



## Osimertinib as first-line therapy in advanced NSCLC: a profile of its use

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### Abstract

Osimertinib (Tagrisso<sup>®</sup>) is an oral, CNS-active, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that selectively inhibits EGFR TKI-activating mutations over wild-type EGFR in patients with advanced non-small cell lung cancer (NSCLC), including the T790M mutation that often underlies acquired resistance to earlier generation EGFR TKIs. Relative to standard of care first-generation EGFR TKIs (erlotinib or gefitinib) as first-line treatment of *EGFR* activating mutation-positive advanced NSCLC, osimertinib significantly prolongs median progression-free survival (PFS), with separation of the Kaplan-Meier PFS survival curves evident by the first assessment timepoint of 6 weeks. Osimertinib prolongs PFS relative to standard EGFR TKI therapy in all prespecified groups, irrespective of the *EGFR* mutation present at study entry and presence of CNS metastases at study entry. Overall survival data are not yet mature. Osimertinib has a generally manageable tolerability profile.

### Adis evaluation of osimertinib as first-line therapy in advanced NSCLC

Potent, irreversible EGFR TKI of certain mutant *EGFR* forms [L858R, exon 19 deletion (ex19del), and T790M], with minimal activity against wild type EGFR

Prolongs PFS relative to erlotinib or gefitinib in patients with advanced NSCLC, including those with CNS metastases, and irrespective of the *EGFR* mutation status (L858R or ex19del)

At the time of data cutoff, overall survival data not yet mature

Generally manageable tolerability profile, with most adverse events being of mild to moderate intensity

### What is the rationale for using osimertinib in NSCLC?

In recent years, a better understanding of the pathophysiology and numerous oncogenic drivers associated with cancer, such as non-small cell lung cancer (NSCLC), has led to the development of targeted antineoplastic agents that have revolutionized cancer management and improved clinical outcomes [1–3]. Key oncogenic drivers of NSCLC, with NSCLC accounting for > 80% of lung cancers, involve mutations in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene, with these activating/sensitizing mutations occurring in ≈ 10 to 15% of Caucasian and ≈ 30 to 40% of East Asian lung cancer patients [1–3].

Although targeted therapy with first (erlotinib, gefitinib) and second (afatinib) generation EGFR tyrosine kinase inhibitors (TKIs) represent a significant paradigm shift in the management of NSCLC, these drugs are inevitably associated with the emergence of resistance in almost all patients (typically at a median time of 9–16 months), most commonly the *EGFR* T790M gatekeeper mutation (accounts for 50–60% of secondary resistance to first-line EGFR TKI therapy) [1–3]. Insights into the mechanisms underlying resistance to earlier generation EGFR TKIs led to the development of third-generation EGFR TKIs that selectively inhibit both *EGFR* TKI-activating mutations [e.g. exon 19 deletion (ex19del) and L858R mutations] and the T790M resistance mutation [1–3]. Given the minimal inhibition of

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wild-type *EGFR* TKI by third-generation EGFR TKIs, these compounds may also reduce the toxicities associated with earlier generation EGFR TKIs [1].

Oral osimertinib (Tagrisso<sup>®</sup>) is the first and, currently, only third-generation EGFR TKI indicated for the treatment of NSCLC. This review focuses on its use as first-line therapy in patients with locally advanced and metastatic NSCLC whose tumours have *EGFR* ex19del or exon 21 L858R mutations (i.e. sensitizing/activating mutations). Its use as the first and currently only third-generation EGFR TKI approved to treat EGFR TKI-experienced patients with metastatic *EGFR* T790M mutation-positive NSCLC has been previously reviewed [4] and is beyond the scope of this article.

### For whom is osimertinib indicated?

Osimertinib is approved in several countries, including those of the EU [5] and the USA [6], for first-line treatment in patients with locally advanced [5] or metastatic [5, 6] NSCLC whose tumours have *EGFR* ex19del or exon 21 L858R mutations [6] (have activating *EGFR* mutations [5]). In many countries, osimertinib is also approved for the treatment of patients with locally advanced or metastatic *EGFR* T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy. Table 1 provides a summary of the prescribing information for osimertinib as approved in the EU [5] and USA [6]. Consult local information for further details.

### How does osimertinib work?

Osimertinib potently and irreversibly inhibits the tyrosine kinase activity of certain mutant EGFR forms [L858R, exon 19 deletion (ex19del) and T790M] at  $\approx 9$ -fold lower concentrations than wild-type EGFR (i.e. exhibits minimal activity against wild type EGFR) [4, 6]. Of the two pharmacologically active metabolites, AZ7550 exhibited similar potency and selectivity to osimertinib and AZ5104 was a more potent inhibitor of ex19del and T790M mutant ( $\approx 8$ -fold) and wild-type ( $\approx 15$ -fold) EGFR than the parent drug [4, 6]. In preclinical in vitro and in vivo studies, osimertinib exhibited potent, sustained antitumour activity [4, 6], including 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 [4]. Osimertinib crosses the blood-brain barrier and inhibits the growth of CNS metastases in animal models [4]. Osimertinib may potentially delay the emergence of resistance, as observed in an in vitro study in which the emergence of resistance in PC9 cells with the

*EGFR* ex19del mutation was delayed with osimertinib compared with other EGFR TKIs [7, 8].

Overtime, as with earlier generation EGFR TKIs, the development of resistance to osimertinib is inevitable [9, 10]. Acquired resistance to osimertinib potentially involves several mechanisms, including the development of C797S resistance mutations at the kinase binding site (primary mechanism), activation of other pathways (e.g. via *HER2* and *CMET* amplification) and small cell transformation [4, 9].

Clinically significant cardiovascular events may potentially occur with osimertinib therapy, with the QTc interval prolongation of osimertinib 80 mg once daily evaluated in 210 treatment-experienced patients with *EGFR* T790M-positive NSCLC [5, 6]. A concentration-dependent QTc interval prolongation of 14 ms was predicted with the 80 mg dose of osimertinib [5, 6].

### What is the pharmacokinetic profile of osimertinib?

Osimertinib exhibits linear pharmacokinetics, with the median peak plasma concentration attained 6 h after oral administration [6]. Steady-state plasma concentrations of osimertinib are reached after 15 days, with once daily administration resulting in a threefold accumulation of the drug. Osimertinib is primarily metabolized via oxidation (predominantly CYP3A4) and dealkylation in vitro, with two pharmacologically active metabolites (AZ7550 and AZ5104) identified in plasma after oral administration. At steady state, exposure to each of these active metabolites was  $\approx 10\%$  of the exposure to osimertinib. The primary route of elimination of osimertinib is in the faeces (68%), with 14% eliminated in the urine and  $< 2\%$  eliminated as unchanged drug [6].

### What is the efficacy of first-line osimertinib in NSCLC?

First-line therapy with oral osimertinib 80 mg once daily was more effective than standard of care EGFR TKIs (i.e. erlotinib or gefitinib) in the pivotal randomized, double-blind, multinational FLAURA trial in 556 adults with previously untreated *EGFR* mutation-positive, advanced NSCLC [11].

At randomization in FLAURA,  $\approx 38\%$  of patients were male, the median age of patients was 64 years,  $\approx 98.5\%$  had adenocarcinoma, 95% had metastatic disease and 5% locally advanced disease, 63% had an *EGFR* ex19del mutation and 37% an *EGFR* L858R mutation,  $\approx 21\%$  had CNS metastases, and  $\approx 41$  and  $\approx 59\%$  of patients had a WHO performance status of 0 and 1 [11]. Treatment was continued until

**Table 1** Summary of prescribing information of oral osimertinib (Tagrisso®) in locally advanced [5] and metastatic [5, 6] NSCLC in the EU [5] and USA [6]

<b>What are the approved indications for osimertinib?</b>	
First-line treatment	EU: Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations USA: Patients with metastatic NSCLC whose tumours have <i>EGFR</i> exon19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
Following EGFR TKI therapy	EU: Adult patients with locally advanced or metastatic <i>EGFR</i> T790M mutation-positive NSCLC USA: Patients with metastatic <i>EGFR</i> T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy
<b>How is osimertinib available and how should it be administered?</b>	
Availability	Tablets containing 40 or 80 mg of osimertinib
Dosage	80 mg once daily, taken without regard to food
Duration of treatment	Continue until disease progression or unacceptable toxicity
Administration in patients who have difficulty swallowing	Immerse tablet in 50 [5] or 60 [6] mL of non-carbonated water Stir until tablet is dispersed into small pieces (does not fully dissolve) and swallow immediately Rinse container with half a glass [5] or 120–240 mL [6] of water and immediately drink
Administration via a nasogastric tube	Disperse tablet in 15 mL of non-carbonated water, and then use another 15 mL of water to transfer any residue to the syringe. Administer this 30 mL as per nasogastric tube instructions, with water flushes (≈30 mL)
<b>How should osimertinib be used in special populations?</b>	
Elderly patients (age ≥ 65 years)	No dosage adjustment required
Patients with renal impairment	Mild, moderate or severe impairment: no dosage adjustment required End-stage renal disease: caution advised [5] or no recommended dose [6] (lack of data)
Patient with hepatic impairment	Mild or moderate: no dosage adjustment required Severe impairment: caution advised [5] or no recommended dose [6] (lack of data)
Paediatric patients	Efficacy and safety have not been established
<b>What precautions should be taken with regard to the risk of potential embryo-foetal /infant toxicity?</b>	
Female patients of child-bearing potential and male patients with a partner of child-bearing potential	Advise of potential risk of embryo-foetal toxicity [5, 6]; only use if benefits outweigh the risks [5] Female patients: advise them to use effective contraception during treatment and for 6 [6] or ≥ 8 [5] weeks after the final dose Male patients: advise them to use effective contraception during treatment and for 4 months after the final dose
Pregnant women	Advise of the potential risk for foetal harm [5, 6]; only use if the benefits outweigh the risks [5]
Women who are breast feeding	Do not breastfeed during treatment [5, 6] and for 2 weeks after the final dose [6]
<b>What other special warnings/precautions pertain/monitoring requirements to the use of osimertinib?</b>	
Interstitial lung disease/pneumonitis	Permanently discontinue treatment in patients diagnosed with these conditions
QTc interval prolongation	Patients with a history or predisposition to QTc interval prolongation or who are taking medications that are known to prolong the QTc interval: monitor ECGs and electrolytes
Cardiomyopathy	Patients with cardiac risk factors: conduct cardiac monitoring, including LVEF assessment
Keratitis	Patients with signs and symptoms of keratitis: promptly refer patients to an ophthalmologist
<b>What are the potential clinically relevant drug interactions between osimertinib and other drugs?</b>	
Strong CYP3A4 inducers (e.g. rifampin)	Avoid concomitant use [5] (if possible [6]); if not possible [6], ↑ osimertinib to 160 mg once daily Resume osimertinib 80 mg once daily 3 weeks after discontinuing the strong CYP3A4 inducer
BCRP substrates (e.g. rosuvastatin)	Monitor for adverse drug reactions of the BCRP substrate (osimertinib ↑ exposure to such drugs)

Unless otherwise indicated, data pertain to both the EU and the USA

*BCRP* breast cancer resistance protein, *CYP* cytochrome P450, *EGFR* epidermal growth factor receptor, *LVEF* left-ventricular ejection fraction, *NSCLC* non-small cell lung cancer, *TKI* tyrosine kinase inhibitor, ↑ increase(s)

disease progression, unacceptable tolerability or withdrawal of consent, with a median duration of treatment exposure at the cutoff date of 16.2 months in the osimertinib group and 11.5 months in the standard EGFR TKI group. After RECIST-defined disease progression, a first anticancer therapy was initiated in 82 of 279 patients in the osimertinib group and 129 of 277 patients in the standard EGFR TKI group (48 of these patients in the standard EGFR TKI group crossed over to osimertinib and 7 received osimertinib outside of the trial as second-line therapy) [11].

In the overall full analysis set (FAS) of FLAURA, osimertinib significantly ( $p < 0.001$ ) prolonged median progression-free survival (PFS) compared with standard EGFR TKI treatment, with a reduction in the risk of disease progression or death of 54% at the time of data cutoff (primary outcome) [Table 2] [11]. The separation of the osimertinib and standard EGFR TKI PFS Kaplan-Meier curves had occurred by the time of the first assessment at 6 weeks. At the time of data cutoff, 136 and 206 patients in the osimertinib and standard EGFR TKI groups had experienced a RECIST-defined progression or death event. Prespecified subgroup analyses for PFS were consistent with the findings in the FAS analysis, with PFS favouring [i.e. hazard ratio (HR)  $< 1$ , with 95% CI not crossing 1] osimertinib over standard EGFR TKI therapy across all subgroups, including in patients with or without known or treated CNS metastases at study entry,

in Asian and non-Asian patients, and irrespective of the type of mutation present at baseline (Table 2) [11].

There were generally no between-group differences for secondary outcomes in FAS analyses, including for the ORR, disease control rate and median time to response (Table 2) [11]. Osimertinib recipients experienced a significantly better median best percentage change in target lesion size than standard EGFR TKI recipients ( $-54.7$  vs  $-48.5\%$ ;  $p = 0.003$ ); best percentage change in target lesion size was defined as the maximum decrease from baseline or minimum increase from baseline in the absence of a decrease [11].

At the time of data cutoff, overall survival data were not yet mature (25% maturity reached), with death occurring in 21% (58 patients) of osimertinib recipients and 30% (83 patients) of standard EGFR TKI recipients by 18 months (HR for death 0.63; 95% CI 0.45–0.88;  $p = 0.007$ ; not significant in this interim analysis) [11]. Consistent with these promising immature overall survival data, the significant PFS benefit with osimertinib over standard EGFR TKI therapy was maintained for the median time-to-event post-progression endpoints of time to first subsequent therapy or death (23.5 vs 13.8 months; HR 0.51; 95% CI 0.40–0.64;  $p < 0.0001$ ), median time from randomization to second progression on subsequent treatment (not yet reached vs 20.0 months; HR 0.58; 95% CI 0.44–0.78;  $p < 0.001$ ) and

**Table 2** Efficacy of oral osimertinib as first-line treatment for advanced NSCLC with *EGFR* mutations in the FLAURA trial [11]

Outcome	Results
Comparators (no. of pts)	Osimertinib vs EGFR-TKI (279 vs 277)
Median progression-free survival in the FAS (primary outcome) and subgroup analyses	In the FAS of 556 pts <sup>a</sup> : 18.9* vs 10.2 months [HR 0.46 (95% CI 0.37–0.57)] In 116 pts with CNS metastases at study entry: 15.2* vs 9.6 months [HR 0.47 (95% CI 0.30–0.74)] In 440 pts without CNS metastases at study entry: 19.1* vs 10.9 months [HR 0.46 (95% CI 0.36–0.59)] In 347 Asian pts: HR 0.55 (95% CI 0.42–0.72) In 209 non-Asian pts: HR 0.34 (95% CI 0.23–0.48) In 349 pts with <i>EGFR</i> exon 19 deletions at study entry: HR 0.43 (95% CI 0.32–0.56) In 207 pts with <i>EGFR</i> L885R mutation at study entry: HR 0.51 (95% CI 0.36–0.71)]
<b>Secondary outcomes in the FAS</b>	
Median overall survival	Not yet reached (data were not yet mature at data cut-off; data maturity 25%)
Objective response rate	80 (95% CI 75–85) vs 76% (95% CI 70–81)
Disease control rate <sup>a</sup>	97 (95% CI 94–99) vs 92% (95% CI 89–95)
Median duration of response	17.2 (95% CI 13.8–22.0) vs 8.5 months (95% CI 7.3–9.8)
Median time to response	6.1 (95% CI 6.0–6.1) vs 6.1 weeks (95% CI not calculable)

Pts were stratified by *EGFR* mutation status and race, and randomized to receive osimertinib 80 mg once daily or a standard of care oral EGFR TKI (i.e. gefitinib 250 mg once daily or erlotinib 150 mg once daily) until disease progression, unacceptable side effects or withdrawal of consent. Results presented are from the data cutoff of Jun 2017 (136 and 206 events of progression or death had occurred in the osimertinib and EGFR TKI groups)

*EGFR* epidermal growth factor receptor, *FAS* full analysis set, *HR* hazard ratio, *pts* patients, *TKI* tyrosine kinase inhibitor

\* $p < 0.001$  vs EGFR TKI

<sup>a</sup>Pts who had a complete response, partial response or stable disease lasting  $\geq 6$  weeks before any disease-progression event

median time to second subsequent therapy (not yet reached vs 25.9 months; HR 0.60; 95% CI 0.45–0.80;  $p < 0.001$ ) [12].

In a prespecified subgroup analysis of FLAURA in patients with documented CNS metastases by neuroradiology (blinded independent central neuroradiology review), osimertinib prolonged PFS compared with standard EGFR TKI therapy [median CNS PFS not reached (95% CI 16.5, not calculable) vs. 13.9 months (95% CI 8.3, not calculable);  $n = 61$  and  $67$  in CNS FAS], corresponding to a CNS PFS HR of 0.48 (95% CI 0.26–0.86; nominal  $p = 0.014$ ) [13]. The confirmed CNS objective response rates (ORR) in the osimertinib and standard EGFR TKI group were 57% and 40%, corresponding to an odds ratio of 2.0 (95% CI 1.0–1.41;  $p = 0.053$ ). The median CNS duration of response in the osimertinib group was not reached (95% CI 11.9, not calculable) and in the standard EGFR TKI group was 14.4 months (95% CI 8.3–18.7) [13].

There was no between-group difference with regard to changes from baseline to 9 months in key patient-reported outcomes, all of which improved in both treatment groups, with improvements in cough symptoms being clinically relevant [14].

### Other clinical data

The data from FLAURA are supported by evidence from the expansion phase of the phase 1/2 AURA trial in EGFR-TKI treatment-experienced patients with *EGFR* T790M mutations, which also enrolled two first-line cohorts of EGFR TKI-naïve patients with *EGFR* mutation-positive NSCLC [15]. In the cohort of 30 patients receiving the approved dosage of osimertinib 80 mg once daily, the ORR was 67%, the disease control rate was 93%, and the median duration of response was 19.3 months [15]. In the cohort of 30 patients receiving osimertinib 160 mg once daily, 87% had an ORR, 100% achieved disease control, the median PFS was 22.1 months and the median response duration was 16.7 months; corresponding results in the pooled cohorts were 77%, 97%, 20.5 months and 18 months [15].

### What is the tolerability profile of osimertinib?

Osimertinib had a generally manageable tolerability as first-line therapy in patients with advanced NSCLC in the FLAURA trial (FAS population) [11]. In the osimertinib and standard EGFR TKI group, 13 and 18% of patients permanently discontinued treatments because of an adverse event (AE). AEs leading to dose interruptions occurred in 25% of osimertinib recipients and 24% of standard EGFR TKI recipients and AEs resulting in dose reductions occurred in

4 and 5% of patients, respectively. Grade 3 or 4 treatment-emergent AEs occurred in 34% of osimertinib recipients and 45% of standard EGFR TKI recipients. The most common (i.e. incidence  $\geq 2\%$ ) possibly causally-related grade 3 AEs occurring in the osimertinib or standard EGFR TKI groups were decreased appetite (2 vs 1%), diarrhoea (2 vs 2%), rash or acne (1 vs 7%), and aspartate (1 vs 4%) or alanine (ALT;  $< 1$  vs 7%) aminotransferase elevations. Four patients (1 vs 0% in the osimertinib group) in the standard EGFR TKI group experienced grade 4 ALT elevations, which was the only possibly causally-related grade 4 AE to occur with an incidence of  $\geq 2\%$  in either group [11].

Overall serious AEs occurred in 22 and 25% of osimertinib and standard EGFR TKI recipients in FLAURA [11]. No fatal adverse events were considered possibly treatment-related in the osimertinib group, with one serious case of diarrhoea considered to be possibly related to standard EGFR TKI therapy. Serious AEs of pneumonia (3%) and interstitial lung disease (ILD; 1%) occurred with the same incidence in both groups. Of the treatment-emergent ILD cases, all 11 cases in the osimertinib group were considered resolved or resolving, as were 5 of 6 cases in the standard EGFR TKI group (the other patient was considered not recovered). Serious prolongation of the QT interval was reported in one osimertinib recipient and no standard EGFR TKI recipients, with no fatal cases of torsades des pointes or prolongation of the QT interval occurring in either group. The maximum change from baseline (411.8 and 408.0 ms) to week 12 in Fridericia's corrected QT (QTcF) interval in the osimertinib and standard EGFR TKI groups was 17.7 and 10.0 ms, after which time QTcF values generally remained stable in both groups [11].

Precautions should be taken to ameliorate the risk and/or severity of several potential AEs (Table 1). Warnings and precautions regarding the use of once-daily osimertinib 80 mg were based on pooled data from 1142 patients with *EGFR* mutation-positive NSCLC participating in FLAURA or in EGFR TKI-experienced patients participating in the AURA clinical trial programme [6]. ILD/pneumonitis occurred in 3.9% of these patients, with 0.4% of cases fatal. A QTc interval of  $> 500$  ms occurred in 0.9% of patients, with 3.6% experiencing an increase in QTc of  $> 60$  ms. No QTc-related arrhythmias were reported. Cardiomyopathy events (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary oedema or decreased ejection volume) occurred in 2.6% of patients, 0.1% of which were fatal. Of the 908 patients with a baseline and  $\geq 1$  follow-up left ventricular ejection fraction (LVEF) assessment, 3.9% experienced a decline in LVEF of  $\geq 10\%$  from baseline and to  $> 50\%$  LVEF. Of the 1142 patients, keratitis occurred in 0.7%. Based on animal data and its mechanism of action, osimertinib can cause foetal harm when administered to pregnant women [6].

## What is the current clinical position of first-line osimertinib in advanced NSCLC?

The third-generation EGFR TKI osimertinib is an effective first-line treatment and has a generally manageable tolerability profile in patients with advanced NSCLC with *EGFR* TKI-activating mutations. In the pivotal FLAURA trial in previously untreated patients with advanced *EGFR* TKI-activating mutation-positive NSCLC, osimertinib significantly prolonged median PFS compared with standard of care EGFR TKI treatment with erlotinib or gefitinib. The early separation of the PFS Kaplan-Meier curves for osimertinib and these first-generation EGFR TKIs supports the hypothesis that third-generation EGFR TKIs such as osimertinib may prevent/delay the development of resistance [11], with the development of resistance inevitable with all EGFR TKIs [1–3, 9, 10]. Consistent with results in the overall population, osimertinib also prolonged PFS (vs erlotinib or gefitinib) in all prespecified subgroups of patients, including in patients with CNS metastases [11]; patients with *EGFR* mutation-positive NSCLC are especially prone to the development of brain metastases [16]. Overall survival data for the FLAURA trial are not yet mature [11]. A limitation of the FLAURA trial was the lack of comparison with the second-generation EGFR TKI afatinib, with no head-to-head comparisons of osimertinib and afatinib conducted to date.

Osimertinib is the first and, currently, only third-generation EGFR TKI approved for use in EGFR TKI-naïve patients with *EGFR* activating mutation-positive NSCLC and/or EGFR TKI-experienced patients with metastatic *EGFR* T790M mutation-positive NSCLC. Based on the findings of FLAURA, US treatment guidelines currently recommend osimertinib as a first-line treatment option in patients with *EGFR* activating mutation-positive NSCLC [17]. The European Society for Medical Oncology (ESMO) guidelines [18] were published prior to the recent positive opinion given by the European Medicines Agency for the use of osimertinib as first-line treatment in patients with locally advanced NSCLC whose tumours have activating *EGFR* mutations [19]. US treatment guidelines [17] also recommended osimertinib as second or subsequent-line therapy in patients with T790M acquired resistance to first- or second-generation EGFR TKIs who have progressed on these earlier generation EGFR TKIs, as do ESMO guidelines [18]. The optimal approach/sequence for using EGFR TKIs remains to be fully determined, with results of ongoing trials awaited with interest. One such trial, the open-label phase 2 APPLE trial [20], is designed to primarily evaluate the best strategy for delivering osimertinib (i.e. upfront vs sequential treatment after first-generation EGFR TKI) in NSCLC patients with *EGFR* mutations, as assessed by PFS at 18 months. Among other secondary endpoints, this trial will

also evaluate the time to symptomatic brain metastases in patients with brain metastases at trial entry [20].

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