Drug Evaluation

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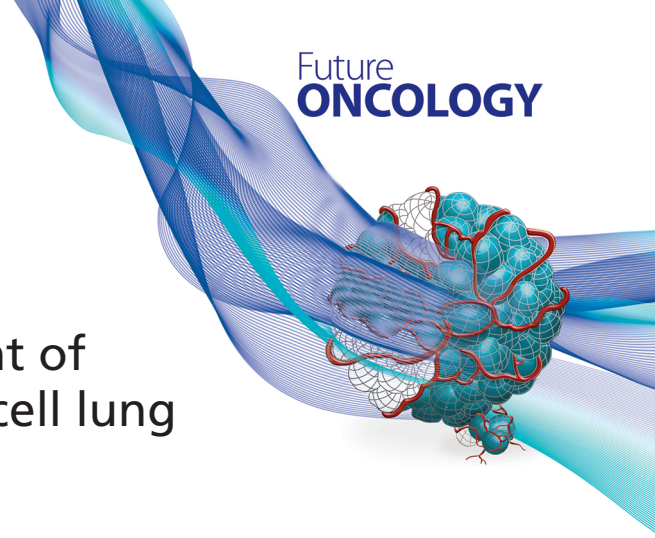

Role of osimertinib in the treatment of EGFR-mutation positive non-small-cell lung cancer

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Mutations in the EGFR occur in approximately 10–35% of non-small-cell lung cancer (NSCLC) patients. Osimertinib is a third-generation oral small molecule inhibitor of EGFR, active against the common targetable activating EGFR mutations in L858R and exon 19 deletion; it also inhibits the T790M mutation. It was initially developed and approved for the treatment of acquired resistance to EGFR inhibition mediated by the T790M pathway activation. Recently, the FLAURA trial showed significantly improved progression-free survival with osimertinib compared with the first generation EGFR tyrosine kinase inhibitors gefitinib or erlotinib; this has led to its approval by US FDA and European Medicines Agency (EMA) as frontline therapy. Ongoing studies will define the resistance mechanisms to osimertinib, novel combination approaches and role in earlier stages of NSCLC.

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Lung cancer is the number one cause of cancer-related death worldwide [1]. Based on SEER data, there will be an estimated 234,030 new cases and 154,050 lung cancer deaths in the USA alone in 2018, of which non-small-cell lung cancer (NSCLC) accounts for over 80% [2]. The distinct molecular category of EGFR mutated NSCLC was first recognized in 2004 [3]. Activating somatic mutations in the kinase domain, including in-frame deletions in exon 19 (ex19del) and the point mutation in exon 21 substituting leucine for arginine (L858R), were found in approximately 10% of NSCLCs in Caucasian patients and in 35% in the Asian population [4,5]. This was the first oncogenic driver mutation identified in never smokers [6,7] and sparked the rigorous development of molecularly targeted therapies for lung cancer.

The first generation, reversible EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib were found to be superior to platinum-based chemotherapy in patients with EGFR mutant advanced NSCLC [8–10]. Acquired resistance invariably develops in approximately 9–10 months [8–10] following EGFR TKI therapy. Second generation EGFR TKIs were developed with the goal of overcoming resistance by blocking additional tyrosine kinases such as HER2 [11]. Afatinib, an irreversible inhibitor of EGFR (ErbB1), HER2/ErbB2 and ErbB4, was superior to platinum doublet chemotherapy, with a median progression-free survival (PFS) of 11–13 months [12,13] in the front-line setting. Other early generation EGFR inhibitors approved internationally, such as icotinib, showed similar results [14]. Never-smokers, females and those with ex19del had slightly better outcomes [15] with EGFR TKI therapy.

Multiple mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been elucidated. In a series of 155 patients who underwent prospective biopsy at the time of resistance to gefitinib or erlotinib, 98 patients (63%) developed *EGFR* T790M mutations and four patients transformed to small-cell lung cancer, while in a smaller sample size, MET amplification was seen in 5% and HER2 amplification in 13% [16]. Similar results were seen with afatinib, with approximately 50% of patients developing T790M at the time of progression, regardless of exposure to a first generation TKI [17]. While biopsy for direct tumor sequencing is still required in some cases for detection of T790M, liquid biopsies based on sequencing of cell-free or circulating tumor DNA

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have been validated for baseline and resistance mutation detection [18–21]. These platforms can spare patients the risks associated with more invasive procedures and enable serial monitoring, which has become essential to caring for patients with EGFR mutated NSCLC.

Osimertinib (Tagrisso™, [formerly AZD9291] AstraZeneca, Cambridge, UK) is an oral third-generation TKI that selectively targets activating EGFR mutations including exon 19 deletion, L858R in exon 21, as well as the common T790M gatekeeper mutation mediating acquired resistance to early generation EGFR TKIs. Here, we review the preclinical data, pharmacology, clinical efficacy and safety results with osimertinib, as well as ongoing translational research investigating mechanisms of resistance.

The T790M mutation is structurally located in the back of the ATP binding cleft, and confers resistance by increasing the affinity of the mutant EGFR to ATP, thereby reducing the potency of reversible kinase inhibitors that bind to the kinase domain [22]. In addition to being the most common acquired resistance mechanism, the T790M mutation can also be found prior to initiation of any EGFR TKI (*de novo*) in a subset of patients. The incidence of *de novo* T790M is variable, as estimates range from 1% using a mass spectrometry assay to 80% using an ultra-sensitive droplet digital PCR detection method [23–25]. Among patients with a baseline T790M mutation, approximately 50% may have a germline mutation [26]; they do not respond to first-generation EGFR TKIs [25]. While multiple compounds including nazartinib (EGF816) and avitinib (AC0010), are under clinical evaluation, there are currently no other approved third-generation EGFR TKIs besides osimertinib [27].

Osimertinib was developed through design and optimization of multiple compounds that inhibit the activating mutations L858R and ex19del as well as the methionine gatekeeper residue in T790M, in order to be 'double mutant selective' [28]. It specifically and irreversibly binds (covalent) to the cysteine-797 residue in the ATP binding site of the EGFR kinase domain [28]. Additionally, osimertinib is almost 200-times more potent against L858R/T790M then the wild-type EGFR [29], which minimizes the skin and gastrointestinal toxicity observed with wild-type EGFR inhibition [30].

Preclinical testing & pharmacology

Osimertinib is a mono-anilino-pyrimidine with molecular formula $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$, and molecular weight of 596 g/mol. The chemical name is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt [31]. *In vitro* cell line testing demonstrated that osimertinib potently inhibits phosphorylation of the EGFR in cells with ex19del and L858R with mean IC_{50} values of 13-54 nmol/l; unlike the first-generation EGFR TKIs, it also inhibits EGFR phosphorylation in cells harboring T790M mutation with IC_{50} of <15 nmol/l [29]. Cell lines harboring less common EGFR variants, including G719S, L861Q and exon 19 insertion were also inhibited by osimertinib, in a comparable manner to early generation TKIs.

Osimertinib was effective in xenograft murine models, with significant tumor reduction in PC-9 cells (harboring ex19del) and H1975 cells (harboring L858R/T790M) after 14 days of low daily dosing at 2.5 mg/kg [29]. Shrinkage was also seen in H3255 (L858R) and PC-9VanR (ex19del/T790M) cells at a dose of 5 mg/kg/day of osimertinib for 14 days. Similar findings were seen in an *in vivo* transgenic tumor model that used tetracycline inducible tumors that express *EGFR* L858R or L858R+ T790M+ [29]. While tumors with only L858R were sensitive to erlotinib, only osimertinib induced significant tumor shrinkage in the L858R+ T790M+ tumors. Confirmation of the pharmacodynamics effects were evident by reduced phospho-EGFR staining and downstream signaling in both animal models from 6 h to over 30 h post-dose [29].

Osimertinib has good oral bioavailability with mean peak plasma concentrations seen after 6 hours; it is not significantly altered by food or changes in gastric pH. Metabolism is primarily mediated by CYP3A4/5 into two active metabolites, AZ5104 and AZ7550 [29]. The half-life after a single dose is approximately 50 hours. No dose adjustments are necessary for mild to severe renal impairment (CrCl >15) or mild to moderate hepatic impairment (total bilirubin 1.5–3× upper limit of normal and any aspartate aminotransferase elevation) [31]. Elimination is primarily by fecal route, although some metabolites can be found in the urine after daily administration. Pharmacokinetic parameters were similar between western and Asian populations and among different formulations [32].

Of note, *EGFR* exon 20 insertions are heterogeneous with varying numbers of base pairs inserted after the C-helix of the tyrosine kinase domain, but as a group they are the third most common type of EGFR mutation behind L858R and del19 [33,34]. Patients with *EGFR* exon 20 insertions (Ex20Ins) are resistant to the first- and second-generation EGFR inhibitors erlotinib, gefitinib and afatinib [35,36]. With just a few exceptions, patients with exon 20 insertions were not included in clinical trials of osimertinib. However, recent pharmacodynamic studies in

cell lines modified by CRISPER/CAS9 to carry the two most prevalent Ex20Ins mutations showed that osimertinib and its metabolite AZ5104 inhibit signaling pathways and cellular growth *in vitro* [37]. Sustained tumor growth inhibition in patient derived xenografts harboring Ex20Ins D770_N771InsSVD or V769_D770InsASV were seen, which supports further study in this population with an unmet clinical need [37].

Clinical efficacy

Phase I/II

The international Phase I/II AURA clinical trial (NCT01802632) included patients with locally advanced or metastatic NSCLC with documented *EGFR* mutation or prior benefit to EGFR targeted therapy following progression on at least one prior EGFR TKI [38]. The dose-escalation portion of the study initially included 6–7 patients per dose cohort (20, 40, 80, 160 and 240 mg) treated with a single dose followed by 1-week pharmacokinetic monitoring; subsequently daily dosing was given in 21-day cycles. As no dose-limiting toxicity was observed and maximum-tolerated dose not defined, an additional 222 patients were enrolled to the 80, 160 and 240 mg/day cohorts. The overall response rate (ORR) of the evaluable group (n = 239) was 51% (95% CI: 45–58) and the median PFS was 8.2 months [38]. Patients with centrally confirmed T790M mutations (total n = 138, evaluable n = 127) had improved outcomes with ORR 61% (95% CI: 52–70) and median PFS of 9.6 months (95% CI: 8.3 to not reached). An increase in rash, dry skin and diarrhea were observed with the 160 and 240 mg dose levels, indicative of wild-type EGFR inhibition; therefore 80 mg/day was chosen as the recommended dose for future trials [38].

The AURA Phase II extension study further established the safety and efficacy of osimertinib 80 mg daily as either second- or third-line therapy in patients with *EGFR* mutated NSCLC with confirmed T790M mutation [39]. A total of 201 patients were treated, with 61 as second line and 140 as third-line. The ORR was 62% (95% CI: 54–68) and the median PFS was 12.3 months (95% CI: 9.5–15.5), with no difference in PFS based on *EGFR*-mutation subtype, ethnicity or line of therapy. In patients with stable asymptomatic brain metastases (n = 74), the median PFS was shorter at 7.1 months compared with 13.7 months in patients without brain metastases, but there was an encouraging 64% ORR in 25 patients evaluable for CNS response by blinded independent central review [39]. This documented the activity of osimertinib against brain metastases. The open label Phase II AURA2 trial (NCT02094261) studied osimertinib 80 mg daily in patients with stage IIIb/IV NSCLC with centrally confirmed T790M mutation, who had progressed on previous EGFR TKI [40]. For the 199 evaluable patients, which including patients with stable CNS disease, the ORR was 70% (95% CI: 64–77) and the median PFS was 9.9 months (95% CI: 8.5–12.3). Serious adverse events possibly related to osimertinib were seen in 11 patients (5%) with one death due to interstitial lung disease (ILD) [40].

Phase III

The AURA3 trial was a randomized international Phase III study comparing osimertinib to platinum-pemetrexed chemotherapy combination in patients with T790M-mutated NSCLC following progression on prior EGFR TKI [41]. The standard of care chemotherapy arm consisted of pemetrexed 500 mg/m^2 plus either cisplatin 75 mg/m^2 or carboplatin dosed to an area under curve of 5 mg/ml/min for up to six cycles, with the option to continue maintenance pemetrexed in responding patients. Osimertinib was superior, with a higher ORR (71 vs 31%; $p < 0.001$) and improved median PFS (10.1 vs 4.4 months, hazard ratio [HR] 0.30; 95% CI: 0.23–0.41; $p < 0.0001$) [41]. A total of 419 patients were randomized in a 2:1 ratio to osimertinib or chemotherapy; following a protocol amendment, 60% of patients who progressed on the chemotherapy on the control group crossed over to receive osimertinib treatment. Patients with CNS metastatic disease (n = 144) treated with osimertinib had significantly longer PFS compared with those treated with chemotherapy (8.5 vs 4.2 months, HR: 0.32, 95% CI: 0.21–0.49). Osimertinib was also very well tolerated, with less grade 3 adverse events compared with chemotherapy (23 vs 47%) [41]. These results confirmed the role of osimertinib as salvage therapy for acquired resistance mediated by T790M mutation.

Building upon the impressive results using osimertinib in the salvage setting, upfront use of osimertnib was tested as a treatment method designed to avoid the development of the T790M mutation. While slightly more than 50% of patients on first generation TKIs develop T790M and derive additional PFS benefit from osimertinib in the salvage setting, the remaining patients develop progressive disease as a result of other resistance mechanisms that do not have an approved targeted therapy. Moreover, there is a potential quality of life benefit in delaying progressive disease rather than waiting for new sites of disease to prompt switching therapy. Promising data were gathered from

Table 1. Efficacy of osimertinib in Phase I, Phase II and Phase III clinical trials.

Clinical trial	Number of patients (group details)	ORR	Median PFS	Ref.
AURA Phase 1 (EGFR+)	253 (T790M+ 138)	51% (T790M+ 61%) (T790M- 21%)	8.2 mos T790M+ 9.6 mos (95% CI: 8.3–NR)	[38]
AURA extension (T790M+)	201	62%	12.3 mos (95% CI: 9.5–13.8)	[39]
AURA2 (T790M+)	210	70%	9.9 mos (95% CI: 8.5–12.3)	[40]
AURA3 (T790M+)	419 (osimertinib: 279) (chemo: 140)	70 vs 30%	10.1 vs 4.4 mos (HR: 0.30; 95% CI: 0.23–0.41)	[41]
FLAURA (EGFR+)	556 (osimertinib: 279) (gefitinib/erlotinib: 277)	80 vs 76%	18.9 vs 10.2 mos (HR: 0.46; 95% CI: 0.37–0.57)	[43]

HR: Hazard ratio; NR: Not reached; ORR: Overall response rate; PFS: Progression-free survival.

the AURA clinical trial, in which 60 treatment-naive patients were treated with osimertinib [42]. In the 80 mg dose group, (n = 30) median PFS was 22.1 months; in the 160 mg dose group (n = 30), the median PFS was 19.3 months. These results were substantially better than previously published reports of gefitinib or erlotinib [42].

The FLAURA Phase III clinical trial compared osimertinib to either gefitinib or erlotinib as initial therapy for patients with advanced *EGFR* mutated NSCLC [43]. In this international double-blind trial, patients were stratified based on type of activating *EGFR* mutation (L858R or ex19del) and Asian versus non-Asian race. Patients were subsequently randomized in a 1:1 fashion to either osimertinib 80 mg daily or a standard EGFR TKI (erlotinib 150 mg daily or gefitinib 250 mg daily). Baseline characteristics were well matched between the osimertinib group (n = 279) and the standard EGFR TKI group (n = 277 with 66% of patients receiving gefitnib and 34% receiving erlotinib). Crossover to osimertinib was permitted and 43% of patients who progressed on standard EGFR TKI received subsequent osimertinib. Treatment with osimertinib led to significantly longer median PFS (18.9 vs 10.2 months, HR:0.46, 95% CI: 0.37 to 0.57; $p < 0.001$) compared with treatment with standard of care first-line EGFR TKIs [43]. While there was no significant difference in the ORR of 80% with osimertinib and 76% with either gefitinib or erlotinib, the median duration of response was longer with osimertinib (17.2 months) over standard EGFR TKI (8.5 months). Importantly, approximately 20% of the 556 patients enrolled had asymptomatic CNS metastatic disease, and the systemic PFS was improved to 15.2 versus 9.6 months with standard of care in patients with CNS disease (HR: 0.47; p = 0.0009) (Table 1) [43].

Safety & tolerability

Osimertinib is safe and well tolerated. In the FLAURA clinical trial, there were fewer grade 3 or higher adverse events in the osimertinib group than the gefitinib or erlotinib group (34 vs 45%) corresponding to fewer permanent discontinuations (13 vs 18%) (Table 2) [43]. Rare but potentially dangerous adverse events seen in the total n = 1142 patients treated on the aforementioned clinical trials have led to the following package insert warnings [31]. ILD was seen in 3.9% of treated patients across all of the above clinical trials and can be fatal if not addressed. Prolongation of the corrected QT interval (QTc) over 500 ms was seen in <1%, but an increase in >60 ms over baseline was seen in 3.6% and should be monitored in patients with risk factors. Cardiomyopathy was seen in 2.6%; therefore left ventricular ejection fraction should be monitored in patients with cardiac risk factors. Lastly, keratitis was seen in 0.7% and patients with eye symptoms should be referred to an ophthalmologist promptly.

Patient-reported outcomes and quality of life assessments are integral to appreciating the tolerability and benefits of osimertinib. Patients enrolled on the AURA3 clinical trial provided data regarding symptoms and quality of life by completing the European Organisation for Research and Treatment of Cancer 13-item Quality of Life Questionnaire-Lung Cancer Module (EORTC QLQ-LC13) and the EORTC 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30) at baseline, 3 months and 1 year into treatment [44]. Baseline scores were well matched between the approximately 82% of patients on both the chemotherapy and osimertinib treatment arms who completed the questionnaire. A higher number of patients treated with osimertinib experienced an improvement in global health status/quality of life then those treated with chemotherapy (37 vs 22%, OR: 2.11, 95% CI: 1.24–3.67; p = 0.07) [44].

Table 2. Summary of drug-related adverse events occurring in at least 15% of patients on the Phase III FLAURA trial comparing osimertinib to standard EGFR tyrosine kinase inhibitor (gefitinib or erolotinib) in the frontline setting.

Adverse reaction ≥15% in any group	Osimertinib (n = 279)		First gen EGFR TKI (n = 277; gefitinib or erolotinib)	
	Grade 1–2, n (%)	Grade 3–4, n (%)	Grade 1–2, n (%)	Grade 3–4, n (%)
Rash	158 (57)	3 (1)	197 (71)	19 (7)
Diarrhea	155 (56)	6 (2)	151 (55)	6 (2)
Dry skin	99 (35)	1 (<1)	97 (35)	3 (1)
Paronychia	96 (34)	1 (<1)	89 (32)	2 (1)
Stomatitis	78 (28)	2 (1)	55 (20)	1 (<1)
Decreased appetite	49 (18)	7 (3)	47 (17)	5 (2)
Pruritus	47 (17)	1 (<1)	43 (16)	0
Cough	46 (16)	0	41 (15)	1 (<1)
Constipation	42 (15)	0	35 (13)	0
Nausea	39 (14)	0	52 (19)	0
AST elevation	24 (9)	2 (1)	56 (20)	12 (4)
ALT elevation	17 (6)	1 (<1)	50 (18)	25 (9)

Grade determined using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
Created using data from [43].

Combinations with immunotherapy

Due to the clinical efficacy of checkpoint inhibitor therapy in non-driver mutant metastatic NSCLC, combination therapies with osimertinib plus checkpoint inhibitors have been investigated. Of note, single agent checkpoint inhibitor therapy with nivolumab, pembrolizumab or atezolizumab was not effective second-line therapy for patients with *EGFR* mutant metastatic NSCLC based on a meta-analysis of patients enrolled on second line clinical trials [45]. A confirmatory Phase II trial of pembrolizumab was not effective in TKI naive *EGFR* mutant metastatic NSCLC patients that had PD-L1 expression of >1% [46]. Two trials testing the combination of osimertinib with durvalumab, namely the Phase III CAURAL trial (NCT02454933) and one arm of the Phase IB TATTON trial (NCT02143466), showed an increased signal of ILD and were stopped early due to safety concerns. As such, combination checkpoint inhibitor and osimertinib combinations are currently not being pursued, but other novel combinations that may address resistance mechanisms are under investigation, as discussed below.

Regulatory affairs

Osimertinib received accelerated US FDA approval in in the USA in November 2015 for patients with targetable EGFR mutations and the T790M mutation based on data from the two AURA Phase II studies (AURA extension and AURA2), followed by full approval in March 2017 based on the PFS benefit seen in the Phase III AURA3 trial. On 18 April 2018, osimertinib received FDA approval in the USA as a first-line treatment for EGFR-mutated NSCLC.

The EMA first approved osimertinib for NSCLC patients with EGFR T790M mutation on 3 February 2016 and the expanded indication as frontline monotherapy for activating EGFR mutated NSCLC was approved on 8 June 2018. Osimertinib was first approved in Japan in March 2017 and in China in March 2017 under a priority review pathway.

Acquired resistance to osimertinib

Osimertinib is a new standard of care for patients with mutant EGFR NSCLC, as it effectively treats or prevents T790M mutations and has significantly improved duration of response over earlier generation TKIs. However, patients typically develop acquired resistance. Acquired resistance mechanisms to EGFR TKIs can be broadly grouped into EGFR-dependent or independent mechanisms. As patients on clinical trials with osimertinib developed progressive disease, genomic testing revealed novel acquired mutations in the EGFR. C797S mutations, initially noted in case reports [47], were found in six out of 15 cases of acquired osimertinib resistance using next-generation sequencing of serially collected cell free plasma DNA [48]. When combined with del19 or L858R and T790M, C797S led to resistance to all EGFR inhibitors in cell lines [49], specifically when on the same allele [50]. Other

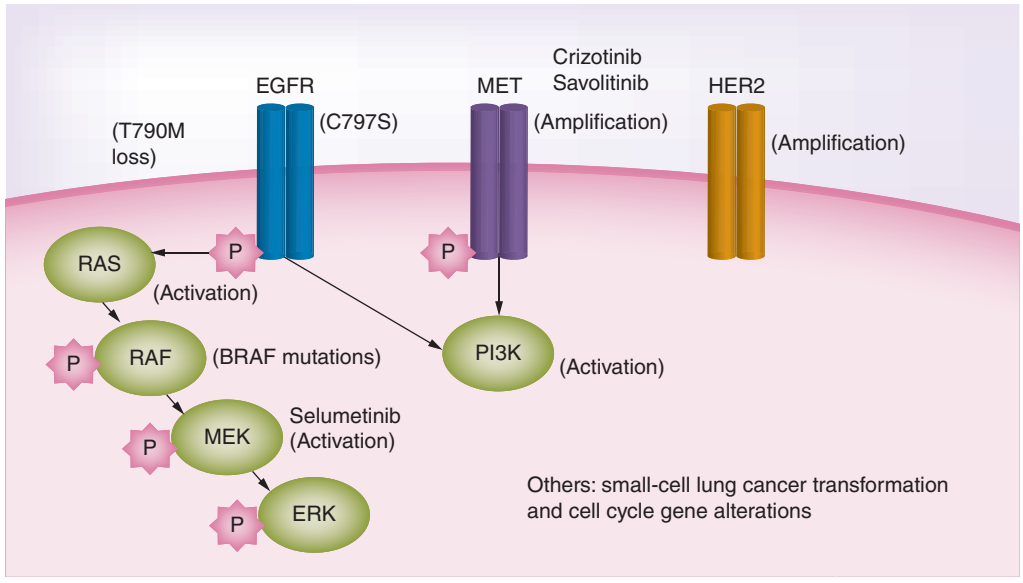

Figure 1. Mechanisms of acquired resistance to osimertinib. EGFR C797S mutations confer resistance to all available EGFR inhibitors. MET amplification leads to downstream PI3K activation. Activating mutations in RAS, RAF and other downstream changes lead to ERK activation. Additionally, a small percentage of patients experience HER2 amplification. Combination therapy trials of osimertinib with the MEK inhibitor selumetinib and the MET inhibitor crizotinib and savolitinib are ongoing.

secondary EGFR mutations in the L792 and L718 residues have recently been described [51]. In a study of 41 patients whose tumors were evaluated by next-generation sequencing at the time of progression on osimertinib, nine patients developed C797S [52]. Interestingly, 28 patients showed a loss of T790M followed by a range of EGFR-independent resistance mechanisms including six with small-cell lung cancer transformation, four with *MET* amplification and two with *BRAF* mutation [52]. Acquired resistance mechanisms just reported from the FLAURA clinical trial include receptor tyrosine kinase mutations in the EGFR, specifically C797 mutations in 7%, HER2 amplification in 2% and *MET* amplification in 15% of patients treated with osimertinib [53]. Downstream intracellular activating mutations were seen in *PI3KCA* (7%), *BRAF* (3%), *KRAS* (3%), along with cell cycle gene alterations [53]. While data on mechanisms mediating primary resistance to osimertinib are currently limited, MET amplification and small-cell lung cancer transformation have been described [54,55].

The *MET* proto-oncogene encodes a receptor tyrosine kinase activated by hepatocyte growth factor [56,57] and can be an independent driver of NSCLC development [58]. Concurrent *de novo MET* amplification and *EGFR* mutation may be a cause of primary resistance to EGFR inhibitors [59]. *MET* amplification was identified as an acquired resistance mechanism in 20% of patients treated with gefitinib or erlotinib, independent of T790M [60,61]. *MET* amplification leads to first-generation EGFR TKI resistance via downstream ERBB3 (HER3)–dependent activation of Phosphatidylinositol 3-kinase (PI3K) [61]. Third-generation EGFR TKI resistance can also be mediated by *MET* gene amplification as seen in osimertinib-resistant HCC827/AR cells [62]. Combination therapy with osimertinib and the multi-target kinase inhibitor crizotinib (PF02341066, effective MET inhibitor) inhibited the growth of both HCC827/ER and HCC827/AR cells *in vitro* and *in vivo* nude mouse model [62]. Recent case reports support this as an acquired resistance mechanism to osimertinib in NSCLC patients who subsequently displayed a partial response to combination therapy with osimertinib and crizotinib [63,64]. In the Phase Ib TATTON study (NCT02143466), 45 patients with EGFR-mutant NSCLC who progressed on at least one prior EGFR-TKI with centrally confirmed MET amplification were treated with osimertinib 80 mg daily and savolitinib (volitinib, HMPL-504, AZD6094) 600 mg daily [65]. Preliminary results are promising with confirmed partial response seen in 20% of patients previously treated with third-generation EGFR TKI, as well as responses in T790M positive and negative patients not yet treated with EGFR TKI [65].

Additional changes downstream of EGFR signaling can also mediate resistance. Post-treatment tumor biopsy testing revealed a KRAS G12S mutation in a patient treated with osimertinib [55]. *In vitro* testing of mutant EGFR cells chronically exposed to escalating doses of osimertinib showed a novel noncanonical E63K mutation in

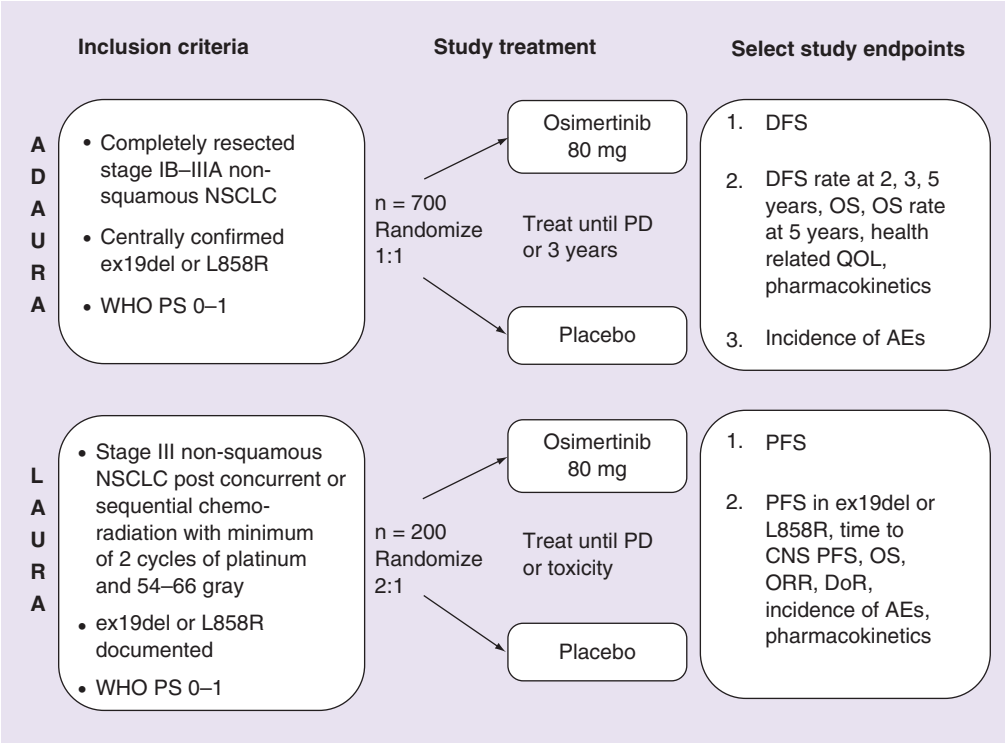

Figure 2. Schema for ongoing adjuvant clinical trials of osimertinib. ADAURA study design: 700 patients will be randomized 1:1 to receive osimertinib 80 mg once daily or placebo once daily until disease recurrence, reach treatment duration of 3 years or other discontinuation criteria is met. FLAURA study design: 200 patients will be randomized 1:2 to receive osimertinib 80 mg daily or placebo once daily until progressive disease or toxicity.
AE: Adverse event; DFS: Disease-free survival; DoR: Duration of response; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival.

NRAS, functionally activating *NRAS* G12V and G12R mutations and gains in KRAS [66]. Interestingly, adding a MEK inhibitor, selumetinib (AZD6244, ARRY-142886) to osimertinib was found to be a potent inhibitor of cell growth in these models, suggesting that the mutant cells become dependent on the MAPK pathway, also termed the RAS-RAF-MEK-ERK pathway [66]. Further analysis of *EGFR*-mutant NSCLC cell lines, HCC827, PC-9, PC-9/GR (T790M), that are sensitive to osimertinib, demonstrated that treatment with osimertinib suppresses ERK-dependent phosphorylation of Bim and Mcl-1 [67]. Bim is a member of the BCL-2 family that is pro-apoptotic, and has three isoforms (short, long and extralong [EL]) based on alternative splicing [68]. In cells sensitive to osimertinib, treatment stabilizes Bim_{EL} levels by preventing its degradation, leading to apoptosis [67]. Mcl-1 is another member of the BCL-2 family that blocks apoptosis [69] and is rapidly degraded unless phosphorylated by ERK [70]. Treatment with osimertinib leads to increased proteasomal degradation of MCL-1 in sensitive cell lines [67]. Combining a MEK inhibitor (PD0325901, GSK1120212, or selumetinib) with osimertinib was effective in overcoming acquired osimertinib resistance and led to apoptosis [67]. This approach is now under active clinical investigation (Figure 1).

Ongoing clinical trials

In an effort to combat acquired resistance and improve outcomes, combination therapies with osimertinib are under active investigation. Ongoing trials include a Phase I/II trial (NCT02803203) underway to investigate combination therapy with osimertinib and bevacizumab in patients with metastatic EGFR mutated NSCLC [71]. NCT03392246 is a Phase II trial of osimertinib in combination with selumetinib, an MEK inhibitor, in EGFR inhibitor naive advanced EGFR mutated NSCLC [72]. Two other trials at the National Cancer Institute are studying second-line osimertinib combination therapies with sapanisertinib, a TORCH inhibitor (NCT02503722) [73] or necitumumab, a human monoclonal antibody against EGFR (NCT02496663) [74] with primary data analysis expected soon.

Other planned trials are assessing the efficacy of osimertinib in non-metastatic NSCLC patients. NCT03433469 is a Phase II trial assessing the efficacy of osimertinib as neoadjuvant therapy given prior to planned definitive resection of stage I–III NSCLC, scheduled to open in December 2018 [75]. ADAURA (NCT02511106) is an ongoing Phase III randomized double-blind, placebo-controlled, clinical trial studying the use of osimertinib for 3 years following complete resection of IB-IIIA NSCLC. Approximately 700 patients will be enrolled and followed for up to 5 years; the expected study completion date is November 2021 [76]. The LAURA trial (NCT03521154) will study the use of maintenance osimertinib following chemotherapy/radiation in unresectable stage III NSCLC [77]. This randomized Phase III, placebo-controlled international trial will enroll approximately 200 patients beginning in summer 2018. Patients may have del19 or L858R alone or in combination with other EGFR mutations and their disease must not have progressed at the time of randomization to osimertinib or placebo within 6 weeks of completion of concurrent or sequential chemoradiation. Primary analysis data are expected in October 2021 (Figure 2) [77].

Conclusion

Osimertinib is a potent and well-tolerated third-generation EGFR TKI. Outcomes from the AURA clinical trials led to approval by the FDA and EMA for patients with NSCLC that developed T790M mutation following earlier generation EGFR TKI. Results from the FLAURA clinical trial support the use of osimertinib in the front-line setting for patients with L858R, del19 or T790M mutations. Clinical trials are ongoing to assess the role of osimertinib in earlier stages of NSCLC, as well as the safety and efficacy of combination therapies that may further reduce acquired resistance.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- Osimertinib (Tagrisso™) is an oral third-generation tyrosine kinase inhibitor that selectively targets activating mutations in the EGFR including exon 19 deletion, L858R in exon 21 and T790M.

Pharmacology

- Osimertinib specifically and irreversibly covalently binds to the cysteine-797 residue in the ATP binding site of the EGFR kinase domain.
- Osimertinib is >200-times more potent against L858R/T790M then the wild-type EGFR [29], which minimizes the skin and gastrointestinal toxicity seen with wild-type EGFR inhibition.
- While no dose-limiting toxicities were seen with higher doses, 80 mg was approved for its robust efficacy and tolerable side effect profile.

Clinical efficacy

- In patients who progressed on first-line EGFR therapy and had documented T790M mutation, overall response rate ranged from 61 to 70% in the AURA Phase I, AURA Phase II extension and AURA2 trials.
- Second-line osimertinib in T790M positive patients has significantly higher overall response rate (70 vs 30%) and progression-free survival (10.1 vs 4.4 months, hazard ratio: 0.3, 95% CI: 0.23–0.41; $p < 0.001$) when compared with standard platinum doublet chemotherapy as shown in the Phase III AURA3 trial.
- Frontline osimertinib significantly improves progression-free survival over gefitinib or erlotinib (18.9 vs 10.2 months, hazard ratio: 0.46, 95% CI: 0.37–0.57; $p < 0.001$).

Safety

- Osimertinib is well tolerated; the most commonly reported side effects are rash, diarrhea and dry skin.
- Interstitial lung disease was seen in 3.9% of the over 1000 patients enrolled on clinical trials of osimertinib and requires prompt diagnosis and treatment.

Regulatory affairs

- Osimertinib was first approved in the USA in November 2015 for NSCLC patients with targetable EGFR mutations and documented T790M mutation.
- On 18 April 2018, osimertinib received FDA approval in the USA as a first-line treatment for EGFR-mutated NSCLC followed by approval in the EU for this expanded indication on 8 June 2018.

Acquired resistance to osimertinib

- An acquired mutation in the EGFR, C797S, mediates resistance to osimertinib and all other currently available EGFR inhibitors.
- *MET* amplification is associated with acquired resistance to gefitinib, erlotinib and osimertinib. Combination therapy with osimertinib and MET inhibitors is under active investigation.
- Activating mutations downstream of the EGFR including (RAS, MAPK and MEK) may mediate acquired resistance, and preclinical studies with MEK inhibitors show promise in overcoming this resistance mechanism.

Ongoing clinical trials

- Combination therapies are under active investigation, including the combination of osimertnib with bevacizumab, savolitinib or selumetinib.
- The ADAURA and LAURA clinical trials will study the use of adjuvant osimertinib following complete surgical resection in stage IB–IIIA NSCLC and chemotherapy/radiation in unresectable stage III NSCLC respectively.

Conclusion

- Osimertinib is a new standard of care for frontline therapy in patients with mutant EGFR NSCLC.

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