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ADIS DRUG EVALUATION

Osimertinib: A Review in T790M-Positive Advanced Non-Small Cell Lung Cancer

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Abstract Osimertinib (Tagrisso™) is an oral, CNS-active, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that targets *EGFR* TKI-sensitizing mutations and, crucially, the T790M mutation that often underlies acquired resistance to EGFR TKI therapy. Osimertinib has been approved in numerous countries for use in patients with T790M-positive advanced NSCLC. In the pivotal, international AURA3 trial in patients with T790M-positive advanced NSCLC who had disease progression after EGFR TKI therapy, osimertinib treatment significantly prolonged progression-free survival (PFS; primary endpoint) compared with platinum-pemetrexed therapy at the time of the primary analysis. PFS results were consistent across predefined subgroups of patients, including those with CNS metastases at baseline. There was no difference between treatment groups in overall survival at 26% maturity. Objective response rates (ORRs) and patient-reported outcomes for prespecified symptoms were also significantly improved with osimertinib relative to platinum-pemetrexed, with CNS ORRs in patients with CNS metastases more than twofold higher in the osimertinib than in the platinum-pemetrexed group. Osimertinib had a manageable tolerability profile, with relatively few patients permanently discontinuing treatment because of adverse events (AEs). With limited treatment options available in this setting, osimertinib is an important option in adult patients with advanced *EGFR* T790M-positive NSCLC.

Osimertinib: clinical considerations in T790M-positive advanced non-small cell lung cancer
Third-generation EGFR TKI that targets the T790M resistance mutation; convenient once-daily regimen
Very good penetration into the CNS and widely distributed in the CNS in animal models
Significantly improves PFS and ORR relative to platinum-pemetrexed; PFS benefit was observed in patients with CNS metastases and other predefined subgroups of patients
Manageable tolerability profile; potentially causally-related AEs were mainly of grade 1 or 2 severity

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1 Introduction

Lung cancer, the symptoms of which are often not manifest until the disease is at an advanced stage [1], has a high fatality rate and accounts for almost 20% of cancer deaths worldwide [2]. Most cases of lung cancer (80–85%) are non-small cell lung cancer (NSCLC) [1]. Activating mutations are present in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene in ≈10–15% of Caucasian patients and ≈30–40% of East Asian patients with NSCLC [3], thus providing a molecular treatment target for tailored therapy [4].

EGFR tyrosine kinase inhibitors (TKIs) are recommended as first-line therapy in *EGFR*-mutated advanced NSCLC [5,

6]. While rates of clinical response to EGFR TKIs are relatively high (≈50–70%), patients typically acquire resistance to the inhibitors, with a median progression-free survival (PFS) of 9–13 months [7]. In 50–60% of cases, the mechanism underlying acquired resistance to EGFR TKIs is the emergence of the *EGFR* T790M gatekeeper mutation [3, 4]. This insight into the biological mechanisms of resistance has informed the development of third-generation EGFR TKIs [4]. Third-generation EGFR TKIs are designed to target *EGFR* TKI-sensitizing mutations and the T790M resistance mutation, thus inhibiting the growth of *EGFR* T790M-positive tumours [3, 4, 8]. By sparing wild-type *EGFR*, these compounds are also anticipated to reduce the toxicities that have been associated with first- (e.g. gefitinib; erlotinib) and second-generation (e.g. afatinib) EGFR TKIs [3, 4, 8].

Osimertinib (Tagrisso™), an orally administered, third-generation EGFR TKI, is approved in numerous countries, including China [9], Japan [10], the USA [11] and those of the EU [12], for the treatment of patients with T790M-positive, advanced NSCLC. Given the limited treatment options available for this patient group [3, 13] and promising results from pivotal phase II trials, osimertinib was initially approved through accelerated assessment procedures [11, 12, 14]. More recently, the US FDA and EU EMA granted full approval to osimertinib on the basis of confirmatory phase III results [11, 12]. This narrative review discusses the clinical efficacy and tolerability of osimertinib, and overviews its pharmacological properties.

2 Pharmacodynamic Properties

Osimertinib targets and binds covalently to certain mutant EGFR forms [L858R, exon 19 deletion (ex19del) and double mutants containing T790M] via a cysteine residue at codon 797 (C797) of the EGFR kinase binding site, resulting in their potent, selective inhibition [11, 12, 15]. Osimertinib exhibited significantly higher inhibitory activity against EGFR phosphorylation in *EGFR* TKI-sensitizing mutant (L858R and ex19del) and T790M mutant (T790M/L858R and T790M/ex19del) NSCLC cell lines [mean 50% inhibitory concentrations (IC_{50}s) 6–54 nmol/L] than in wild-type cell lines (mean IC_{50}s 480–1865 nmol/L) [12, 15]. Osimertinib produces two pharmacologically active metabolites, AZ7550 and AZ5104 (Sect. 3), with AZ7550 exhibiting similar potency and selectivity to osimertinib and AZ5104 being a more potent inhibitor of ex19del and T790M mutant (≈8-fold) and wild-type (≈15-fold) EGFR than the parent drug [11, 15].

Oral osimertinib exhibited potent antitumour activity in preclinical studies [15, 16]. Osimertinib induced significant, dose-dependent, sustained tumour regression in mouse mutant *EGFR* (ex19del, L858R, L858R/T790M and ex19del/T790M) NSCLC xenograft models and mouse mutant *EGFR* (L858R and L858R/T790M) transgenic lung adenocarcinoma models [15]. Within 5 days of treatment, osimertinib induced significant tumour shrinkage of both L858R and L858R/T790M *EGFR*-mutant tumours (no viable tumour), whereas afatinib treatment was effective against L858R tumours (no viable tumour) but not L858R/T790M tumours (viable tumour present at 5 days). Immunohistochemical staining of L858R/T790M xenograft tissue confirmed that EGFR phosphorylation and downstream signalling pathways were inhibited following a single dose (5 mg/kg) of osimertinib [15].

In clinical trials [17–20], including phase II and III trials discussed in Sect. 4 [17–19], osimertinib exhibited high antitumour efficacy in patients with *EGFR* T790M-positive NSCLC. While there was no relationship between osimertinib exposure and efficacy across a dosage range of 20–240 mg/day in a phase I trial, increased exposure was associated with higher adverse reaction rates [21]. Osimertinib crosses the blood-brain barrier (Sect. 3) and inhibited the growth of CNS metastases in mouse models [16] and in patients with *EGFR* T790M-positive advanced NSCLC [17, 18] (Sect. 4).

As with earlier generation EGFR TKIs, patients eventually develop resistance to osimertinib treatment [22]. Small studies of acquired resistance to osimertinib in patients with *EGFR* T790M-positive NSCLC (n = 2–22) suggest the mechanisms underlying resistance vary, but potentially include the development of a C797S resistance mutation at the kinase binding site, activation of alternative pathways (e.g. MAPK, MET and HER2 amplification), transformation to small cell carcinoma and ligand-dependent EGFR activation [22–25].

There is the potential for clinically significant cardiovascular effects to occur with osimertinib (Sect. 5). The effect of osimertinib on the QTc interval was examined in patients with *EGFR* T790M-positive NSCLC receiving osimertinib 80 mg/day (recommended dosage) in phase II and III trials discussed in Sect. 4. In the AURA2 trial (n = 210), osimertinib was associated with a 16.2 ms maximum mean change from baseline in QTc interval [11]. A concentration-dependent QTc interval prolongation of 14 ms was predicted with the 80 mg dose of osimertinib [11, 12]. In a pooled analysis of clinical trials (n = 833 treated with osimertinib), a QTc increase from baseline of >60 ms occurred in 24 patients (2.9%) and a QTc of >500 ms occurred in six patients (0.7%) [11, 12].

3 Pharmacokinetic Properties

In patients with advanced NSCLC, oral osimertinib exhibited linear, dose-proportional pharmacokinetics across a dose range of 20–240 mg [11, 12, 26]. Repeated once-daily

osimertinib doses resulted in ≈3-fold accumulation, with steady-state exposure reached after 15 days [11, 12, 26].

Osimertinib was absorbed slowly, with maximum plasma concentrations attained in a median time of 6 h (t_{max}) in patients with advanced NSCLC [11, 12, 26]. At the recommended 80 mg/day dosage, osimertinib exposure was not affected to a clinically meaningful extent by food in patients with advanced (*EGFR* mutation-positive) NSCLC [27] or in healthy volunteers [26], or by omeprazole-induced gastric pH elevation in healthy volunteers [27]. The absolute bioavailability of osimertinib is 70% [12]. At steady-state, plasma concentrations of osimertinib in patients with advanced NSCLC were generally sustained within a 1.6-fold range over the dosing interval [26]. Osimertinib was extensively distributed into tissue (mean steady-state volume of distribution 997 L) [11, 12].

Osimertinib is expected to be highly protein bound [11, 12] and binds covalently to human plasma proteins, serum albumin and hepatocytes [12]. In preclinical studies in mice and monkeys, osimertinib penetrated the blood-brain barrier and was widely distributed in the CNS (area under the concentration-time curve CNS to plasma ratios ≈2 [16]) [16, 28]. In two evaluable patients with *EGFR* T790M-positive NSCLC, cerebrospinal fluid concentrations of osimertinib were 0.77 and 3.44 nmol/L, corresponding to ≈0.2 and 1% of the steady-state plasma concentrations [29].

In vitro, osimertinib was primarily metabolized via oxidation (predominantly by CYP3A) and dealkylation [11, 12]. AZ7550 and AZ5104 each had a median t_{max} of 24 h [12]. The geometric mean exposure of AZ7550 and AZ5104 at steady state was ≈10% of the exposure of osimertinib [20, 26]. In a population pharmacokinetic (PPK) analysis in patients with advanced NSCLC, osimertinib had a mean half-life of 48 h and an oral clearance of 14.2 L/h [26]. In healthy volunteers, osimertinib (single 20-mg dose [30]) is predominantly eliminated via the faeces (68%; 1.2% of the dose as the parent drug) and, to a lesser extent, in the urine (14%; 0.8% as the parent) [11, 12, 30].

Based on a PPK analysis in patients with NSCLC, the pharmacokinetics of osimertinib and AZ5104 were not affected to a clinically meaningful extent by age, sex, formulation (capsule vs. tablet), smoking status, body weight, serum albumin or ethnicity [21].

Based on elimination route data, hepatic or severe renal impairment may increase osimertinib exposure [12]. In the EU [12], while no dose adjustments are recommended, caution is advised when administering osimertinib to patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST] or moderate (total bilirubin 1.5–3.0 × ULN and any AST) hepatic impairment; osimertinib is not recommended in patients with severe hepatic impairment (total bilirubin 3.0–10 × ULN) and the treatment of patients with severe (CL_{CR} <30 mL/min) or end-stage renal disease (ESRD) (CL_{CR} <15 mL/min) should be approached with caution. In the USA, dosage recommendations have not been determined for patients with ESRD or severe hepatic impairment [11].

In vitro, osimertinib is a competitive inhibitor of CYP3A4/5 and BCRP transporters [11, 12]. The use of strong CYP3A inducers should be avoided during treatment with osimertinib, as concomitant administration may decrease osimertinib plasma concentrations [11, 12]. In the EU, concomitant use of St. John's wort is specifically contraindicated and moderate CYP3A4 inducers should be avoided or used with caution [12]. US labelling recommends that the osimertinib dosage is increased to 160 mg/day during co-administration with strong CYP3A4 inducers if concurrent use is unavoidable [11]. Based on clinical trials, co-administering osimertinib with CYP3A4 inhibitors or substrates is unlikely to produce clinically significant pharmacokinetic interactions [11, 12]. Patients receiving concomitant drugs with BCRP-dependent disposition may require monitoring for adverse reactions to the concomitant agent [11, 12].

4 Therapeutic Efficacy

Based on dose-exposure-response analysis and results from the phase I dose-finding component of the phase I/II AURA trial [20], an osimertinib dosage of 80 mg/day (tablet formulation) was selected for further evaluation in the phase II and III setting. This section discusses the results of phase II [AURAext (i.e. the AURA extension trial) [18] and AURA2 [19]] and III (AURA3 [17]) trials in patients with *EGFR* T790M-positive advanced NSCLC who had progressed after previous treatment with an approved EGFR TKI.

Eligible patients were adults with histologic or cytologic evidence of locally advanced or metastatic NSCLC [17–19] with evidence of radiological disease progression following (first-line in AURA3 [17]) EGFR TKI therapy [18, 19]. Patients with stable, asymptomatic CNS metastases that had not been treated with glucocorticoids for ≥4 weeks prior to trial drug initiation could be enrolled [17–19]. Patients were required to have documented presence of an *EGFR* mutation and central confirmation of T790M from a tissue biopsy sample using the cobas® *EGFR* Mutation Test, as well as a WHO performance status of 0 or 1 [17–19]. In AURA3, patients were also required to provide a blood sample at screening to test for T790M using the plasma-based circulating tumour DNA (ctDNA) cobas® *EGFR* Mutation Test v.2 [17]. At baseline, patients had a median age of 62–64 years [17–19]. The majority of patients were White (32–38%) or Asian (58–65%), female (64–88%), had never smoked (67–68%), had metastatic disease (94–98%) and had either the *EGFR* ex19del (65–

71%) or L858R mutation (25–32%). CNS metastases were present in 34–41% of patients [17–19].

4.1 Phase II Trials

AURAext [18] and AURA2 [19] were open-label, multicenter trials in which all patients received osimertinib 80 mg once daily [n = 201 (AURAext) and n = 210 (AURA2)]. The primary efficacy endpoint was the objective response rate (ORR) according to RECIST v1.1 criteria, as evaluated by a blinded independent central review (BICR) [18, 19]. ORR was defined as the proportion of patients with measurable disease who achieved either a complete or partial response, verified at a subsequent scan ≥4 weeks later. The primary analysis was conducted in the evaluable for response analysis set (all patients who received ≥1 dose of osimertinib and had measurable disease at baseline, according to BICR). Duration of response (DoR), tumour shrinkage, disease control rate (DCR), and PFS were assessed according to RECIST v1.1 by BICR in the evaluable for response analysis set. At the time of analysis, the median duration of exposure to osimertinib was 13.2 months in AURAext and 12.9 months in AURA2 [18, 19].

Osimertinib was associated with a BICR-assessed ORR of 62% (122/198; 95% CI 54–68) in AURAext and 70% (140/199; 95% CI 64–77) in AURA2 [18, 19]. In a sensitivity analysis in AURA2, the investigator-assessed ORR in the full analysis set (73%; 153/210) was consistent with the primary endpoint result [19]. The median DoR was 15.2 months (95% CI 11.3–not calculable) in AURAext and 11.4 months (95% CI 9.0–not calculable) in AURA2 [18, 19]. Tumour shrinkage occurred in the majority of patients (94% in each study), with a mean best percentage change from baseline in target lesion size of −43% in AURAext and −52% in AURA2. Disease control was achieved by 90% of patients in AURAext and 92% of patients in AURA2 [18, 19].

Overall survival (OS) data were considered immature at data cutoff, with deaths having occurred in 27% (AURAext) and 21% (AURA2) of patients [18, 19]. OS at 1 year was 79% in AURAext and 81% in AURA2 [18, 19].

The median PFS by BICR was 12.3 months (95% CI 9.5–13.8) in AURAext and 9.9 months (95% CI 8.5–12.3) in AURA2 [18, 19]. PFS was generally consistent across AURAext and AURA2 subgroups, including those based on line of therapy (second- vs. third-line or beyond), presence of CNS metastases, race (Asian vs. non-Asian), and mutation co-occurring with *EGFR* T790M (ex19del vs. L858R) [18, 19]. ORRs in the range of 53–68% (AURAext) and 59–77% (AURA2) were reported in each predefined subgroup [18, 19]. In a subset of AURAext patients (n = 25) with at least one measureable CNS lesion on baseline brain scan according to RECIST v1.1 by neuroradiologist BICR, the CNS ORR was 64% (95% CI 43–82) [18].

4.2 Phase III AURA3 Trial

This randomized, open-label, international trial compared the efficacy of osimertinib with that of platinum-based therapy plus pemetrexed (platinum-pemetrexed) in patients with *EGFR* T790M-positive NSCLC who had disease progression after EGFR TKI therapy [17]. After stratification by race (Asian or non-Asian), patients received oral osimertinib (80 mg once daily) (n = 279) or intravenous pemetrexed (500 mg/m^2 of body surface) plus either carboplatin (target area under the curve 5) or cisplatin (75 mg/m^2) every 3 weeks for up to six cycles (n = 140), with treatment continuing until disease progression, the development of unacceptable side effects or a request by the patient or physician for treatment discontinuation. At baseline, demographic and clinical characteristics were similar across treatment arms. After discontinuing the randomized treatment, 67 of 279 patients in the osimertinib group and 96 of 136 patients (82 of whom crossed over to osimertinib) in the platinum-pemetrexed group received other anticancer therapies. The primary endpoint was investigator-assessed duration of PFS according to RECIST v1.1, with the analysis conducted after ≈221 PFS events (≈54% maturity). All efficacy analyses were conducted in the intention-to-treat (ITT) population. At the time of data cutoff for the primary efficacy analysis (April 15, 2016), the median duration of follow-up was 8.3 months [17].

Osimertinib significantly prolonged median duration of PFS relative to platinum-pemetrexed based on investigator assessments (Table 1), with a 70% reduction in the risk of disease progression or death [17]. At the time of the primary efficacy analysis, progression events had occurred in 50% of osimertinib recipients and 79% of platinum-pemetrexed recipients. At 6 months, 69% of osimertinib recipients and 37% of platinum-pemetrexed recipients were alive and progression free, with respective rates in each group at 12 months of 44 and 10%. The primary efficacy analysis was confirmed in a sensitivity analysis in which median duration of PFS was evaluated by BICR (Table 1) [17].

Improvements in PFS favoured [i.e. hazard ratio (HR) 95% CIs <1] osimertinib over platinum-pemetrexed in all predefined subgroups, including those based on race (Asian vs. non-Asian), presence of CNS metastases, mutation co-occurring with *EGFR* T790M at baseline (ex19del vs. L858R), smoking history, sex, age at screening (<65 years vs. ≥65 years), duration of previous EGFR TKI therapy (≥6 months) and T790M-positive status as determined by both tumour and plasma tests (all HRs <0.5) [17]. In patients with CNS metastases, osimertinib recipients had a median PFS of 8.5 months versus

Table 1 Efficacy of osimertinib versus platinum-pemetrexed therapy in patients with *EGFR* T790M-positive advanced non-small cell lung cancer in AURA3 [17]

Endpoint	Osimertinib (n = 279)[d]	Platinum-pemetrexed (n = 140)[d]	Hazard ratio (95% CI)[e]	Odds ratio (95% CI)[e]
Median PFS[a] (INV) (months) [b]	10.1	4.4	0.30 (0.23–0.41)*	
Median PFS[a] (BICR) (months)	11.0	4.2	0.28 (0.20–0.38)*	
Overall survival[c] (%)	24.7	28.6	0.72 (0.48–1.09)	
ORR (INV) (% of patients)	71	31		5.39 (3.47–8.48)*
Median duration of response (INV) (months)	9.7[f]	4.1		
Disease control rate (INV) (% of patients)	93	74		4.76 (2.64–8.84)*
Mean best tumour shrinkage (INV) (% change)	−46	−24		

BICR blinded independent central review assessed, *INV* investigator assessed, *ORR* objective response rate, *PFS* progression-free survival

*$p < 0.001$ vs. platinum-pemetrexed

[a] Time from randomization until disease progression or death in the absence of progression, irrespective of whether the patient had discontinued randomized treatment or received another anticancer therapy before progression

[b] Primary efficacy endpoint

[c] First analysis of overall survival, performed approximately 4 months after the primary PFS analysis; analysis not adjusted for crossover effects

[d] Two osimertinib recipients and one platinum-pemetrexed recipient had T790M-negative tumours and were randomized in error

[e] Ratio after adjustment for Asian or non-Asian race

[f] Significantly longer than in platinum-pemetrexed group based on non-overlapping confidence intervals (95% CI 8.3–11.6 vs. 3.0–5.6)

4.2 months in the platinum-pemetrexed group (HR 0.32; 95% CI 0.21–0.49; n = 93 and 51) [17].

Data cutoff for the first OS analysis was scheduled for 4 months after the primary PFS analysis. At the time of this first OS analysis, there was no significant difference in the risk of death with osimertinib relative to platinum-pemetrexed (OS data 26% mature) (Table 1) [17]. Further OS analyses are planned at ≈50 and 70% maturity [17].

Osimertinib treatment offered benefits over platinum-pemetrexed for other secondary efficacy outcomes. Investigator-assessed ORRs and DCRs were significantly higher in the osimertinib than in the platinum-pemetrexed group, with osimertinib recipients approximately five times more likely to achieve each of these outcomes (Table 1). ORRs in a subgroup of patients with T790M-positive status as confirmed by both tumour and plasma tests [77% (89/116) with osimertinib vs. 39% (22/56) with platinum-pemetrexed; 95% CI 2.49–10.15; $p < 0.001$] were consistent with those in the overall population (Table 1) [17]. The median DoR was prolonged in osimertinib recipients compared with platinum-pemetrexed recipients (Table 1). Patient-reported outcomes for prespecified symptoms (appetite loss, cough, chest pain, dyspnoea and fatigue) were better in osimertinib than platinum-pemetrexed recipients during the first 6 months ($p \leq 0.001$ for each symptom) [17].

Osimertinib also demonstrated efficacy in treating CNS metastases [12]. In a subgroup of patients with measurable baseline CNS lesions, the confirmed CNS ORRs by neuroradiologist BICR in the osimertinib (n = 30) and platinum-pemetrexed (n = 16) groups were 70 and 31% [odds ratio (OR) 5.1; 95% CI 1.4–21.0; $p = 0.015$] [12]. The DCR was significantly higher in the osimertinib group than in the platinum-pemetrexed group (87% vs. 68%), with osimertinib recipients three times more likely to achieve disease control (OR 3; 95% CI 1.2–7.9; p = 0.021). In patients with a response, the DoR was 8.9 months in osimertinib recipients and 5.7 months in platinum-pemetrexed recipients. In patients with measurable or non-measurable baseline CNS lesions, CNS PFS by neuroradiologist BICR was significantly prolonged with osimertinib therapy versus platinum-pemetrexed [11.7 vs. 5.6 months (HR 0.32; 95% CI 0.15–0.69; p = 0.004)] after progression events in 19 (25% maturity) osimertinib recipients and 16 (32% maturity) platinum-pemetrexed recipients [12].

5 Tolerability

Osimertinib had a manageable tolerability profile in patients with *EGFR* T790M-positive advanced NSCLC during phase II and III trials [17–19]. In AURA3, adverse events (AEs) of any grade occurred in 98% of osimertinib recipients and 99% of platinum-pemetrexed recipients [17]. AEs of any grade that were considered to be possibly causally-related to treatment by the investigators were reported in 83% of osimertinib recipients and 89% of platinum-pemetrexed recipients; 6 and 34%, respectively, had events of at least grade 3 severity [17]. Median duration of exposure was 8.1 months in the osimertinib group and 4.2 months in the platinum-pemetrexed group [17]. The AEs profile with osimertinib in AURA3 was consistent with

pooled data from patients in phase II trials ($n = 411$) [11, 12], in which 333 patients were exposed to osimertinib for ≥6 months (97 patients for ≥9 months) [11].

In AURA3, the most common (≥20%) possibly causally-related AEs (any grade) in the osimertinib group were diarrhoea, rash, and paronychia, while those in the platinum-pemetrexed group were nausea, decreased appetite, anaemia, fatigue and neutropenia (Fig. 1) [17]. Possibly causally-related AEs with osimertinib were predominantly of grade 1 or 2 severity. Grade 3 or 4 AEs that were possibly causally-related in the osimertinib group included diarrhoea (1% in the osimertinib group and 1% in the platinum-pemetrexed group), rash (<1 and 0%), decreased appetite (<1 and 3%), anaemia (<1 and 10%) and interstitial lung disease (ILD) (<1 and 1%). No osimertinib recipients experienced possibly causally-related grade ≥ 3 neutropenia (vs. 11% of platinum-pemetrexed recipients) or thrombocytopenia (0 vs. 7%) [17]. During AURA3, permanent discontinuation of treatment due to AEs occurred in 7% of osimertinib recipients and 10% of platinum-pemetrexed recipients [17]. Discontinuation due to AEs considered to be possibly causally-related to treatment occurred in 4% of osimertinib recipients (most commonly because of pneumonitis). In the osimertinib group, AEs resulted in dose interruptions in 14% of patients and dose reductions to osimertinib 40 mg/day in 3% of patients. In the platinum-pemetrexed group, AEs led to pemetrexed, cisplatin and carboplatin administration delays in 12–21% of patients and dose reductions in 11–29% of patients [17].

Serious AEs (including those with a fatal outcome) occurred in 18% of osimertinib recipients and 26% platinum-pemetrexed recipients, which were possibly causally-related to treatment in 3 and 13% of recipients [17]. The most

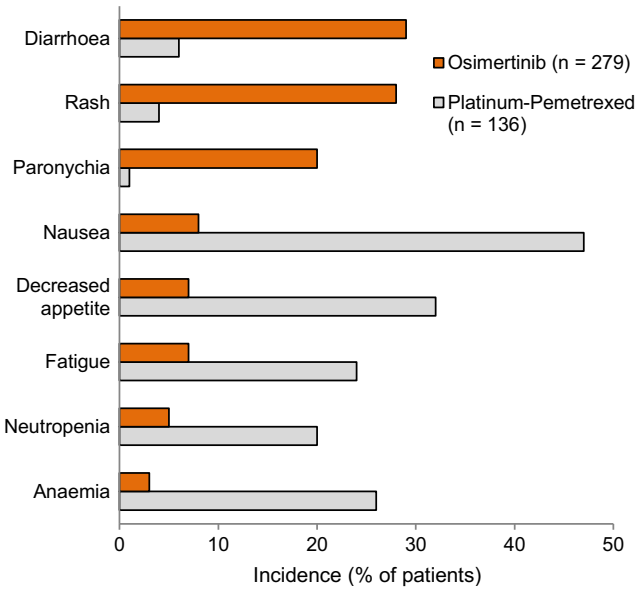

Fig. 1 Incidence of adverse events (any grade) possibly causally-related to treatment and occurring in ≥20% of patients in either treatment arm of the AURA3 trial [17]. Rash, paronychia and haematological adverse events were reported as grouped terms

common serious AEs in the osimertinib group (≥1% of patients) were pulmonary embolism [4 (1%) osimertinib and 2 (1%) platinum-pemetrexed recipients], pneumonia [3 (1%) and no patients] and dyspnoea [3 (1%) and no patients]. In the platinum-pemetrexed group, the most common serious AEs (≥2% of patients) were deep vein thrombosis [no osimertinib recipients and 4 (3%) platinum-pemetrexed recipients], anaemia [no patients and 3 (2%)] and epilepsy [no patients and 3 (2%)]. Fatal AEs were reported in four (1%) osimertinib recipients [respiratory failure ($n = 2$), pneumonitis ($n = 1$) and ischaemic stroke ($n = 1$)] and one (1%) platinum-pemetrexed recipient (hypovolemic shock) [17].

EU and US labelling for osimertinib carry warnings of ILD [11, 12]. In AURA3, AEs resembling ILD occurred in 10 (4%) patients receiving osimertinib (9 events of grade 1 or 2 severity and one death) and in one (1%) patient receiving platinum-pemetrexed (grade 3 severity) [17]. Osimertinib treatment should be withheld in any patient with acute onset [12] or worsening of respiratory symptoms [11, 12] that may indicate ILD. If ILD is confirmed, osimertinib should be permanently discontinued [11, 12].

QTc interval prolongation can occur with osimertinib (Sect. 2) [11, 12]. In AURA3, dose reductions or interruptions due to ECG-assessed QT interval prolongation occurred in 1.8% of patients treated with osimertinib [11, 17]. No QTc-related arrhythmias were reported in patients treated with osimertinib in clinical trials ($n = 833$) [11, 12]. In the US, patients predisposed to QTc prolongation or who are taking medicinal products that prolong the QTc interval should be periodically monitored with ECGs and electrolytes during osimertinib therapy [11]. In the EU, this monitoring should also be considered and administration of osimertinib in patients with congenital long QTc syndrome should be avoided where possible [12].

The US and EU labels also carry warnings of cardiomyopathy [11] and changes in cardiac contractility [12] respectively. In clinical trials, cardiomyopathy (defined as cardiac failure, congestive heart failure pulmonary oedema or ejection fraction decrease) occurred in 1.9% (16/833) of osimertinib recipients and was fatal in 0.1% (1/833) of recipients [11]. In the USA, cardiac monitoring should be conducted in patients with cardiac risk factors [11]; this monitoring should also be considered in the EU [12].

6 Dosage and Administration

Osimertinib is approved in the USA for the treatment of patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on or after EGFR TKI therapy [11] and in the EU for the treatment of adult patients with locally advanced or metastatic *EGFR* T790M-positive NSCLC [12]. In Japan, osimertinib is approved for *EGFR* T790M-positive inoperable or recurrent NSCLC resistant to EGFR TKI

therapy [10]. *EGFR* T790M status should be determined using a locally approved test [10, 11] or a validated tissue-based or plasma-based test [12]. Due to the potential for plasma-based ctDNA tests to yield false negative results, clinicians are advised to follow-up negative ctDNA test results with a tissue test wherever possible [11, 12]. Osimertinib is available as 40 mg or 80 mg film-coated tablets [10–12]. The recommended dosage of osimertinib is 80 mg taken orally once a day with or without food [11, 12]. Treatment should continue until disease progression or unacceptable tolerability [11, 12]. Local prescribing information should be consulted for details concerning missed doses, contraindications, warnings, precautions, management of tolerability issues, drug interactions and use in specific patient populations [10–12].

7 Place of Osimertinib in the Management of T790M-Positive Advanced NSCLC

Based on high-level evidence and uniform NCCN consensus, NCCN treatment guidelines recommend osimertinib as a second-line and beyond treatment option in patients with *EGFR* T790M-positive metastatic NSCLC that has progressed following therapy with an approved first- or second-generation EGFR TKI [5]. This recommendation was made based on results from AURA3 [5]. Similarly, ESMO guidelines recommend the use of osimertinib in patients with *EGFR* T790M-positive advanced NSCLC and clinically relevant disease progression following previous treatment with an EGFR TKI [6].

Osimertinib is approved in several countries, including China [9], Japan [10] and the USA [11], as a first-in-class treatment for patients with *EGFR* T790M-positive advanced NSCLC who have progressed following EGFR TKI therapy; in the EU, osimertinib is indicated more broadly for patients with *EGFR* T790M-positive advanced NSCLC (Sect. 6) [12]. Osimertinib was initially approved in the aforementioned indications under accelerated approval in the USA [11] and under a conditional approval scheme in the EU [12]. These initial approvals were based on positive results in the phase II AURAext and AURA2 trials, in which osimertinib was associated with ORRs of 62 and 70% in patients with *EGFR* T790M-positive advanced NSCLC who had progressed after previous treatment with an EGFR TKI (Sect. 4.1).

More recently, confirmatory phase III results have become available and resulted in the FDA and EMA granting full approval status to osimertinib [11, 12]. In AURA3, osimertinib significantly prolonged the median duration of PFS relative to platinum-pemetrexed (by ≈6 months) in patients with T790M-positive advanced NSCLC and was associated with a 70% reduction in the risk of disease progression or death (Sect. 4.2). PFS benefits with osimertinib relative to platinum-pemetrexed therapy were demonstrated across all predefined subgroups, including those based on race (Asian vs. non-Asian) and the presence of CNS metastases (Sect. 4.2). The ORR and patient-reported symptoms were also significantly improved with osimertinib relative to platinum-pemetrexed (Sect. 4.2). More mature OS results from AURA3 are awaited with interest and will further elucidate the position of osimertinib in the treatment of patients with advanced *EGFR* T790M-positive NSCLC. It should also be noted that, as with earlier generation EGFR TKIs, patients eventually develop resistance to osimertinib (Sect. 2).

The brain is a common site for disease progression following EGFR TKI treatment in patients with NSCLC [16]. Osimertinib demonstrated antitumour efficacy against CNS metastases in subsets of evaluable patients in AURAext and AURA3 (Sect. 4). This activity is consistent with pharmacokinetic data suggesting osimertinib crosses the blood-brain barrier (Sect. 3). The NCCN recommendation for osimertinib includes use in patients with symptomatic brain metastases [5].

Osimertinib had a manageable tolerability profile in patients with *EGFR* T790M-positive NSCLC in phase II and III trials (Sect. 5). In AURA3, the majority of possibly causally-related AEs were of grade 1 or 2 severity, with the most common (any grade) being diarrhoea, rash and paronychia (Sect. 5). The rate of discontinuation due to AEs considered to be possibly causally-related to treatment was low (4%) in osimertinib recipients (Sect. 5). There is a risk of QT interval prolongation and ILD/pneumonitis with osimertinib treatment (Sect. 5).

EGFR T790M status can be determined using either a tissue-based or plasma-based approved test (Sect. 6). Plasma-based testing offers a minimally-invasive alternative to a biopsy, with a biopsy carrying additional risks and not always being clinically feasible [13]. The cobas® *EGFR* Mutation Test v2 is FDA-approved for the detection of T790M in plasma samples [31]. AURA3 results support the use of this test, with benefits of osimertinib over platinum-pemetrexed therapy in a subgroup of patients with T790M-positivie status by both tumour and plasma tests being consistent with those in the ITT population (Sect. 4.2).

In conclusion, osimertinib is an effective treatment in adult patients with advanced *EGFR* T790M-positive NSCLC, with a manageable tolerability profile. Current evidence suggests that osimertinib is an important option for this patient group.

Data Selection Osimertinib

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Osimertinib, AZD-9291, Mereletinib, Tagrisso, NSCLC, non-small cell lung, T790M. Records were limited to those in English language. Searches last updated 28 June 2017

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Compliance with Ethical Standards

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