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REVIEW

Osimertinib and other third-generation EGFR TKI in *EGFR*-mutant NSCLC patients

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Osimertinib was the first third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) to receive FDA and EMA approval for metastatic *EGFR*-mutant non-small-cell lung cancer (NSCLC) patients that have acquired the EGFR *T790M* resistance mutation. Clinical trials have demonstrated the efficacy of osimertinib in this patient population and clinical trials of other third-generation *EGFR* TKI are currently under way. Additional challenges in this patient population, such as the upfront efficacy of osimertinib, validation of *T790M* in liquid biopsies as a dynamic predictive marker of efficacy, along with combination with immune checkpoint inhibitors are being explored, representing an extraordinary time of development for *EGFR*-mutant NSCLC.

Key words: osimertinib, EGFR TKI, acquired resistance, NSCLC

Introduction

Activating epidermal growth factor receptor (*EGFR*) mutations predict sensitivity to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, icotinib and afatinib with higher overall response rate (ORR) and progression-free survival (PFS) compared with upfront platinum doublet chemotherapy, making them the standard of care [1, 2]. However, tumours invariably develop acquired resistance (AR) ∼9–12 months after treatment initiation [1]. Several mechanisms of AR have been reported, such as secondary *EGFR* mutations, bypass track signalling pathways and histologic transformation [3].

The substitution of threonine to methionine at amino acid position 790 (*T790M*) in exon 20 of the *EGFR* gene reduces first-generation EGFR TKIs binding by enhancing the ATP binding affinity of the kinase domain of the *EGFR*-mutant receptor [4]. This mutation accounts for AR in ∼50%–60% of the patients [3, 5]. *MET* amplification is the second most common mechanism of AR to EGFR TKIs in up to 20% of cases [6] irrespective of the T790M mutational status [7]. Histologic transformation to small-cell lung cancer (SCLC) accounts for 5%–10% of *EGFR*-mutant tumours with AR. Those *EGFR* mutant tumours harbouring completely inactivated Rb and p53 have a 43 times greater risk of small-cell transformation [8]. These transformed SCLC tumours express neuroendocrine markers, maintain the original *EGFR*-sensitizing mutation and respond to standard SCLC chemotherapy [3].

Knowledge of AR mechanisms to EGFR TKIs was one of the triggers behind the development of third-generation EGFR-TKIs, which are active against exon 19 and 21 mutations as well as the *T790M* mutation. Among them, osimertinib (AZD9291) was the first to receive FDA and EMA approval in November 2015 and February 2016, respectively, for metastatic *EGFR*-mutant and acquired EGFR *T790M* mutation–positive non-small-cell lung cancer (NSCLC) patients [9, 10] progressing on or after EGFR TKI therapy. This article provides an overview of preclinical and clinical data on osimertinib and other third-generation EGFR TKIs currently in development. The potential use of osimertinib in the adjuvant setting and the combination of EGFR TKIs with immune checkpoint inhibitors in resistant *EGFR*-mutation NSCLC patients will be also reviewed.

Osimertinib

Osimertinib is a mono-anilino-pyrimidine compound that specifically binds to the EGFR kinase domain irreversibly by

Table 1. IC_{50} values in different EGFR mutant T790M resistant cancer cell lines treated with reversible (gefitinib, erlotinib) and irreversible (afatinib, dacomitinib, osimertinib) tyrosine kinase inhibitors (adapted from Cross [ ])

	H1975 (*L858R/T790M*)	PC-9VanR (*Del19/T790M*)	PC-9 (*Del19*)	H3255 (*L858R*)[a]	*EGFR* WT
Osimertinib	15	6	17	49–60	480
Dacomitinib	40	6	0.7	1.2–1.3	12
Afatinib	22	3	0.6	0.8–1	15
Gefitinib	3102	741	7	11–12	59
Erlotinib	6073	1262	6	8–11	91

[a]95% confidence interval.
WT, wild type.

targeting the cysteine-797 residue in the ATP binding site via covalent bond formation. In cell lines, osimertinib potently inhibited phosphorylation of *EGFR* in PC-9 (*Del19*) and H3255 (*L858R*) cell lines with mean IC_{50} values ranging from 13 to 54 nmol/l. In H1975 (*L858R/T790M*) and PC-9 VanR (*Del19/T790M*) resistant cell lines, activity of osimertinib was reported with mean IC_{50} potency of <15 nmol/l (Table 1) [11]. Osimertinib is more selective to the mutated receptor as evidenced by a high IC_{50} (range from 480 to 1865 nmol/l) in inhibiting phosphorylation of EGFR in wild-type cell lines. Interestingly, osimertinib was not potent against lines harbouring non-T790M resistance mechanisms, such as *MET* amplification or *NRAS* [11].

Osimertinib is metabolized to produce at least two circulating metabolites, AZD5104 and AZD7550. In biochemical assays, AZD7550 had a comparable potency and selectivity profile to osimertinib, although AZD5104 showed greater potency against *EGFR Del19*, *T790M* mutations (both ~8-fold) and wild-type EGFR (~15-fold) [11]. In tumour xenograft and transgenic mouse models harbouring sensitizing and resistance *EGFR* mutations, osimertinib exposure resulted in a profound and sustained tumour regression [11]. Due to the higher selectivity to the mutated receptor, osimertinib is associated with less severe gastrointestinal and skin toxicity compared with first- or second-generation EGFR TKIs [12]. Mean half-life of osimertinib is 48.3 h with minimal food effect on exposure and no differences according to ethnicity (Asian and Non-Asian), body weight, sex or age [13]. Additionally, data from a pharmacokinetic study (NCT02163733) showed that administration of omeprazole does not have an effect on osimertinib exposure [14].

Clinical activity with osimertinib

Phase I experience

A phase I/II dose escalation study of osimertinib (AURA, NCT01802632) was carried out in patients with locally advanced or metastatic *EGFR*-mutant NSCLC patients who had disease progression on previous treatment with an EGFR TKI [15]. The study included dose-escalation and dose-expansion cohorts. Patients were only preselected according to T790M status in the expansion cohort. Sequential cohorts of patients ($N = 253$) received five dose levels of osimertinib ranging from 20 to 240 mg daily. Among 31 patients in the dose-escalation cohort, no dose-limiting toxicity was observed and the maximum tolerated dose was not reached. An additional 222 patients were treated in five dose-expansion cohorts. The *T790M* was detected in 138 patients (62%), not detected in 62 patients (28%), and of unknown status in 22 patients (10%) [15]. Of the 253 patients treated across all dose levels, 239 were assessable for response. The ORR and disease control rate (DCR) in the whole population were 51% [95% confidence interval (CI), 45–58] and 84% (95% CI, 79–88), respectively, without differences according to ethnicity. The median PFS was 8.2 months. Among the 138 patients with centrally confirmed *T790M* mutations, 127 patients were assessable for response. Outcomes were substantiality better in *T790M*-positive tumours compared with *T790M*-negative tumours, with an ORR of 61% (95% CI, 52–70) versus 21% (95% CI, 12–34), a DCR of 95% (95% CI, 90–98) versus 61% (95% CI, 47–73) and median PFS of 9.6 months (95% CI, 8.3 to not reached) versus 2.8 months (95% CI, 2.1–4.3), respectively [15]. The most common adverse events (AEs) were diarrhoea (47%), skin toxicity (rash/acne 40%), nausea (22%) and decreased appetite (21%), and the majority of these were grade 1 or 2 in severity. The 80 mg daily dose was selected as the recommended dose for further clinical trials based on its optimal therapeutic index [15] (Table 2).

In an updated report of the dose expansion cohort in the AURA trial (NCT01802632) with osimertinib 80 mg daily in patients with centrally confirmed *T790M*-positive NSCLC, 61 of 63 patients were assessable for response. The ORR was 71% (95% CI, 57–82) and median PFS was 9.7 months (95% CI, 8.3–13.6) [16].

Phase I extension and phase II studies with osimertinib

Further confirmation of the efficacy and safety of osimertinib 80 mg daily was provided by the extension part of the AURA study in 201 *T790M*-positive advanced NSCLC patients [17]. The ORR and DCR was 62% (95% CI, 54–68) and 90% (95% CI, 85–94), respectively. Median PFS was 12.3 months (95% CI, 9.5–15.5), with 12-month PFS and OS of 52% and 79%, respectively (Table 2). Subset PFS analysis did not report differences

Table 2. Efficacy of osimertinib in phase I, phase II and phase III clinical trials as second-line treatment in EGFR-mutant NSCLC patients

	AURA ph I [15]	AURA extension (T790M+) [17]	AURA2 (T790M+) [18]	AURA3 (T790M+) Osimertinib versus CT [19]	FL-AURA (EGFR+) Osimertinib versus gefitinib [30]
N	253 T790M+: 138	201	210	419 (279 osimertinib and 140 to CT).	556 (279 osimertinib and 277 gefitinib or erlotinib)
ORR	51% T790M+: 61% T790M−: 21%	62%	70%	71% versus 31%, $P<0.001$	80% versus 76%
PFS	8.2 mo. T790M+: 9.6 months T790M−: 2.8 months	12.3 months Brain M1: 7.1 months {C4}	9.9	10.1 versus 4.4 months HR 0.30; 95% CI 0.23–0.41 $P < 0.0001$	18.9 versus 10.2 months HR 0.46; 95% CI 0.37–0.57 $P < 0.0001$

CT, chemotherapy; ORR, overall response rate; PFS, progression-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

according to line of therapy, *EGFR*-mutation subtype, ethnicity or previous exposure to EGFR TKIs. The most common casually related AEs were diarrhoea (43%; grade ≥ 3, $<1\%$) and rash (grouped terms; 40%; grade ≥ 3, $< 1\%$). Interstitial lung disease (ILD) was reported in 4% of patients ($n = 8$, grade 3–5 in six patients). Among those patients with asymptomatic and stable brain metastases ($n = 74$), median PFS was shorter compared with those patients without brain metastases (7.1 versus 13.7 months). In the CNS response analysis set, the ORR was 64% [17], suggesting encouraging results with osimertinib in *EGFR*-mutant NSCLC patients with brain metastases.

The phase II AURA2 trial (NCT02094261) demonstrated similar results [18] (Table 2). The study enrolled 210 *T790M*-positive metastatic NSCLC patients who had progressed after previous therapy with an approved EGFR TKI. The ORR and DCR were 70% (95% CI 64–77) and 92% (95% CI 87–95), respectively, including patients with CNS metastases. Overall, median PFS was 9.9 months (95% CI, 8.5–12.3), with 6- and 12-month PFS of 71% and 44%, respectively. The most common all-causality grade 3 and 4 AEs were pulmonary embolism (3%), prolonged electrocardiogram QT (2%), decreased neutrophil count (2%), anaemia, dyspnoea, hyponatremia, increased alanine aminotransferase, and thrombocytopenia (1%, each) [18].

A pre-planned pooled analysis of AURA extension [17] and AURA2 trial [18] was carried out and included 411 patients (129 patients at second-line and 282 as third-line or beyond). The ORR was 66% (95% CI, 67–71), with median duration of response of 12.3 months (95% CI, 11.1–13.8). Pooled median PFS and OS were 9.9 and 26.8 months, respectively. At 12 and 24 months, 80% and 56% of patients were alive, respectively. The most common (investigator assessed) possibly causally related AEs were rash [grouped term 42%, (grade 3, 1%)] and diarrhoea [39% (<1%)]. Four patients died due to possibly causally related toxicity [19].

Comparison of osimertinib to chemotherapy

The robust efficacy of osimertinib in patients with *T790M*-mediated AR resulted in accelerated approval by the FDA in November 2015. Recently, the results of the confirmatory phase III study of osimertinib versus platinum-based chemotherapy were reported. The AURA3 (NCT02151981) was an open-label randomized phase III trial in second-line setting [20], comparing osimertinib to platinum plus pemetrexed (up to six cycles and followed by optional pemetrexed maintenance) for patients with centrally confirmed *T790M*-positive advanced NSCLC after first-line EGFR TKI. The trial enrolled 419 patients with 60% of patients in the chemotherapy arm crossing over to receive osimertinib at progression. Osimertinib significantly improved PFS compared with chemotherapy [10.1 versus 4.4 months, hazard ratio (HR) 0.30; 95% CI, 0.23–0.41, $P < 0.0001$], and ORR (71% versus 31%, $P < 0.001$, Table 2). Grade 3 AEs were lower with osimertinib (23% versus 47%). In the osimertinib group, the most common AEs reported were diarrhoea (41%), rash (34%), dry skin (23%) and paronychia (22%). ILD-like AEs were reported in 4% of patients. Data on OS are not yet available [20]. These results clearly demonstrate the efficacy of osimertinib as standard treatment in *T790M*-positive NSCLC patients after disease progression on a first- or second-generation EGFR TKI.

Osimertinib as first-line therapy

In EGFR TKI-naive patients, *de novo T790M* mutations were described with variable frequency, ranging from <1% to 80%, depending on detection method [21–23], and predict for less benefit to reversible EGFR TKIs [24, 25]. Unlike gefitinib or afatinib, chronic treatment with osimertinib did not cause AR in PC-9 cells *in vitro* through gain of *T790M* [26]. Therefore, upfront osimertinib therapy for patients with an activating *EGFR* mutation could avoid this mechanism of resistance, given its superior potency against *T790M*.

In the phase I AURA trial, 60 treatment-naive patients with metastatic *EGFR*-mutant NSCLC (77% *T790M*-negative) received upfront osimertinib at 80 mg/day ($N = 30$) or 160 mg/day ($N = 30$). According to treatment dose group, 80 and 160 mg, the ORR was 67% and 87% (77% across doses) and PFS was 22.1 and 19.3 months (20.5 months across doses), respectively [27]. These results are encouraging relative to the efficacy of

gefitinib or afatinib in the first-line setting [28, 29] and suggest osimertinib as a potential option in the first-line setting, independent of *T790M*-status.

The phase III FLAURA trial (NCT02296125) compared osimertinib to erlotinib or gefitinib (standard of care) as first-line treatment in patients with advanced NSCLC and common *EGFR* mutations. Patients with stable CNS metastases were allowed. In the control arm, cross-over to osimertinib was allowed in case of disease progression and confirmation of T790M mutation–based resistance. The primary end point of the trial was PFS. Among 556 patients enrolled (∼20% with brain metastases), a significant improvement in PFS (18.9 versus 10.2 months, HR 0.46, $P < 0.0001$) was reported with osimertinib irrespective of race or *EGFR* mutation subtype compared with standard of care. Osimertinib also improved the systemic PFS in patients with brain metastases compared with standard of care (15.2 versus 9.6 months, HR 0.47, $P = 0.0009$). There were no differences in ORR (80% versus 76%), but osimertinib resulted in a two-fold increase in the median duration of response (17.2 versus 8.5 months). OS data were immature but preliminary results showed promising results (HR 0.63, $P = 0.00068$) in favour of osimertinib, despite the fact that cross-over was allowed. Lower grade ≥3 AEs (34% versus 45%) and a lower discontinuation rate were reported with osimertinib compared with standard of care treatment [30]. These results suggest osimertinib as a new standard in first-line treatment of patients with *EGFR*-mutant advanced NSCLC.

Recently, mechanisms of AR to osimertinib as first-line treatment have been described in cell-free DNA samples from 19 patients included in the phase I AURA trial cohort. Putative genomic resistance mutations were identified in 9 of 19 patients with detectable circulating tumour DNA (ctDNA). There was no evidence of acquired *T790M* mutation in any plasma ctDNA sample analysed. Two cases of acquired EGFR *C797S* resistance mutations were detected: one in a patient with a *de novo T790M* mutation, and one in the absence of *T790M*. Also, an acquired MEK1 *G128V* variant, HER2 exon 20 insertion, JAK2 V617F and MET copy number gains have been described as mechanisms of AR with upfront osimertinib [27]. However, no specific treatment strategies have been established at osimertinib resistance. In preclinical models, if the C797S mutation develops in cells wild-type for T790M (when third-generation TKIs are administered in the first-line setting), the cells are resistant to third-generation TKIs, but retain sensitivity to first-generation TKIs [31]. Efficacy, toxicity and treatment options after osimertinib resistance may help to define the best strategy for sequencing upfront EGFR TKI in this population.

Osimertinib efficacy in central nervous system metastases

Globally, the incidence of brain and leptomeningeal metastases among *EGFR*-mutant NSCLC patients is 31% [32] and ∼9% [33–35], respectively. Erlotinib [36], gefitinib [37] and afatinib [38] have a modest degree of intracranial activity. However, preclinical data demonstrated greater penetration and brain exposure with osimertinib than with gefitinib, rociletinib or afatinib [39]. CNS activity of osimertinib had been reported in the AURA study phase II extension component [17], the phase II AURA2 trial [18], and was recently confirmed in the phase III AURA3 trial. In the phase III AURA3 trial, among 144 patients with stable and asymptomatic brain metastases, PFS was also longer with osimertinib compared with chemotherapy (8.5 versus 4.2 months, HR 0.32; 95% CI, 0.21–0.49) [20]. Among those patients with CNS disease assessable for response ($n = 46$), CNS ORR was 70% with osimertinib compared with 31% with chemotherapy with a median duration of response of 8.9 versus 5.7 months, respectively. Also, the cumulative incidence of CNS progression at 6 months was lower with osimertinib compared with chemotherapy (11.5% versus 28.2%) [40]. AURA3 confirmed the CNS efficacy of osimertinib, with higher and more durable responses while also delaying the onset of brain metastases in this population. A phase II trial (NCT 02971501) assessed the PFS of osimertinib with or without bevacizumab. Indeed, preliminary results from the phase I (BLOOM) trial have reported long-lasting clinical and radiological activity of osimertinib at 160 mg among 21 EGFR TKI pre-treated *EGFR*-mutant NSCLC patients with leptomeningeal metastases (cytologically confirmed) and controlled extracranial disease. Baseline *T790M* mutation was detected in cerebrospinal fluid in two patients and in plasma in six [41]. The ongoing phase II (BLOOM) study (NCT02228369) is enrolling *T790M*-positive (tested in plasma or tissue) NSCLC patients with leptomeningeal disease. Globally, these results endorse the efficacy of osimertinib in cerebral nervous system metastases among *T790M*-positive NSCLC patients.

T790M detection in plasma ctDNA in osimertinib studies

Liquid biopsies based on ctDNA analysis have been described as surrogate samples for molecular analysis replacing molecular analysis of tumour tissue [42] and may allow real-time sampling of multifocal clonal evolution [43, 44]. Also, ctDNA analysis can be used to monitor clonal evolution [45] and identify mechanisms of AR to treatment [44]. Retrospective exploratory analyses have reported that acquired *T790M* mutations (tested by cobas *EGFR* Mutation Testv2) among *EGFR*-mutant NSCLC patients was detected in 50% of patients, in concordance with tumour biopsy–derived genotyping which was 61% [46]. Among patients with sufficient material for concurrent ctDNA and tumour-derived genotyping, ctDNA identified the *T790M* mutation in 5 of 25 (20%) patients in whom the concurrent tissue biopsy was negative [46]. Recently, the cobas plasma *EGFR* Mutation Testv2 detected the *T790M* mutation in 61% of tumour tissue *T790M* mutation–positive patients from AURA extension and AURA phase II trials [47]. New techniques are being developed to increase the sensitivity of detecting *EGFR* sensitizing and resistance *EGFR*-mutations [48].

A retrospective analysis from the AURA I trial demonstrated that patients who were *T790M* positive in plasma had outcomes with osimertinib that were equivalent in RR and PFS to patients found to be positive by a tissue-based assay. Indeed, *T790M* was detected in plasma in 31% of *T790M*-negative tumours [49]. In the AURA3 trial, patients with *T790M*-positive status on both tumour and plasma analysis ($n = 172$) had an RR of 77% with osimertinib, and median PFS with osimertinib was 8.2 months

compared with 4.2 with chemotherapy (HR 0.42, 95% CI, 0.29–0.61), an outcome improvement similar to that in the intent-to-treat population [20]. However, all these data are retrospective and in a population with a known *T790M* status in the tumour.

Prospective validation of liquid biopsy as a surrogate marker for making treatment decisions has started to emerge. Recently, in a cohort of heavily pretreated *EGFR*-mutant NSCLC patients with progression and unknown *T790M* status in the tumour were prospectively treated on the basis of the ctDNA analysis. Those patients with *T790M* positivity in plasma achieved an ORR of 62.5% and 6-month PFS of 66.7%, similar to those patients treated on the basis of tissue analysis [50]. Interestingly, responses were also seen in patients with very low allele fractions of T790M mutation in plasma (<0.5%) [50]. Liquid biopsies also have the potential to function as dynamic surrogate markers of treatment efficacy. Clearance of plasma *EGFR* mutations after 6 weeks of osimertinib therapy was found to be associated with improved RR (70% versus 35%) and median PFS (10.9 versus 5.5 months) among 143 patients with *T790M*-positive NSCLC included in the phase I AURA trial (NCT01802632) [51]. These results support the feasibility of detecting *T790M* from plasma ctDNA samples for making treatment decisions and evaluating efficacy. Additionally, a recent algorithm for plasma and tissue *T790M* testing in patients with AR has been proposed, suggesting that those patients with a negative plasma result should undergo a tissue test [49, 52]. At the present time, EMA and FDA have accepted the use of information from ctDNA analysis to help to select *EGFR*-mutant NSCLC patients for osimertinib [9, 10].

Future directions

Optimal sequence of TKIs

As therapeutic options for this patient population, the issue of optimal sequencing of available agents is still an important question. Moreover, it is unknown whether switching treatment according to molecular progression (i.e. ctDNA *T790M* mutation positivity without RECIST progression) instead of RECIST progression could have an impact on treatment outcomes. Based on the predictive value of liquid biopsies, the three-arm phase II APPLE trial (NCT02856893) [53] in treatment-naive and common *EGFR* mutation NSCLC patients will explore upfront osimertinib, upfront gefitinib switching to osimertinib in case of *T790M*-positivity in plasma and upfront gefitinib and switching to osimertinib according to RECIST criteria regardless of T790M status. The primary end point of the trial is 18-month PFS on osimertinib for assessing whether liquid biopsies could become the new standard procedure for defining disease progression versus RECIST progression in this population and also assessing whether a sequenced strategy is more appropriate than upfront osimertinib.

Dual vascular endothelial growth factor receptor and EGFR blockade inhibit tumour growth in EGFR TKI resistance xenograft models [54]. Two phase II clinical trials have reported improvement in outcome with erlotinib plus bevacizumab combination as first-line treatment in *EGFR*-mutant NSCLC patients [55, 56]. Combination of osimertinib and bevacizumab as first-line strategy is being tested in a phase I/II clinical trial (NCT02803203) and osimertinib and ramucirumab as a second-line strategy among *T790M*-positive tumours in a phase I clinical trial (NCT02789345).

Osimertinib in the adjuvant setting

The role of EGFR TKIs in patients with early NSCLC has not been defined [57, 58]. Following surgical resection, adjuvant platinum-based chemotherapy remains the standard of care, even for patients with an activating EGFR mutation. The ADAURA trial (NCT02511106) is a double-blind, randomized, placebo-controlled trial that will study the efficacy of osimertinib in 700 completely resected *EGFR*-mutant stage IB–IIIA NSCLC patients after adjuvant chemotherapy. The primary end point of the study is disease-free survival. The study is presently accruing patients.

Osimertinib and immune checkpoint inhibitors

Immune checkpoint inhibitors are considered the standard second-line treatment in advanced NSCLC patients based on survival improvement reported in four randomized phase III clinical trials [59–62]. Recently, another phase III trial has reported significant improvement in PFS and ORR with pembrolizumab as first-line treatment compared with standard platinum-based chemotherapy among tumours with high PD-L1 expression ($\geq$ 50%) [63]. However, a recent meta-analysis has reported lack of survival benefit with these agents among EGFR-mutant tumours [64] and a retrospective study has reported lower RR with immune checkpoint inhibitors in *EGFR*-mutant versus *EGFR*-wild-type NSCLC patients [65]. The lack of association with smoking and the limited mutational tumour burden of *EGFR*-mutant tumours [66, 67] may explain the lack of efficacy among this population.

Preclinical data have reported *T790M*-positive tumours as immunogenic [68], and tumours with AR to EGFR TKIs express higher levels of PD-L1 than sensitive tumours [69]. However, in the clinic, *T790M* mutation correlates with lower PD-L1 expression and PD-L1 expression was a negative prognostic factor [70]. *EGFR*-mutant NSCLC patients and *T790M*-negative tumours were more likely to benefit from nivolumab after EGFR-TKI treatment, probably as a result of higher PD-L1 expression than is present in *T790M*-positive patients [71]. Other trials testing the combination of osimertinib and immune checkpoint inhibitors, such as the phase III CAURAL trial (NCT02454933) and the multi-arm phase IB TATTON trial (NCT02143466) investigating osimertinib (80 mg/d) in combination with durvalumab (anti-PD-L1 monoclonal antibody), were stopped for safety concerns regarding increased incidence of ILD. Exploratory analysis from the TATTON trial ($n = 34$) reported encouraging clinical activity with RR of 67% in 9 patients with T790M-positive tumours compared with 21% in 14 T790M-negative NSCLC. ILD was reported in 38% of patients, which is higher than would be expected with either drug alone, including five patients (15%) with grade 3–4 events [72]. Results from the other two arms in the TATTON trial (osimertinib plus selumetinib and osimertinib plus AZD6094) are awaited.

Other third-generation EGFR TKIs

Rociletinib and olmutinib are other third-generation TKIs in development. Rociletinib has demonstrated promising results with a 59% ORR for patients with an activating *EGFR* mutation and the *T790M* mutation. However, updated data decreased the observed ORR to 28–34% [73]. This decrease, along with toxicity issues such as hyperglycaemia, led to halting of the clinical development of rociletinib. Olmutinib also demonstrated initial successes with ORR of 56% and median PFS of 8.3 months in *T790M*-positive NSCLC patients [74]. While it was initially approved in South Korea, its clinical development is currently uncertain, as two cases of toxic epidermal necrolysis and one case of Stevens–Johnson syndrome have been reported.

However, there are several other third-generation EGFR TKIs currently in clinical development. Avitinib is a third-generation irreversible EGFR TKI that targets both *EGFR* activating mutations as well as the *T790M* mutations. Enrolment is currently ongoing in a phase I trial for patients who progress on a first-generation EGFR TKI, with or without the *T790M* mutation. Overall, the drug has been well tolerated and ORR for 48 assessable patients was 41.7% with a DCR of 87.9% [75]. The drug ASP8273 is also an irreversible EGFR TKI that targets the *T790M* mutation. Preliminary results from the phase I study have been reported; 60 patients have been enrolled and no dose-limiting toxicities were noted. ORR is 36% and the median PFS is 6.7 months [76]. However, the phase III SOLAR trial (NCT02588261) comparing ASP8273 with erlotinib or gefitinib as first-line treatment in *EGFR*-mutant NSCLC patients has been discontinued and no further development programs for ASP8273 have been announced. The phase I with the EGFR TKI EGF816 enrolled 127 patients with a *T790M* mutation that could be evaluated for response, with an ORR of 44% and estimated PFS of 9.2 months [77]. Finally, the EGFR TKIs PF-06747775 and AZD3759 are at an early stage in clinical development. Interestingly, AZD3739 was specifically designed to penetrate the blood–brain barrier, as CNS metastasis is a common location of progression for EGFR patients. The early data are promising for this patient population, with 40% of patients demonstrating CNS tumour shrinkage [78]. Further studies are ongoing for these drugs and will potentially increase the therapeutic options.

Discussion

Conclusion

Osimertinib is the first FDA and EMA approved third-generation EGFR TKI and has proven to be both well-tolerated and effective in patients with the acquired *T790M* resistance mutation, significantly improving the treatment options for this disease. The results of the FLAURA study support the use of osimertinib as first-line therapy and represent a new standard for this patient population. Further research into how to improve on these findings are currently under way, including combining osimertinib with other drugs, examining its use in adjuvant settings and furthering research into resistance mechanisms. The development of osimertinib has clearly improved the therapeutic landscape for *EGFR*-mutant NSCLC and presents exciting opportunities for clinicians and patients.

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