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ADISINSIGHT REPORT

Osimertinib: First Global Approval

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Abstract Osimertinib (Tagrisso™, AZD9291) is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that is being developed by AstraZeneca for the treatment of advanced non-small cell lung cancer (NSCLC). Osimertinib has been designed to target the *EGFR* T790M mutation that is often present in NSCLC patients with acquired EGFR TKI resistance, while sparing wild-type *EGFR*. In November 2015, the tablet formulation of osimertinib was granted accelerated approval in the USA for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC (as detected by an FDA-approved test) who have progressed on or after EGFR TKI therapy. Osimertinib has also been granted accelerated assessment status for this indication in the EU, and is in phase III development for first- and second-line and adjuvant treatment of advanced *EGFR* mutation-positive NSCLC in several countries. Phase I trials in patients with advanced solid tumours are also being conducted. This article summarizes the milestones in the development of osimertinib leading to this first approval for NSCLC.

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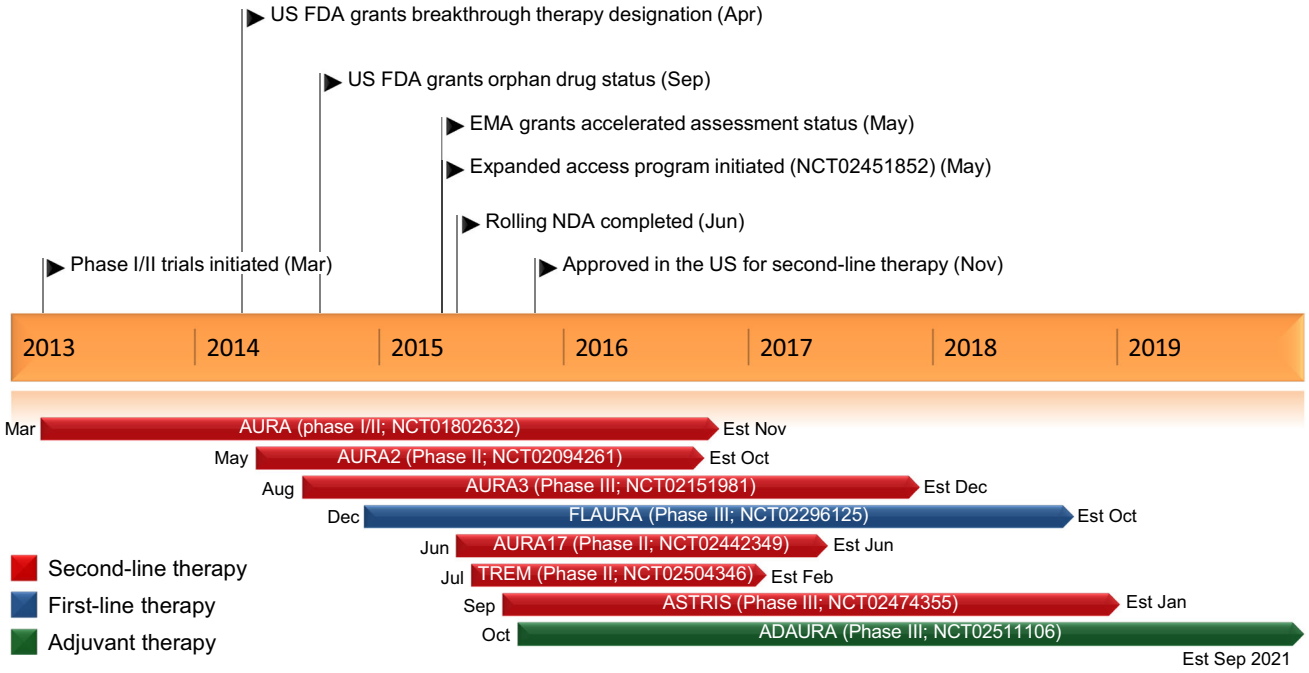
1 Introduction

In non-small cell lung cancer (NSCLC), first-generation epidermal growth factor tyrosine kinase inhibitors (EGFR TKIs) [gefitinib and erlotinib] are particularly effective in tumours with activating *EGFR* mutations [e.g. exon 19 deletions (Exon19del) and L858R mutations] and are often used as first-line therapy [1, 2]. As many patients develop resistance to EGFR TKI therapy, second-generation EGFR TKIs (afatinib and dacomitinib) have also been developed, although these are often associated with toxicities (e.g. diarrhoea and skin rash), most likely caused by inhibition of wild-type EGFR [3]. The most common mechanism of acquired resistance to EGFR TKIs (50–60 % of cases) is a *EGFR* T790M gatekeeper mutation [2, 3]. Thus, third-generation EGFR TKIs have been developed to target this *EGFR* T790M mutation and sensitizing *EGFR* mutations, while sparing wild-type EGFR [1, 3].

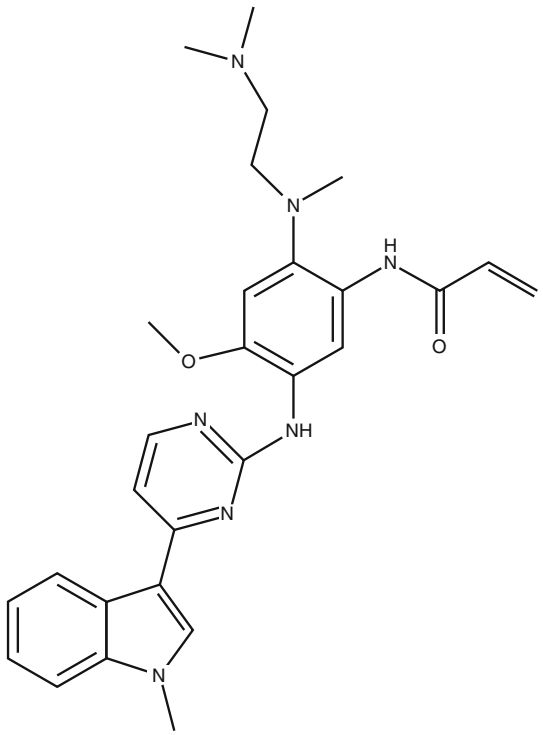
Osimertinib (Tagrisso™, AZD9291) is a third-generation EGFR TKI that targets tumours with certain *EGFR* mutations, including T790M [1, 3, 4]. In November 2015 [5], the US FDA granted accelerated approval of the tablet formulation of osimertinib for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC (as detected by an FDA-approved test) who have progressed on or after EGFR TKI therapy [4]. Continued approval of osimertinib in this indication may be contingent on description and verification of clinical benefit in confirmatory trials [4]. The approval of osimertinib was based on tumour response rate and duration of response in two phase II trials in pretreated patients with advanced, *EGFR* T790M mutation-positive NSCLC; a phase II extension of the phase I/II AURA trial (NCT01802632) and an additional phase II trial (AURA2; NCT02094261) [6].



Key development milestones of osimertinib in NSCLC

The recommended dosage of osimertinib is 80 mg once daily until unacceptable toxicity or disease progression (PD) [4]. Osimertinib tablets (available as 40 and 80 mg) can be taken with or without food, or in patients who have difficulty swallowing solids, dispersed in ≈50 mL of non-carbonated water and immediately consumed or administered via nasogastric tube [4].

Osimertinib was granted US FDA breakthrough therapy designation, orphan drug status and fast track status for NSCLC in 2014 [7], and was granted US FDA priority review designation by early September 2015 [8]. In May 2015, osimertinib was granted accelerated assessment status in the same indication in the EU [9], and received priority review status in Japan in the third quarter of 2015 [10]. The tablet formulation of osimertinib is currently under phase III development as first- and second-line and adjuvant therapy in this indication in several countries, although clinical development of osimertinib in combination with the PD-1 inhibitor durvalumab has been temporarily suspended due to reports of interstitial lung disease (ILD). A phase I trial investigating the pharmacokinetics, safety and tolerability of osimertinib in patients with solid tumours is ongoing in the USA and several EU countries.



Chemical structure of osimertinib

1.1 Company Agreements

In October 2014, AstraZeneca built on its existing partnership with the University of Cambridge by entering into a pivotal material transfer agreement, in which the university's researchers will gain access to key compounds from AstraZeneca's investigation pipeline, including osimertinib [11]. In October 2015, AstraZeneca entered into a collaborative agreement with Eli Lilly to investigate the use of osimertinib as combination therapy (with ramucirumab or necitumumab) in patients with solid tumours [12]. Under the terms of the agreement, both companies will contribute resources, and Eli Lilly will lead the execution of the trials. Further information regarding this agreement, including financial terms and which tumours will be studied, were undisclosed. This agreement was an extension of an existing collaboration between these companies to evaluate the use of ramucirumab and durvalumab in a phase I trial in patients with solid tumours [12].

2 Scientific Summary

2.1 Pharmacodynamics

Osimertinib is a novel, irreversible, third-generation EGFR TKI, with almost 200 times greater affinity for EGFR molecules with the L858R/T790M mutation than wild-type EGFR in vitro [13]. Osimertinib potently inhibited EGFR phosphorylation in T790M mutant cell lines [mean 50 % inhibitory concentration (IC_{50}) <15 nmol/L], while exhibiting less potent inhibition of EGFR phosphorylation in wild-type cell lines (mean IC_{50} 480–1865 nmol/L). Osimertinib has two pharmacologically-active metabolites; AZ7550, which has a very similar profile to osimertinib, and AZ5104, which exhibits a reduced selectivity margin against wild-type EGFR compared with the parent drug [13]. In vitro, the activity of HER2, HER3, HER4, ACK1 and BLK were also inhibited by osimertinib at clinically relevant concentrations [4].

In murine models of *EGFR* T790M-resistant lung cancer, osimertinib 5 mg/kg/day for 1–2 weeks induced significant and sustained tumour shrinkage relative to afatinib and vehicle only control, with inhibition of EGFR phosphorylation and downstream signalling observed after a single dose of osimertinib 5 mg/kg [13].

Based on analysis of cell-free plasma from patients with NSCLC, the *EGFR* C797S mutation is thought to be a common mediator of acquired resistance to osimertinib [14]. In the phase I/II AURA trial (Sect. 2.3.1) in patients with *EGFR* T790M mutation-positive NSCLC receiving second-line osimertinib treatment, analyses of patients who developed osimertinib-resistance identified several potential mechanisms of resistance [14–16]. Acquired osimertinib resistance may be mediated by the *EGFR* C797S mutation [14], amplification of *HER2*, *MET* [15] or alternative pathways [16], and histological transformation or EGFR ligand-dependent activation [16]. These studies also observed depopulation of *EGFR* T790M mutant cells [14–16], suggesting that baseline population of wild-type *EGFR* T790 cells may mediate the development of resistance [15]. Combination therapy may be needed to prevent or stop the emergence of resistance [14, 15]. Indeed, emerging preclinical and clinical evidence suggests combining osimertinib with another EGFR TKI may delay or prevent the development of MET signalling-associated resistance, while preclinical findings indicate the combination of an EGFR TKI with the MEK 1/2 inhibitor selumetinib may address or delay resistance associated with the MEK/ERK pathway [17].

In terms of potential predictive biomarkers for response to osimertinib in the phase I/II AURA trial (Sect. 2.3.1), among patients with *EGFR* mutation-positive NSCLC receiving second-line osimertinib treatment, those with detectable plasma levels of *EGFR* T790M DNA with no central T790M tissue results had a greater than twofold higher clinical response rate than those without detectable levels of *EGFR* T790M DNA (85 vs. 33 %) [18]. In tissue biomarker analysis of paired biopsy cohorts from AURA, the majority of post-treatment tumours showed inhibition of EGFR pathway components in response to osimertinib treatment [19].

In the phase II AURA2 trial (Sect. 2.3.1), a central tendency analysis of steady-state QTc data in 210 patients with *EGFR* T790M mutation-positive NSCLC receiving osimertinib 80 mg once daily (tablet formulation) showed a maximum mean change from baseline in QTC interval of 16.2 ms [4]. In an analysis of pooled data from the phase II extension of AURA and AURA2 (data cut-off 1 June 2015), QT prolongation was reported

in 17 patients (4 %) receiving osimertinib 80 mg once daily [20].

2.2 Pharmacokinetics

In healthy volunteers, single-dose administration of osimertinib 20 mg had equivalent bioavailability as capsule versus tablet formulations [21]. Single-dose oral administration of an osimertinib 20 mg tablet with a high-fat meal in healthy volunteers resulted in minimal increases in osimertinib exposure compared with fasting conditions [21]. In addition, administration of a single osimertinib 80 mg tablet with food in patients with *EGFR* mutation-positive NSCLC had no clinically relevant effect on osimertinib exposure compared with administration in the fasted state [22]. In patients with EGFR TKI-resistant NSCLC in the phase I/II AURA trial (Sect. 2.3.1), osimertinib was absorbed slowly after single-dose capsule administration, with C_{max} being reached in a median of 6 h and osimertinib exposure being approximately dose-proportional over the 20–240 mg dosing range [23]. During multiple once-daily administration in these patients, the pharmacokinetics of osimertinib were linear, with ≈4.5-fold accumulation [21] and steady state being reached after 22 days [23]. At steady state, the C_{max} to C_{min} ratio of osimertinib was 1.6-fold and the mean volume of distribution was 986 L [4].

Based on its physiochemical properties, osimertinib is expected to have high plasma protein binding [4]. In a mouse *EGFR* mutation-positive brain metastasis xenograft model, osimertinib concentrations were 5- to 25-fold higher in brain tissue than plasma after oral osimertinib 5–25 mg/kg dosing [24]. In this mouse model, osimertinib distribution to the brain was approximately tenfold higher than that of gefitinib at clinically relevant doses, and osimertinib 25 mg/kg/day resulted in sustained regression of brain metastases. Based on clinical osimertinib pharmacokinetic data and tumour growth simulations, an osimertinib dosage of 80 mg daily is predicted to be sufficient to deliver efficacy in *EGFR* mutation-positive brain metastases [24]. In phase II trials (AURA extension and AURA2) [Sect. 2.3.1], the cerebrospinal fluid concentrations of osimertinib were 0.77 and 3.44 nmol/L in two patients, which corresponded to ≈0.2 and 1 %, respectively, of the predicted osimertinib plasma concentrations at steady state [25].

In vitro, osimertinib was mainly metabolized via oxidation and dealkylation pathways [4]. After oral administration of osimertinib in patients with EGFR TKI-resistant NSCLC, two pharmacologically active metabolites (AZ7550 and AZ5104) were detected in the plasma, each with a geometric mean exposure of ≈10 % of the parent drug after multiple dosing [23]. In these patients, the apparent mean half-life of osimertinib was 55 h [23] and the oral clearance was 14.2 L/h [4]. Elimination of osimertinib is predominantly via the faeces (68 %), with a lesser amount excreted in the urine (14 %); unchanged parent drug accounts for ≈2 % of the eliminated drug [4].

The pharmacokinetic profile of osimertinib does not appear to be affected to a clinically significant extent by age, sex, bodyweight, ethnicity, mild or moderate renal or mild hepatic impairment [4]. However, there are no data available regarding the use of osimertinib in patients with severe renal impairment or moderate to severe hepatic impairment, and there is no recommended dosage of osimertinib in these patient populations. Females and male patients of reproductive potential should be advised to use effective contraception during and after osimertinib treatment. Osimertinib may cause foetal harm when administered during pregnancy, and pregnant women should be advised of these potential risks. Nursing mothers should stop breastfeeding during osimertinib therapy and for 2 weeks after the last dose [4].

2.2.1 Drug Interactions

There are no clinical data available regarding specific drug interaction between osimertinib and CYP inhibitors, inducers or substrates, or transporters [4]. However, concomitant use of osimertinib with strong CYP3A inhibitors or inducers may result in increased or decreased osimertinib plasma concentrations and should be avoided. If concomitant use of strong CYP3A inhibitors with osimertinib is required, patients should be monitored more closely for pulmonary, cardiac or other toxicities with osimertinib. Concomitant use of osimertinib with sensitive substrates of CYP3A, BCRP or CYP1A2 with narrow therapeutic indices may result in increased or decreased plasma concentrations of these drugs, and should also be avoided [4]. In healthy volunteers, osimertinib exposure was not altered to a clinically relevant extent when a single dose of osimertinib 80 mg was administered after 5 days of omeprazole 40 mg [4, 22].

Features and properties of osimertinib

Alternative names	Tagrisso™, AZD9291
Class	Acrylamides, aniline compounds, antineoplastics, dimethylamines, indoles, pyrimidines
Mechanism of action	EGFR tyrosine kinase inhibitor (third-generation)
Route of administration	Oral
Pharmacodynamics	Irreversibly inhibits phosphorylation of EGFR with T790M mutation, and less potently inhibits wild-type EGFR; also inhibits HER2, HER3, HER4, ACK1 and BLK activity
	Sustained tumour shrinkage in mouse models of *EGFR* $T790M^+$-resistant lung cancer
Pharmacokinetics	Median t_{max} = 6 h; mean V_{ss} = 986 L; oral CL = 14.2 L/h; mean $t_{½}$ = 55 h; steady state reached in 22 days; excretion is ≈68 % faecal and ≈14 % urinary
	Potential drug interactions with strong CYP3A inhibitors or inducers, and substrates of CYP3A, BCRP or CYP1A2 with narrow therapeutic indices
Adverse events	
Most frequent	Diarrhoea, rash, dry skin, nail toxicity
Rare	ILD/pneumonitis, QTc interval prolongation, cardiomyopathy
ATC codes	
WHO ATC code	L01 (antineoplastic agents)
EphMRA ATC code	L1 (antineoplastics)
Chemical name	N-[2-[2-(dimethylamino)ethyl-methylamino]-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl]prop-2-enamide

CL clearance, *EGFR* epidermal growth factor receptor, *ILD* interstitial lung disease, $t_{½}$ half-life, t_{max} time to maximum concentration, V_{ss} apparent volume of distribution at steady state

2.3 Therapeutic Trials

2.3.1 Second-Line or Later Monotherapy in NSCLC

Osimertinib treatment was associated with tumour responses in the majority of patients with locally advanced or metastatic EGFR TKI-resistant NSCLC in the randomized, multinational, open-label phase I/II AURA trial (NCT01802632) [23]. The phase I part of AURA enrolled patients with locally advanced or metastatic NSCLC and a known EGFR TKI-sensitizing mutation or radiologically documented PD during EGFR TKI therapy after previous clinical benefit. Patients received oral osimertinib 20, 40, 80, 160 or 240 mg/day (capsule formulation) as part of a dose-escalation cohort ($n = 31$) or five expansion cohorts at different doses ($n = 222$). Patients in the dose-expansion cohorts were required to undergo central testing to confirm *EGFR* T790M mutation status. The primary efficacy outcome measure was objective response rate (ORR; percentage of patients with ≥1 confirmed response before any evidence of PD) in the evaluable population (all patients who received ≥1 dose of osimertinib and had a baseline and ≥2 post-baseline Response Evaluation Criteria in Solid Tumours (RECIST) assessments, or any patient who withdrew before the second RECIST assessment) [data cut-off 1 August 2014]. Response was evaluated according to RECIST version 1.1 by investigators and independent central review (ICR) [23].

Among all patients with EGFR TKI-resistant NSCLC in the phase I part of AURA ($n = 239$ evaluable), osimertinib was associated with an ORR [confirmed partial response (PR) or complete response (CR)] of 51 % and a disease control rate (CR, PR or SD) of 84 % [23]. In the overall population, the ORR was generally similar at each of the osimertinib dosages. In patients with a confirmed *EGFR* T790M mutation ($n = 127$ evaluable), osimertinib was associated with an ORR of 61 % and a disease control rate of 95 %, while those with no detectable *EGFR* T790M mutation ($n = 61$ evaluable) had an ORR of 21 % and a disease control rate of 61 %. Of the patients with confirmed response in the dose-expansion cohorts ($n = 105$), the duration of response was ≥6 months in 85 % of patients (although data for 79 % of patients was censored at the time of data cut-off) and the median progression-free survival (PFS) was 8.2 months (41 % maturity). Among patients with a detectable *EGFR* T790M mutation, the median PFS was 9.6 months (30 % maturity) and 88 % of patients had an estimated duration of response of ≥6 months, while in those with no detectable *EGFR* T790M mutation, the duration of response was ≥6 months in 69 % of patients and the median PFS was 2.8 months (71 % maturity) [23].

In an updated analysis of the phase I part of AURA (data cut-off 2 December 2014), 252 patients were enrolled in the dose-expansion cohorts, and 163 patients were confirmed as *EGFR* T790M mutation-positive [26]. In this analysis, osimertinib was associated with an investigator-confirmed ORR of 59 % in *EGFR* T790M mutation-positive patients (92/157 evaluable) and 23 % in *EGFR* T790M mutation-negative patients (16/69 evaluable). At the recommended phase II osimertinib dosage of 80 mg/day, *EGFR* T790M mutation-positive patients had a confirmed ORR of 66 % (investigator assessment) or 54 % (ICR) and a median PFS of 10.9 months (investigator assessment; 40 % maturity) or 13.5 months (ICR; 38 % maturity). In these patients, the median duration of response was not calculable in the investigator assessment, and 12.4 months in the ICR [26].

Based on the phase I findings of AURA, osimertinib at a dosage of 80 mg once daily (tablet formulation) was further evaluated in patients with *EGFR* T790M mutation-positive NSCLC and progression after EGFR TKI therapy in a phase II extension cohort of AURA (NCT01802632) [27] and an additional phase II trial (AURA2; NCT02094261) [28]. Both of these studies are ongoing, and preliminary data (data cut-off 9 January 2015) are available [27, 28]. In patients with *EGFR* T790M mutation-positive NSCLC in the phase II extension of AURA ($n = 201$), osimertinib was associated with an ORR by ICR of 58 % (115/199 evaluable patients; primary endpoint) and a disease control rate of 92 % after a median treatment exposure of 4.9 months [27]. In the phase II AURA2 trial in this patient population ($n = 210$), osimertinib was associated with an ORR by ICR of 64 % (127/198 evaluable patients; primary endpoint) and a disease control rate of 90 % after a median treatment duration of 4.0 months [28]. In both trials, the median duration of response and median PFS had not reached maturity [27, 28].

The efficacy of osimertinib in patients with *EGFR* T790M mutation-positive NSCLC is supported by several pooled analyses of phase II AURA extension and AURA2 data [20, 25, 29, 30]. In the pooled evaluable population ($n = 397$), osimertinib was associated with an ORR by ICR of 61 % and a disease control rate of 91 % [20]. Furthermore, the ORR was >50 % across several subgroups, including lines of therapy (second- vs. ≥third-line), ethnicity (Asian vs. non-Asian) and *EGFR* T790M mutation subtype (Exon19del vs. L858R) [20]. Osimertinib was associated with an ORR of 62 % (98/158 evaluable) among patients with brain metastases at baseline, and 69 % (165/239 evaluable) among those without brain metastases [25]. In a qualitative interview subanalysis, patients reported a high degree of treatment satisfaction with osimertinib (9.0 out of 10) and a low level of difficulty in coping with disease symptoms/treatment-related adverse effects (2.0 out of 10) [29]. In EORTC patient-reported outcome questionnaires (QLQ-LC13 and QLC-C30), most disease symptoms showed improvement in the majority of patients [30].

Preliminary data from an ongoing phase I trial (data cut-off 10 September 2015) have indicated that osimertinib 160 mg once daily is effective in the treatment of patients with *EGFR*-mutation positive NSCLC and leptomeningeal disease who have progressed on prior EGFR TKI therapy (BLOOM; NCT02228369) [31]. Among the 11 evaluable patients, investigator-assessed imaging improvement was observed in 8 patients (73 %); all of the 6 patients who reached the 12-week assessment showed continued improvement by imaging. Furthermore, among the nine patients with baseline neurological symptoms, five patients (56 %) experienced investigator-assessed symptomatic improvement [31].

In an observational study of four patients with *EGFR* mutation-positive NSCLC and disease progression after previous EGFR TKI therapy, osimertinib was associated with a clear clinical and radiographic improvement, with two patients achieving complete remission following osimertinib treatment [32].

2.3.2 First-Line Monotherapy in NSCLC

Osimertinib was associated with promising anticancer activity in advanced *EGFR* mutation-positive NSCLC in an ongoing phase I first-line expansion cohort of AURA (NCT01802632) [33, 34]. In this expansion cohort, 60 EGFR TKI treatment-naive patients with *EGFR* mutation-positive advanced NSCLC received osimertinib 80 or 160 mg/day for a median of 260 and 171 days, respectively (data cut-off 2 December 2014). First-line treatment with osimertinib was associated with an ORR of 70 % overall, 60 % in patients receiving the 80 mg/day dosage and 80 % in those receiving the 160 mg/day dosage. Osimertinib was also associated with a disease control rate of 97 % overall, 93 % in patients receiving the 80 mg/day dosage and 100 % in those receiving the 160 mg/day dosage. The median PFS had not been reached; however, osimertinib was associated with 3- and 6-month PFS rates of 93 and 87 % [33, 34].

2.3.3 Combination Therapy in NSCLC

In a phase Ib trial investigating the use of osimertinib as combination therapy (TATTON; NCT02143466), PR was observed in three patients receiving osimertinib plus durvalumab, two patients receiving osimertinib plus selumetinib and two patients receiving osimertinib plus savolitinib (a MET inhibitor) [35]. However, due to reports of ILD

with osimertinib plus durvalumab, this treatment arm of TATTON as well as a phase III trial comparing the efficacy of osimertinib plus durvalumab with that of osimertinib monotherapy (CAURAL; NCT02454933), were temporarily suspended in October 2015 [36]. It should be noted that the osimertinib plus selumetinib and osimertinib plus savolitinib treatment arms of the TATTON trial are still recruiting patients. In the randomized, multi-arm, TATTON trial (initiated in August 2014), adult patients with advanced *EGFR* mutation-positive NSCLC who progressed on EGFR TKI therapy received osimertinib 80 mg/day and escalating dosages of either durvalumab, savolitinib or selumetinib ($n = 42$) [data cut-off 8 January 2015] [35].

2.4 Adverse Events

Osimertinib has a generally acceptable tolerability profile in patients with locally advanced or metastatic *EGFR* mutation-positive NSCLC [4, 23, 26, 33]. In patients with EGFR TKI-resistant NSCLC in the dose-escalation cohort of AURA, there were no dose-limiting toxicities with osimertinib 20–240 mg/day, and therefore the maximum tolerated dosage was not defined [23]. In the phase I analysis of AURA, the overall incidence of any adverse event with osimertinib was 96 %, while 32 % of patients reported grade 3–5 adverse events, 22 % reported serious adverse events, and adverse events led to dose reduction or drug withdrawal in 7 and 6 % of patients. The incidence of any treatment-related adverse events (based on site investigator-assessment) was 80 %, while grade 3–5 or serious treatment-related adverse events occurred in 13 and 6 % of patients, and treatment-related adverse events led to osimertinib discontinuation in 3 % of patients [23].

In the phase I analysis of AURA, the most common adverse events (of any grade) with osimertinib (occurring with ≥20 % incidence) were diarrhoea (47 %), rashes and acne (group term; 40 %), nausea (22 %), decreased appetite (21 %) and dry skin (20 %) [23]. The incidences of some adverse events, including diarrhoea and rash, increased in a dose-dependent fashion. Potential pneumonitis-like events were reported in six patients (2.4 %), all of whom stopped treatment and had resolved or were resolving at the time of analysis. Eleven patients (4.3 %) experienced prolongation of QTc interval and six patients (2.4 %) reported hyperglycaemia during osimertinib treatment; none of these patients required dosage reduction or drug discontinuation. Of the seven fatal adverse events with osimertinib, one case of pneumonia was considered to be possibly treatment-related [23].

In the updated phase I analysis of AURA, the adverse events with osimertinib were mostly grade 1–2, with grade 3 or higher treatment-related adverse events being reported in 17 % of patients and the most commonly reported adverse events being diarrhoea (50 % of patients) and rash (46 %) [26].

In the phase II extension of AURA and the phase II AURA2 trial in patients with previously treated *EGFR* T790M mutation-positive NSCLC (pooled data; $n = 411$), the most common adverse events of any grade with osimertinib 80 mg/day (occurring with ≥20 % incidence) were diarrhoea (42 %), rash (41 %), dry skin (31 %) and nail toxicity (25 %) [4]. Adverse events led to dosage reductions in 4.4 % of patients and drug discontinuation in 5.6 % of patients. The most common adverse events that led to dosage reduction or interruption were prolonged QTc interval (2.2 %) and neutropenia (1.9 %), and the most common adverse events that resulted in discontinuation were ILD/pneumonitis and cerebrovascular accidents/infarctions. Serious adverse events that occurred in ≥2 % of patients were pneumonia and pulmonary embolus. Fatal adverse events that occurred in more than one patient were ILD/pneumonitis (four patients; 1.0 %), pneumonia (four patients; 1.0 %) and cerebrovascular accident/cerebral haemorrhage (two patients; 0.5 %) [4].

In the first-line expansion cohort of AURA in treatment-naive patients with *EGFR* mutation-positive advanced NSCLC, grade 3 or higher adverse events with osimertinib 80 or 160 mg/day were reported in 33 % of patients; two patients (3.3 %) reported grade 3 diarrhoea and one patient (1.7 %) reported grade 3 skin rash [33].

When used in combination with durvalumab, savolitinib or selumetinib in patients with previously treated *EGFR* mutation-positive NSCLC in TATTON ($n = 20$), 16 patients (80 %) of patients reported mild to moderate adverse events and 4 patients (20 %) reported severe adverse events [35]. Dose-limiting toxicities included fatigue (with osimertinib plus savolitinib) and transaminase elevation (with osimertinib plus selumetinib) [35].

Based on clinical trial data, the US prescribing information for osimertinib carries warnings and precautions regarding the increased risk of ILD/pneumonitis, QTc interval prolongation and cardiomyopathy during treatment [4]. Osimertinib should be withheld in patients who develop worsening respiratory symptoms indicative of ILD, an QTc interval >500 ms, asymptomatic decreases in left ventricular ejection fraction of 10 % from baseline (below 50 %) or any grade 3 or higher adverse event. Osimertinib treatment should be permanently discontinued in patients with confirmed ILD/pneumonitis, QTc interval prolongation with life-threatening arrhythmia, symptomatic congestive heart failure, or a grade 3 or higher adverse event that does not improve after 3 weeks of withheld therapy [4].

Key clinical trials of osimertinib

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Osimertinib	Advanced NSCLC after prior EGFR-TKI therapy	I	Ongoing	Multinational	NCT01802632 (AURA)	AstraZeneca
Osimertinib	Treatment-naive *EGFR* mutation-positive advanced NSCLC	I	Ongoing	Multinational	NCT01802632 (AURA first-line expansion)	AstraZeneca
Osimertinib	Advanced *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	II	Ongoing	Multinational	NCT01802632 (AURA extension)	AstraZeneca
Osimertinib	Locally advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	II	Ongoing	Multinational	NCT02094261 (AURA2)	AstraZeneca
Osimertinib	Locally advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	II	Ongoing	Asia Pacific	NCT02442349 (AURA17)	AstraZeneca
Osimertinib	Locally advanced/metastatic *EGFR* mutation-positive NSCLC after prior EGFR-TKI therapy	II	Recruiting	Norway	NCT02504346 (TREM)	Oslo University Hospital
Osimertinib, platinum-based chemotherapy[a]	Locally advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	III	Ongoing	Multinational	NCT02151981 (AURA3)	AstraZeneca
Osimertinib	Advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	III	Recruiting	Multinational	NCT02474355 (ASTRIS)	AstraZeneca
Osimertinib, gefitinib, erlotinib	Treatment-naive, locally advanced or metastatic, *EGFR* mutation-positive NSCLC	III	Recruiting	Multinational	NCT02296125 (FLAURA)	AstraZeneca
Osimertinib, placebo	Stage Ib–IIIa *EGFR* mutation-positive NSCLC after tumour resection (±adjuvant chemotherapy)	III	Recruiting	Multinational	NCT02511106 (ADAURA)	AstraZeneca
Osimertinib	Advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	EAP	Available	USA	NCT02451852	AstraZeneca
Osimertinib, AZD3759	Advanced *EGFR* mutation-positive NSCLC after prior EGFR-TKI therapy with leptomeningeal disease	I	Recruiting	Multinational	NCT02228369 (BLOOM)	AstraZeneca
Osimertinib, gefitinib, tremelimumab, selimetinib + docetaxel[b]	Locally advanced/metastatic NSCLC	IIa	Ongoing	USA	NCT02179671	AstraZeneca
Osimertinib + durvalumab, osimertinib + savolitinib, osimertinib + selumetinib	Advanced *EGFR* mutation-positive NSCLC after prior EGFR-TKI therapy	Ib	Recruiting[c]	Multinational	NCT02143466 (TATTON)	AstraZeneca
Osimertinib + durvalumab, osimertinib	Locally advanced/metastatic *EGFR* T790M mutation-positive NSCLC after prior EGFR-TKI therapy	III	Suspended	Multinational	NCT02454933 (CAURAL)	AstraZeneca

EAP expanded access program, *EGFR* epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *TKI* tyrosine kinase inhibitor

[a] Pemetrexed plus cisplatin or pemetrexed plus carboplatin

[b] All treatment arms sequentially switched to durvalumab

[c] The osimertinib plus durvalumab arm of this trial has been temporarily suspended

2.5 Companion Diagnostic

In July 2014, AstraZeneca and Roche entered into a collaborative agreement to develop a plasma-based companion diagnostic test (cobas® EGFR Mutation Test v2) for use with osimertinib [37]. The plasma-based diagnostic test is used to identify the *EGFR* T790M mutation from circulating plasma DNA, and provides an alternative to tissue biopsy for *EGFR* T790M mutation detection [37]. The cobas® EGFR Mutation Test v2 was submitted to the US

FDA for premarket approval in July 2015 [38] and was approved by the US FDA in November 2015 [5].

2.6 Ongoing Clinical Trials

2.6.1 NSCLC

There are a number of ongoing phase I trials trials of osimertinib in patients with locally advanced or metastatic NSCLC, including those that are investigating the pharmacokinetics of osimertinib in Chinese patients (NCT02529995), how the pharmacokinetics of osimertinib are affected by the CYP inducer rifampicin (NCT02197247) or the CYP3A4 inhibitor itraconazole (NCT02157883), and how osimertinib affects the pharmacokinetics of simvastatin (NCT02197234) or rosuvastatin (NCT02317016). A further three open-label, phase I trials are planned to investigate the use of osimertinib in combination with navitoclax (NCT02520778), necitumumab (NCT02496663) and sapanisertib (NCT02503722).

Follow-up is ongoing in the phase I/II AURA trial (NCT01802632) in patients with *EGFR* mutation-positive NSCLC, including the phase I dose expansion cohorts [23, 26] and phase II extension [27] in patients previously treated with EGFR TKIs, and the phase I expansion first-line cohort in treatment-naive patients [33, 34]. This trial has enrolled 974 patients and is expected to be completed in November 2016. Follow-up is also ongoing in the phase II AURA2 trial (NCT02094261) in patients with *EGFR* T790M mutation-positive NSCLC and disease progression during or after EGFR TKI therapy [28]; 472 patients have been enrolled and it is expected to finish in October 2016.

A further two open-label, phase II trials investigating the use of osimertinib in patients with *EGFR* T790M mutation-positive NSCLC and disease progression during or after EGFR TKI therapy are ongoing; AURA17 (NCT02442349) was initiated in June 2015 in Asia Pacific, has enrolled 175 patients and is expected to be completed in June 2017, and TREM (NCT02504346) was initiated in July 2015 in Norway, is recruiting ≈150 patients and has an estimated completion date of February 2017. The primary endpoint of both of these trials is ORR.

Two open-label, multinational, phase III trials of osimertinib have been initiated in patients with *EGFR* T790M mutation-positive NSCLC and disease progression during or after EGFR TKI therapy. The randomized AURA3 trial (NCT02151981) was initiated in August 2014, and is comparing the efficacy and safety of osimertinib with platinum-based doublet chemotherapy (pemetrexed plus cisplatin or pemetrexed plus carboplatin) [39]; patients in the chemotherapy arm who develop PD (according to RECIST 1.1) will be eligible cross-over to osimertinib treatment. The trial has a primary endpoint of PFS (according to RECIST 1.1), has enrolled ≈410 patients and expected to be completed in December 2017. In collaboration with Parexel, AstraZeneca initiated the ASTRIS trial (NCT02474355) in September 2015 to investigate the efficacy of osimertinib monotherapy in a real-world setting. The primary endpoint is overall survival. This trial aims to enrol 1325 patients and has an estimated completion date of January 2019.

In December 2014, AstraZeneca initiated a randomized, double-blind, multinational, phase III trial (FLAURA; NCT02296125) to compare the efficacy and safety of osimertinib with that of standard of care therapy (gefitinib or erlotinib) in ≈530 treatment-naive patients with locally advanced or metastatic *EGFR* mutation-positive NSCLC [40]. The trial has a primary endpoint of PFS and is expected to be completed in October 2018.

In May 2015, AstraZeneca initiated an expanded access program for adult patients with advanced or metastatic *EGFR* T790M mutation-positive NSCLC who have previously received EGFR TKI therapy in the USA (NCT02451852).

In July 2014, AstraZeneca (in collaboration with Quintiles) initiated a randomized, open-label phase IIa trial in the USA (NCT02179671) to investigate the use of various sequences of selected small molecules (osimertinib, gefitinib or selumetinib plus docetaxel) or a first immune-mediated therapy (tremelimumab), with a sequential switch to a second immune-mediated therapy (durvalumab) in patients with locally advanced or metastatic NSCLC. The primary endpoint is confirmed complete response rate. The ongoing trial has enrolled 40 patients and is expected to be completed in November 2017.

In October 2015, AstraZeneca (in collaboration with Parexel) initiated a randomized, double-blind, multinational phase III trial (ADAURA; NCT02511106) to compare the efficacy and safety of osimertinib with that of placebo in patients with *EGFR* mutation-positive stage Ib–IIIa NSCLC following complete tumour resection (with or without adjuvant chemotherapy). The primary endpoint is disease-free survival. The trial is recruiting ≈700 patients and is expected to be completed in September 2021.

2.6.2 Solid Tumours

In December 2014, AstraZeneca initiated a two-part, open-label, multinational, phase I trial (NCT02161770) to investigate the pharmacokinetics, safety and tolerability of osimertinib in patients with advanced solid tumours and mild or moderate hepatic impairment or normal hepatic function. The trial is enrolling ≈30 patients and is expected to be completed in June 2017.

3 Current Status

Osimertinib received its first global approval on 13 November 2015 for patients with metastatic *EGFR* T790M mutation-positive NSCLC (as detected by an FDA-approved test) who have progressed on or after EGFR TKI therapy in the USA [5]. Osimertinib was granted accelerated approval by the US FDA based on tumour response rate and duration of response, and continued approval in this indication may be contingent on verification and description of clinical benefit in confirmatory trials [4].

Compliance with Ethical Standards

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