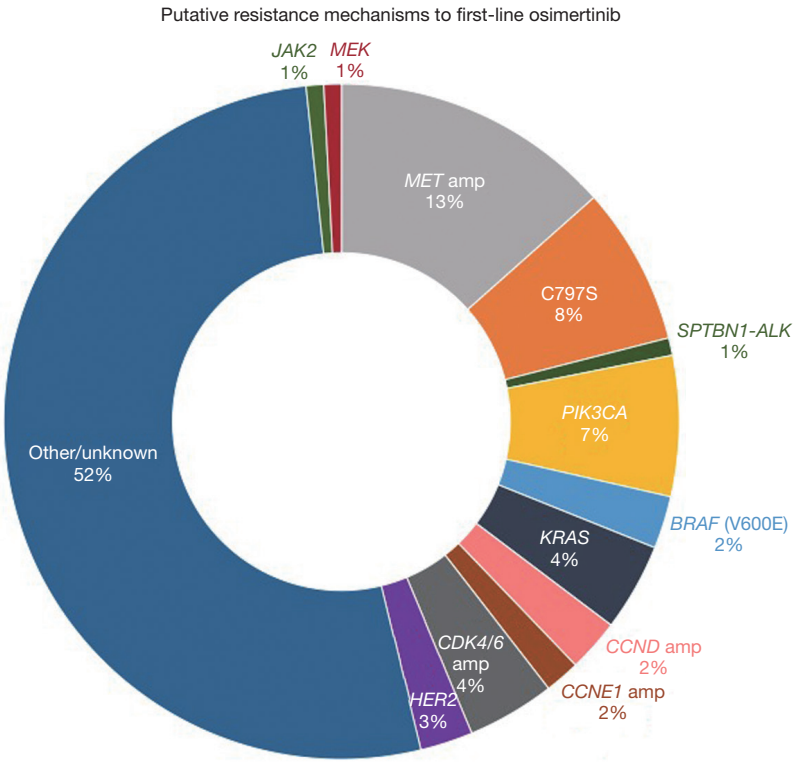

Figure 2 Approximate frequencies of acquired resistance mechanisms to first-line osimertinib, a 3rd generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), based on FLAURA results (79). Histologic transformation is not included as a mechanism due to the use of ctDNA.

is suppressed by osimertinib and unable able to develop without exposure to prior first- or second-generation EGFR-TKI. This is in stark contrast to standard-of-care 1st generation EGFR-TKI which demonstrates T790M as the most common resistance mechanism, seen in over half of these patients. As understanding of resistance mechanisms to 1st line osimertinib has evolved, so have efforts to identify combinatorial strategies to overcome these resistant *EGFR*-mutant NSCLCs (*Table 1*).

The landscape of resistance mechanisms to targeted therapy continues to evolve with the increasing availability and cost-effectiveness of next-generation sequencing, whether using peripheral blood or tissue samples. The current practice model of identifying oncogenic drivers and development of targeted therapies against these mutations has translated into clinical success. Unfortunately, this strategy does not account for other concurrent mutations and is limited by the development of resistance mechanisms. TKI therapy seemingly applies selective pressures to increase genomic complexity (80). Furthermore, development of resistance has been associated with higher mutational burden and worse prognosis (81). This highlights the importance of identifying pathways to resistance and subsequent therapies to either prevent or directly treat resistant clones.

On target EGFR-TKI resistance mechanisms

C797S

The C797S mutation is a substitution of cysteine at position 797 of *EGFR* exon 20 for serine, thus altering the binding site of osimertinib and mechanistically mediating resistance. This mutant accounts for 20–25% of resistance to osimertinib when used as second-line or later therapy (75,76). *In vitro* experiments have demonstrated allelic variation for the acquisition of C797S, as the mutant can occur either on the same (*cis*) or different (*trans*) allele with respect to T790M. *Cis* mutants with C797S and T790M have been suggested to be more resistant to EGFR-directed therapy including combination first and third

generation TKIs whereas *trans* mutants retain sensitivity to combination TKI therapy (77). This approach has been attempted in the clinical setting where identification of patients with *trans* T790M and C797S mutants have had brief success with combination osimertinib and first-generation TKI (82,83). Development of *cis* mutation may also play a role in acquired resistance to combination therapy in initially *trans* mutants (83). Amongst C797S-mediated resistance to third-generation TKI, *cis* mutants seem to be much more common than *trans* mutants (84).

In front-line therapy with third generation TKI, C797S develops in the absence of T790M (79). This is a unique scenario that includes those with activating *EGFR* mutations (i.e., either exon 19 deletion or L858R) and C797S without T790M. *In vitro* experiments have suggested sensitivity to first generation TKIs in this setting whereas the addition of T790M confers additional resistance (77).

EGFR T790M/C797S

The so-called triple mutant of activating *EGFR* mutation, T790M, and C797S has been a challenging scenario to treat especially in the setting of *cis* mutants. A pre-clinical study of triple-mutated T790M, C797S, and exon 19 deletion has suggested synergistic efficacy for combination brigatinib, an anaplastic lymphoma kinase inhibitor with additional activity against EGFR, and cetuximab, an antibody against EGFR (85). Combination therapy has been tested pre-clinically in L858R triple mutants as well (86). EGFR allosteric inhibitors of the EGFR ATP-binding site such as EAI045 have been postulated to have activity in this setting, as the L858R mutation helps enlarge the allosteric binding site. Cetuximab further exposes this allosteric binding site through repositioning and disruption of the EGFR dimer, which has been observed in pre-clinical models of L858R triple mutants (86). Combination EAI045 and cetuximab in both double-mutated (L858R, T790M) and triple-mutated (L858R, T790M, C797S) offered synergistic efficacy in the mouse model (87). Whether these strategies translate into successful therapy in the clinical setting is yet to be known.

MET aberrations (amplification and mutation)

The mesenchymal epithelial transition (*MET*) factor is a proto-oncogene encoding for a receptor tyrosine kinase c-MET whose ligand is hepatocyte growth factor (HGF). Activation results in downstream signaling effects via MAPK, PI3K, SRC, and STAT pathways (88,89). Shared downstream effects contribute to synergism between *MET* and *EGFR* on oncogenesis (90). *MET* alterations, specifically amplification, have been identified as a driver mutation in a variety of malignancies including lung cancer, and are typically associated with a poor prognosis (91). *MET* mutations have also been described as a resistance mechanism to third generation EGFR-TKI albeit at a lower frequency that *MET* amplification (76). *MET* amplification occurs as a resistance mechanism though all generations of EGFR-TKI but appears to be more frequent for progression with osimertinib than previous generation EGFR-TKI (*Figures 1*,*2*).

MET amplification in the setting of first and second generation EGFR-TKI accounts for only 5% of acquired resistance (57). In front-line osimertinib, *MET* amplification accounts for nearly 15% of acquired resistance (79). Multiple trials are ongoing to examine the efficacy of combination EGFR-TKI with MET inhibitors, including the TATTON and SAVANNAH trials (*Table 1*). Preliminary data for the TATTON trial investigating savolitinib with osimertinib after progression on prior EGFR-TKI has shown promising preliminary results in c-MET positive patients, defined by FISH (amplification of *MET*/*CEP*7 ratio ≥2 or polysomy with copy number ≥5), NGS (≥20% tumor cells, ≥200× sequencing depth of coverage, and ≥5 copies over tumor ploidy), or IHC (staining 3+ in ≥50% of tumor cells). In patients with prior 1st or 2nd generation EGFR-TKI, objective response rate was 52% with a stable disease rate of 35%. In patients with prior 3rd generation EGFR-TKI, objective response rate was 25% with a stable disease rate of 44%. Most common grade ≥3 AEs included rash, transaminitis, and fatigue (92,93).

HER2

HER2 or ErbB2 is another receptor tyrosine kinase but without a known ligand. *HER2* overexpression and amplification biases the receptor equilibrium towards dimerization, either homodimers or heterodimers with other ErbB receptors. This triggers downstream signaling through pathways such as PI3K and RAS/MAPK that ultimately promote cell survival and proliferation (94). *HER2* overexpression is most well-known for its role in breast cancer oncogenesis, and targeted antibody therapy against HER2 has been critical to the success of treating breast cancer. *HER2* mutations appear to be a distinct

mechanism of *HER2* activation and oncogenesis compared to *HER2* gene overexpression/amplification, and the two entities rarely overlap (95). *HER2* overexpression/amplification represents approximately 12% of acquired resistance to previous generation EGFR-TKI (96). This is in contrast to 1st line osimertinib where the frequency of *HER2* overexpression/amplification is closer to 2% although this may be underestimated due to detection with plasma ctDNA (79).

HER2 is targeted through either small molecular inhibitors or antibodies, and clinical efficacy has been mixed in NSCLC. HER2-directed antibody therapy such as trastuzumab is a well-known success story in *HER2*-overexpressed breast cancers; however, this success has not translated to lung cancer based on a prior phase II trial in the second-line setting after chemotherapy (97). In cases with *EGFR* mutations, *HER2* overexpression, and progression on prior EGFR-TKI, the combination of trastuzumab and paclitaxel has shown modest clinical efficacy with objective response rate of 46% and median duration of response 5.6 months (95% CI, 3.8–7.3) (98).

Afatinib is a 2nd generation EGFR-TKI with HER2 activity and may have activity in *HER2* exon 20 mutated NSCLC based on a small exploratory phase II study (99). Osimertinib has also been suggested to have additional activity against HER2 (100). In *in vivo* mouse models, osimertinib was effective against HER2-mediated resistance in *EGFR* exon 19 deletion with *HER2* overexpression, but not against exon 20 insertion *HER2* mutants. Notably, the addition of a BET inhibitor may have a synergistic effect via enhanced pro-apoptotic signaling when combined with osimertinib (100).

Fusion bypass tracts

In addition to resistance via C797S, *MET* amplification, and *HER2* overexpression in osimertinib therapy, fusion mutants have also been described as a mechanism of acquired resistance. This commonly includes fusions with *BRAF* or *RET* (101). Cell lines of *PCPB2-BRAF* fusions were found to be sensitive to trametinib, a MEK inhibitor, but not BRAF inhibitors. In a *CCDC6-RET* fusion cell line model, combination osimertinib and BLU-667, a RET inhibitor, was found to cause lower levels of downstream ERK and AKT phosphorylation while also reducing cell viability. This strategy of combinatorial osimertinib and BLU-667 was utilized in two patients with *RET* fusions and demonstrated encouraging responses (101).

EGFR exon 20 insertions

EGFR exon 20 insertions represent the third most common set of *EGFR* activating mutations and are considered "insensitive" activating mutations owing to a lack of response to 1st generation EGFR-TKIs, except for the proximal A763_Y764insFQEA variant (17). The mechanism for resistance is multi-factorial including steric hindrance, conformational change "locking" EGFR in an activated state, unchanged ATP-binding affinity, and unchanged EGFR-TKI affinity compared to wild type *EGFR* (9).

Poziotinib is a small, selective, and flexible small molecular inhibitor of EGFR and HER2 that can bypass effects of steric hindrance. Poziotinib has shown efficacy in pre-clinical models including patient-derived xenografts and mouse models of *EGFR* and *HER2* exon 20-mutated NSCLC. This treatment strategy was then evaluated in a small phase II trial of *EGFR* exon 20-mutated NSCLC (19,102) where updated analysis included 40 evaluable patients. Starting dose was set at 16 mg but 45% of patients required reduction to 12 mg or less due to toxicity. Most common grade ≥3 adverse events were rash and diarrhea. Objective response at 8 weeks was 58% (95% CI, 40.9–73.0%), disease control rate was 90% (95% CI, 76.3–97.2%), and median PFS was 5.6 months (95% CI 5.06–NA months).

TAK-788 is a small molecular inhibitor of EGFR and HER2 with activity against *EGFR* exon 20 insertions (103). In a phase II trial of 34 patients, 62% of patients harbored *EGFR* exon 20 insertions. Fourteen patients were evaluable for response, of which three patients had partial response and six patients had stable disease. Notably, all patients with partial responses had *EGFR* exon 20 insertions. Most common AEs included diarrhea, nausea, fatigue and serious AEs included pulmonary toxicity (103).

TAS6417 is a TKI that binds to the ATP-binding pocket of EGFR with activity against exon 20 insertion and is EGFR wild-type sparing. This selective EGFR-TKI has shown promise in pre-clinical cell line studies demonstrating reduced levels of EGFR phosphorylation and downstream signaling markers such as AKT and ERK while showing increased levels of apoptotic markers. Tumor response has been seen in both *in vitro* and *in vivo* PDX models (104).

Osimertinib is a front-line option in T790M-mutated NSCLC; however, it has additional activity against exon 20 insertion mutants. This effect was first seen in *in vitro* cell line experiments (105). Subsequent examination of *EGFR*

exon 20 insertion in cell-line and mouse xenograft studies have supported osimertinib and its metabolite AZ5104 as a viable therapy option. Furthermore, osimertinib and AZ5104 were more efficacious for tumor growth inhibition than afatinib (106). For *HER2* exon 20 insertions, osimertinib has shown limited success in mouse models, although this may be overcome by combination with BET-inhibition (100). Adding an EGFR-monoclonal antibody (necitumumab) to osimertinib may also have activity against select *EGFR* exon 20 insertions (107). In another study, six Chinese patients with *EGFR* exon 20 insertions were treated with osimertinib; this resulted in a median PFS 6.2 months (95% CI, 5.0–12.9) over a median follow-up time of 6.2 months (108).

Anexelekto (AXL)

AXL is a receptor tyrosine kinase that is a member of the TAM (TYRO3, AXL, MERTK) family. Activation occurs via both GAS6 ligand-dependent and GAS6 ligand-independent mechanisms. AXL activation causes homodimerization, phosphorylation, and subsequently activation of multiple downstream pathways including PI3K, MEK, NF-κB, and JAK-STAT. This ultimately leads to proliferation, migration, and stemness. AXL activation also suppresses inflammation through inhibiting toll-like receptor responses, T-cell activation, NK-cell activity, and cytokine release (109). *AXL* and its ligand *GAS6* as oncogenic drivers have been reported in a variety of malignancies, including lung cancer, and usually portends a poor prognosis and advanced disease (110). *AXL* expression has furthermore been implicated as a marker of resistance to multiple types of therapy, including chemotherapy and targeted therapy (109-111). This effect is additionally noted in *EGFR* NSCLC treated with osimertinib (112).

AXL expression frequency in NSCLC has been variably reported to be between approximately 30% to upwards of 90% with some differences likely attributable to inconsistent measurement modalities as *AXL* is typically evaluated using IHC (111). Its role in *EGFR*-mutated NSCLC has been investigated in preclinical and clinical studies. Furthermore, *AXL* expression is correlated with expression of other markers (e.g., vimentin) involved in epithelial-mesenchymal transition (EMT), suggesting transformation as a potential mechanism of *AXL*-mediated resistance (113). Mice xenograft models of *EGFR*-mutated NSCLC have shown *AXL* and *GAS6* are associated with acquired resistance to erlotinib. In *in vitro* and *in vivo* models, EGFR-TKI sensitivity was restored with AXL inhibition, either genetically or pharmacologically with AXL-targeted antibodies or small molecular inhibitors. EGFR-TKI sensitive lines were induced to become EGFR-TKI resistant with overexpression of wild-type *AXL* as well. Therefore, *AXL* has been implicated to be both necessary and sufficient for erlotinib resistance (113). Similar results have been seen in studies of gefitinib-resistant *EGFR*-mutated *in vitro* models where *AXL* knockout restored gefitinib sensitivity, and *AXL* overexpression promoted gefitinib resistance (114).

The role of *AXL* in EGFR-TKI resistance has additionally been examined in patient tumors. In 35 patients with *EGFR*-mutated NSCLC patients progressive on 1st generation EGFR-TKIs, *AXL* and *GAS6* expression by IHC were examined in addition to other mechanisms of resistance. Identified resistant mechanisms included T790M (29%), *MET* amplification (19%), *GAS6* (25%), *AXL* (20%), and vimentin as a surrogate for EMT (20%). Three patients with baseline *AXL* mutations developed *GAS6* overexpression after progression on EGFR-TKI (113). In a study of 26 Korean patients, a similar frequency of *AXL* mutants (19.2%) in EGFR-TKI-resistant NSCLC was seen (115).

AXL has been implicated in resistance to 3rd generation EGFR-TKI (112,116). Preclinical studies have suggested that osimertinib reduces expression of *SPRY4*, which suppresses AXL phosphorylation, thus leading to AXL activation and subsequent HER3, MET, and EGFR activation (112). Knockdown of 2 out of 3 of *HER3*, *AXL*, or *EGFR* led to synergistic reductions of cell viability (112). *AXL* and *GAS6* expression have been inversely correlated to 1st and 3rd generation EGFR-TKI susceptibility (112,116). Decreasing *AXL* expression in PDX models and *in vitro* models restores osimertinib sensitivity through suppression of AKT signaling, and combining AXL inhibition and osimertinib may prevent emergence of resistant clones (112,116).

Histologic transformation

Transformation of *EGFR*-mutated NSCLC represents an alternative means of acquired resistance that often necessitates treatment with chemotherapy. Although next-generation sequencing represents a comprehensive method of identifying genomic changes, it is unable to detect histological changes especially when blood-based analysis is used. The most common transformation is to small cell lung

cancer, although epithelial-mesenchymal transitions and sarcomatoid transformations are also seen (55,60,62,117). These tumors typically maintain their founder *EGFR* mutant; however, in T790M disease this often is lost after transformation. Recurrent mutations such as *p53*, *Rb1*, and *PIK3CA* may be genomic clues indicative of transformation if histological examination is unavailable (117). *AXL*-mediated EMT has also been suggested to promote histologic transformation (113).

Aurora kinase A (AKA)

AKA is a serine/threonine kinase that regulates cell cycle progression, mitosis, and meiosis by controlling bipolar spindle assembly and chromosome separation (118). Overexpression effects include genomic instability, cell-cycle dysregulation, de-differentiation and ultimately tumorigenesis (118,119). In NSCLC, EGFR therapy may cause upregulation of TPX2, an upstream activator of AKA. Activation of AKA causes apoptotic escape, mitotic abnormalities, and persistence and heterogeneity of EGFR-TKI-resistant clones (120). The addition of an AKA inhibitor, MLN8237, to 3rd generation TKI in *in vitro* and *in vivo* cell models has increased apoptosis, enhanced magnitude of response, and delayed emergence of resistance. Furthermore, AKA is likely necessary for survival of 3rd generation TKI-resistant clones as MLN8237 demonstrated activity when added sequentially after development of resistance (120).

Immunotherapy in EGFR-mutant NSCLC

EGFR-TKIs are standard-of-care first-line therapy options for *EGFR*-mutated NSCLC. Therefore, many immunotherapy clinical trials have excluded such tumors. Meta-analyses of clinical trials that have included *EGFR* mutants have shown that single-agent immune checkpoint inhibition with PD-1/PD-L1 antibodies does not provide an overall survival benefit in *EGFR*-mutated disease (121,122). This is likely due to lack of mutational load and smoking associated signature that relates to an increase in neoantigen specific T-cell activity (123). Interestingly, *EGFR*-mutant NSCLC with increased tumor mutational burden has been suggested to have inferior survival and earlier time to treatment discontinuation (81).

The combination of immunotherapy with EGFR-TKIs has generally not been successful owing to increased toxicities. Several clinical trials have examined this therapeutic strategy. Erlotinib with atezolizumab has been evaluated in a phase Ib study of 28 patients, 43% of whom had grade 3 adverse events most commonly pyrexia, rash, diarrhea, and transaminitis, with serious adverse events reported in half of all patients (124). Erlotinib with nivolumab was evaluated in a phase I study of 21 patients, and grade 3 events including transaminitis, diarrhea, and weight loss were seen in 23.8% of patients although no grade 4 or 5 toxicities were noted (125). Gefitinib with durvalumab has been evaluated in a phase I expansion trial with two arms: concurrent together (n=10), or gefitinib alone for 4 weeks followed by concurrent therapy (n=10). While response rates were approximately 80% amongst both arms, therapy was discontinued owing to transaminitis in 3 patients and pneumonitis in 1 patient—all from the second arm (126). The TATTON phase Ib trial explored osimertinib with durvalumab but unfortunately 38% of patients developed interstitial lung disease, whereas monotherapy with either alone resulted in only 2–3% of patients developing interstitial lung disease. This safety issue has halted this arm of the TATTON trial (127). The phase III CAURAL trial attempted to investigate osimertinib with durvalumab but was similarly stopped early due to concern of lung disease based on the TATTON trial (128).

Angiogenesis

Vascular endothelial growth factor (VEGF) is known for its role in angiogenesis; however, it has been implicated to have additional function in creating an immune-tolerant tumor microenvironment (129). Therefore, anti-VEGF therapy may synergistically enhance immunotherapy efficacy. On this basis, IMpower 150 sought to evaluate the efficacy of first-line atezolizumab, bevacizumab, and chemotherapy (carboplatin and paclitaxel) in metastatic non-squamous NSCLC, including in a subset of patients with *EGFR* and *ALK* mutations (130). Patients were randomized between three arms: (I) atezolizumab and chemotherapy followed by atezolizumab maintenance, (II) atezolizumab, bevacizumab, and chemotherapy followed by atezolizumab and bevacizumab maintenance, (III) bevacizumab and chemotherapy followed by bevacizumab maintenance. Data for the PD-L1, anti-VEGF, and chemotherapy arm compared to the anti-VEGF and chemotherapy arm have been reported. The former was associated with longer median PFS in the wild-type (8.3 *vs.* 6.8 months; HR 0.62; 95% CI, 0.52–0.74; P<0.001) and intention-to-treat populations (8.3 *vs.* 6.8 months; HR 0.61; 95% CI, 0.52–

0.72). A longer median OS was observed in the wild-type population (19.2 *vs.* 14.7 months; HR 0.78; 95% CI, 0.64–0.96; P=0.02). Furthermore, median PFS was longer in the subset of patients with a higher T-cell gene expression signature (11.3 *vs.* 6.8 months; HR 0.51; 95% CI, 0.38–0.68; P<0.001). The subset of patients with *EGFR* or *ALK* mutations also seemingly derived median PFS benefit (9.7 *vs.* 6.1 months; HR 0.59; 95% CI, 0.37–0.94), although this was demonstrated in post-hoc analysis and included only 13.5% of the intention-to-treat population. Such a strategy of VEGF and PD-1 directed therapy would benefit from further validation in prospective randomized clinical trials in NSCLC with driver mutations.

The role of combinatorial VEGF inhibition and erlotinib has been examined in the NEJ026 trial. Patients were randomized to erlotinib plus bevacizumab 15 mg/kg every 21 days versus erlotinib monotherapy. One hundred twelve patients in each arm were evaluable for efficacy and safety at interim analysis. Median PFS for erlotinib and bevacizumab therapy *vs.* erlotinib monotherapy was 16.9 *vs.* 13.3 months, respectively (HR 0.605; 95% CI, 0.417–0.877; P=0.016). Grade 3 or higher adverse events were higher in the combinatorial arm (88% *vs.* 46%) and was mostly attributable to rash, with less common serious adverse events of neutropenia and liver dysfunction (131). The underlying mechanism of benefit for adding bevacizumab is unclear. It has been postulated to be due to the anti-angiogenesis and pro-apoptotic effects, although VEGF seems to have an additional role in immunomodulation of the tumor microenvironment (129).

Conclusions

The advent of next-generation sequencing and identification of driver mutations and their respective targeted therapies has revolutionized care of patients with metastatic lung cancer. While EGFR-TKIs are effective and safe therapies for *EGFR*-mutated NSCLC, survival is still limited by development of a diverse group of acquired resistance mechanisms that drive recurrent disease. We have discussed here the current landscape of resistance mechanisms to EGFR-targeted therapy within the context of contemporary treatment of *EGFR*-mutated NSCLC. As next-generation sequencing of both tissue and peripheral blood increases in clinical practice, our understanding of this process will evolve. There is a clear and present need to develop treatment strategies to either prevent or directly treat acquired resistance to next generation EGFR-TKI.

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Footnote

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