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Clinical Trial Brief Report

Clinical Cancer Research

Postprogression Outcomes for Osimertinib versus Standard-of-Care EGFR-TKI in Patients with Previously Untreated EGFR-mutated Advanced Non–Small Cell Lung Cancer

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Abstract

Purpose: In the phase III FLAURA study, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib significantly improved progression-free survival (PFS) versus standard-of-care (SoC) EGFR-TKI (gefitinib or erlotinib) in patients with previously untreated EGFR (exon 19 deletion or L858R) mutation-positive advanced non–small cell lung cancer (NSCLC). Interim overall survival (OS) data were encouraging, but not formally statistically significant at current maturity (25%). Here we report exploratory postprogression outcomes.

Patients and Methods: Patients were randomized 1:1 to receive osimertinib (80 mg orally, once daily) or SoC EGFR-TKI (gefitinib 250 mg or erlotinib 150 mg, orally, once daily). Treatment beyond disease progression was allowed if the investigator judged ongoing clinical benefit. Patients receiving SoC EGFR-TKI could cross over to receive osimertinib after independently confirmed objective disease progression with documented postprogression T790M-positive mutation status.

Results: At data cutoff (June 12, 2017), 138 of 279 (49%) and 213 of 277 (77%) patients discontinued osimertinib and SoC EGFR-TKI, respectively, of whom 82 (59%) and 129 (61%), respectively, started a subsequent treatment. Median time to discontinuation of any EGFR-TKI or death was 23.0 months [95% confidence interval (CI), 19.5–not calculable (NC)] in the osimertinib arm and 16.0 months (95% CI, 14.8–18.6) in the SoC EGFR-TKI arm. Median second PFS was not reached (95% CI, 23.7–NC) in the osimertinib arm and 20.0 months (95% CI, 18.2–NC) in the SoC EGFR-TKI arm [hazard ratio (HR), 0.58; 95% CI, 0.44–0.78; $P = 0.0004$].

Conclusions: All postprogression endpoints showed consistent improvement with osimertinib versus SoC EGFR-TKI, providing further confidence in the interim OS data.

Introduction

Postprogression outcomes are intermediate clinical endpoints between progression-free survival (PFS) and overall survival (OS) that further define efficacy, and may have particular use when OS data are immature (1, 2). Osimertinib is a third-generation, central nervous system active, EGFR tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFRm and EGFR T790M resistance mutations. In the phase III FLAURA study of osimertinib versus standard-of-care (SoC) EGFR-TKIs (gefitinib or erlotinib) as first-line treatment for advanced non–small cell lung cancer (NSCLC) harboring EGFR sensitizing mutations [EGFRm; exon 19 deletion (ex19del) or L858R], PFS was significantly improved with osimertinib [HR, 0.46; 95% confidence interval (CI), 0.37–0.57; $P < 0.001$; ref. 3]. Interim OS data (25% maturity) were encouraging, but not formally statistically significant (HR, 0.63; 95% CI, 0.45–0.88; $P = 0.007$; ref. 3). Here we report postprogression outcomes from the FLAURA study, previously published in part by Soria and colleagues (3).

Patients and Methods

Study population, design, and endpoints

The study was approved by the institutional review board or independent ethics committee associated with each study center. The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics

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Translational Relevance

The analysis of postprogression outcomes of the FLAURA trial confirmed the consistent benefit of osimertinib versus standard-of-care EGFR–tyrosine kinase inhibitors and demonstrated that osimertinib preserves clinical benefit beyond first progression, providing further confidence in the interim overall survival data. In addition, patients who received osimertinib as a first-line therapy still benefited from subsequent therapies. These data are supportive of preliminary analyses (Ramalingam and colleagues, 2018) showing no evidence for mechanisms of acquired resistance that lead to aggressive disease biology. Taken together, these results suggest that first-line osimertinib does not cause any biological changes and/or resistance to subsequent anticancer therapies that would lead to more aggressive disease or rapid disease progression.

and human biologic samples of the trial sponsor, AstraZeneca. Informed consent was obtained from all patients prior to enrolment into the study. Full details of the FLAURA phase III study have previously been published (3). In brief, patients with previously untreated EGFRm locally advanced or metastatic NSCLC, eligible to receive first-line gefitinib or erlotinib treatment, were enrolled.

Enrolled patients were stratified by tumor EGFRm status (ex19del or L858R) and race (Asian or non-Asian), and randomly assigned in a 1:1 ratio to receive osimertinib (80 mg orally, once daily) or SoC EGFR-TKI (gefitinib 250 mg orally, once daily or erlotinib 150 mg orally, once daily). Treatment continued until objective disease progression (per RECIST version 1.1), the development of unacceptable side effects, or withdrawal of consent. Treatment beyond disease progression was allowed if the investigator judged continued clinical benefit. The nature and timing of any subsequent therapies were not protocol mandated but chosen by the investigator. Crossover from the SoC EGFR-TKI arm to open-label osimertinib was allowed following independently confirmed disease progression and documented postprogression T790M-positive mutation status without any intervening anticancer therapy.

PFS, the primary endpoint, was determined by investigator assessments. Exploratory postprogression endpoints included second PFS (PFS2), time to second-line therapy, time to third-line therapy, and time to discontinuation of any EGFR-TKI (TDTKI).

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Study assessments

Tumor assessments according to RECIST v1.1 were performed at baseline and every 6 weeks for 18 months, then every 12 weeks until disease progression. After progression, patients were followed for survival every 6 weeks, irrespective of treatment discontinuation, with data collection on subsequent therapies and response or progression, as per local practice guidelines. PFS2 was defined as the time from randomization to the earliest of the progression events subsequent to the first progression, or death after starting a subsequent anticancer treatment. Time to second-line therapy was defined as the time from randomization to the earliest start date of the second-line therapy following study treatment discontinuation, or death. Time to third-line therapy was defined as time from randomization to the earliest start date of the third-line therapy following study treatment discontinuation, or death. TDTKI was defined as the time from randomization to the last dose of any EGFR-TKI, or death, without interruption by any non-EGFR–TKI therapy (i.e., includes study treatment and any sequential EGFR-TKI treatment). See Fig. 1A for a summary of postprogression endpoints. A summary of some of these endpoints has been previously been reported in Soria and colleagues (2018); here we provide the first report of TDTKI together with more detail on the other postprogression endpoints.

Statistical analysis

A log-rank test, stratified by race and mutation type, was used to compare treatment arms for each exploratory endpoint; the Breslow approach was used to handle tied events. Any patient alive and not known to have reached any of these exploratory endpoints, or to have died at time of analysis, was censored at their last RECIST assessment before or at disease progression. HRs and CIs were obtained directly from U and V statistics.

Results

Time to study treatment discontinuation

In total, 556 patients received at least 1 dose of study treatment: osimertinib, $n = 279$; SoC EGFR-TKI, $n = 277$ (3). Patient baseline characteristics have previously been reported, and were largely balanced across the 2 treatment arms (3). At data cutoff (June 12, 2017), 138 patients (49%) and 213 patients (77%) discontinued study treatment or died in the osimertinib and SoC EGFR-TKI arms, respectively (3). Reasons for study treatment discontinuation have previously been reported (3). Median time to discontinuation of study treatment was 20.8 months (95% CI, 17.2–24.1) in the osimertinib arm and 11.5 months (95% CI, 10.3–12.8) in the SoC EGFR-TKI arm (Fig. 1B). A similar proportion of patients remained on randomized treatment beyond investigator-assessed RECIST progression; 91 (67%) and 145 (70%) patients in the osimertinib and SoC EGFR-TKI arms, respectively (3). The median duration of study treatment beyond progression was 8.1 weeks (95% CI, 6.3–12.3) and 7.0 weeks (95% CI, 5.9–8.1) in the osimertinib and SoC EGFR-TKI arms, respectively (3).

Subsequent treatments

Of those patients who discontinued study treatment, 82 of 138 (59%) in the osimertinib arm and 129 of 213 (61%) in the SoC EGFR-TKI arm started a second-line therapy (3). The most common second-line therapies were platinum-based chemotherapy [46/82 (56%)] in the osimertinib arm, and osimertinib [55/129 (43%)] in the SoC EGFR-TKI (Fig. 2). Median time to second-line therapy was considerably longer in the osimertinib arm than the SoC EGFR-TKI arm; 23.5 months [95% CI, 22.0–not calculable (NC)] versus 13.8 months (95% CI, 12.3–15.7; HR, 0.51; 95% CI, 0.40–0.64; $P < 0.0001$; Fig. 1C; ref. 3). In the osimertinib and SoC EGFR-TKI arms, respectively, 128 (46%) and 167 (60%) patients discontinued any EGFR-TKI treatment or died. Median TDTKI was longer in the osimertinib arm than the SoC EGFR-TKI arm: 23.0 months (95% CI, 19.5–NC) versus 16.0 months (95% CI, 14.8–18.6; Fig. 1D). Time to third-line therapy, PFS and OS data are

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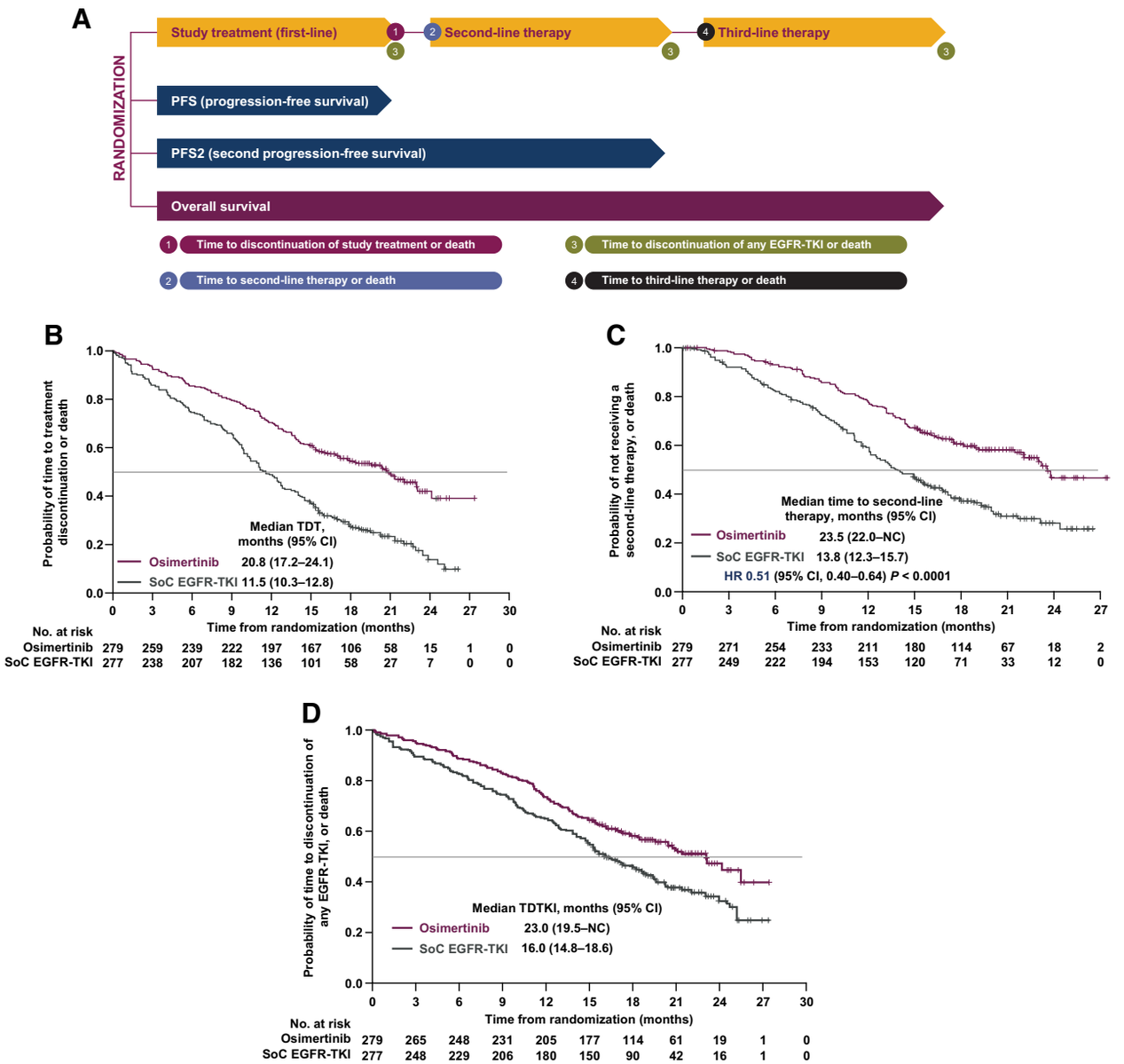

Figure 1.

A, Postprogression endpoints overview and Kaplan–Meier estimates of time to discontinuation of study treatment (TDT; **B**), time to second-line therapy (**C**), and time to discontinuation of any EGFR-TKI (**D**). Tick marks indicate censored data.

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NC, not calculable; SoC, standard-of-care; TDT, time to discontinuation of study treatment; TDTKI, time to discontinuation of any EGFR-TKI; TKI, tyrosine kinase inhibitor.

presented in Fig. 3, as reported by Soria and colleagues (2018; ref. 3).

Second PFS

At data cutoff, 73 patients (26%) and 106 (38%) in the osimertinib and SoC EGFR-TKI arms, respectively, had second-progression (i.e., second-progression) events, or died (3). Of all randomized patients, there were 48 (17%) and 65 (23%) deaths in the absence of second progression in the osimertinib and SoC EGFR-TKI arms, respectively. Median PFS2 was not reached (95% CI, 23.7–NC) in the osimertinib arm and was 20.0 months (95% CI, 18.2–NC) in the SoC EGFR-TKI arm (HR, 0.58; 95% CI, 0.44–0.78; $P = 0.0004$; ref. 3). Kaplan–Meier curves for PFS2 are shown in Fig. 4.

Discussion

The postprogression endpoints reported here demonstrate that the PFS benefit observed with osimertinib in the FLAURA study is preserved beyond first disease progression, providing

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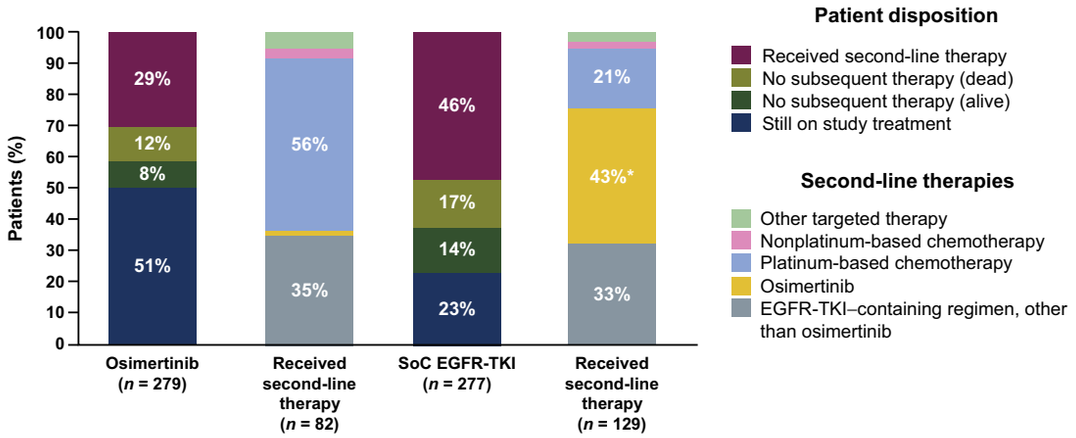

Figure 2.

Second-line therapies received by those patients who discontinued study treatment.

* 55 patients received osimertinib as second-line therapy in the SoC EGFR-TKI arm (48 were crossover patients and 7 received open-label osimertinib; all had a T790M-positive status by local assessment). Other targeted therapies include anti-PD-1/PD-L1–containing therapy, anti-VEGF therapy, protein kinase inhibitors, other therapeutic products, all other nontherapeutic products.

EGFR, epidermal growth factor receptor; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

confidence in the encouraging interim OS data (3). HRs for each postprogression endpoint all favored osimertinib (Fig. 3), supporting it as a first-line therapy for patients with EGFRm advanced NSCLC.

Among patients who received a second-line therapy after SoC EGFR-TKI, 43% had osimertinib; however, this may rise because 23% of patients in the SoC EGFR-TKI arm were still receiving study treatment at the time of analysis. Furthermore, some patients who may have received second-line osimertinib in clinical practice may not have crossed over due to this study's crossover criteria; for example, ineligibility for rebiopsy due to rapid disease progression and unavailability of plasma testing preventing determination of T790M status. Therefore, this proportion of patients is in-line with the estimated rate of patients acquiring T790M, as recently observed in a population-based multi-institutional study of patients with EGFR-mutated NSCLC (4). Notably, 39% of the 213 patients in the SoC EGFR-TKI arm who discontinued study treatment received no subsequent therapy, of whom 21% had died. In the osimertinib and SoC EGFR-TKI arms, 12% and 17% of all patients died before receiving a subsequent therapy; these proportions are slightly lower than those recently reported from Flatiron, a real world evidence study, where 22% of patients who received a first-line EGFR-TKI therapy died without receiving a subsequent treatment (5).

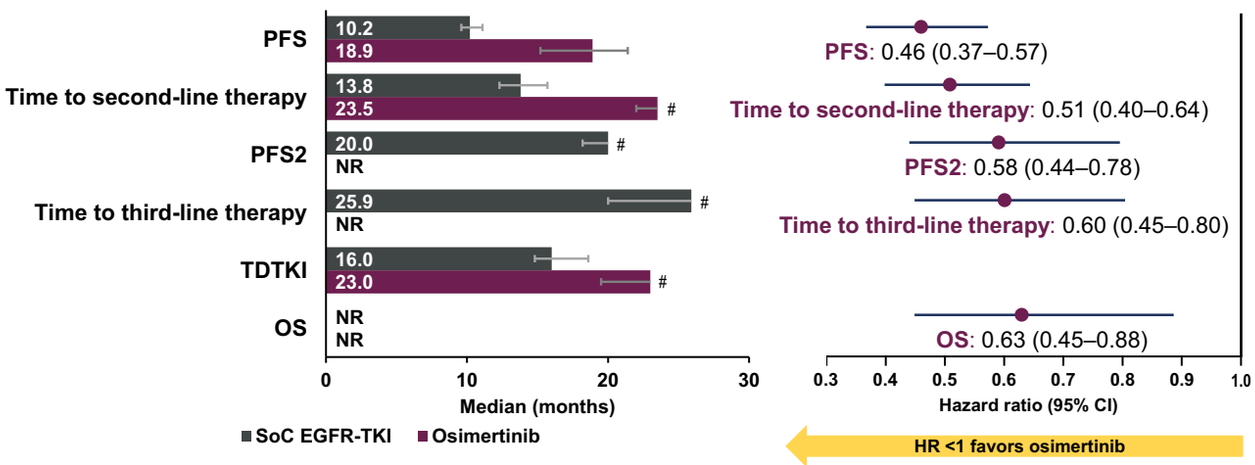

Figure 3.

Summary of the postprogression endpoint median values and HRs.

#, Upper confidence interval not calculable.

TDTKI does not have a HR as this analysis was not predefined for this postprogression endpoint.

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; SoC, standard-of-care; TKI, tyrosine kinase inhibitor.

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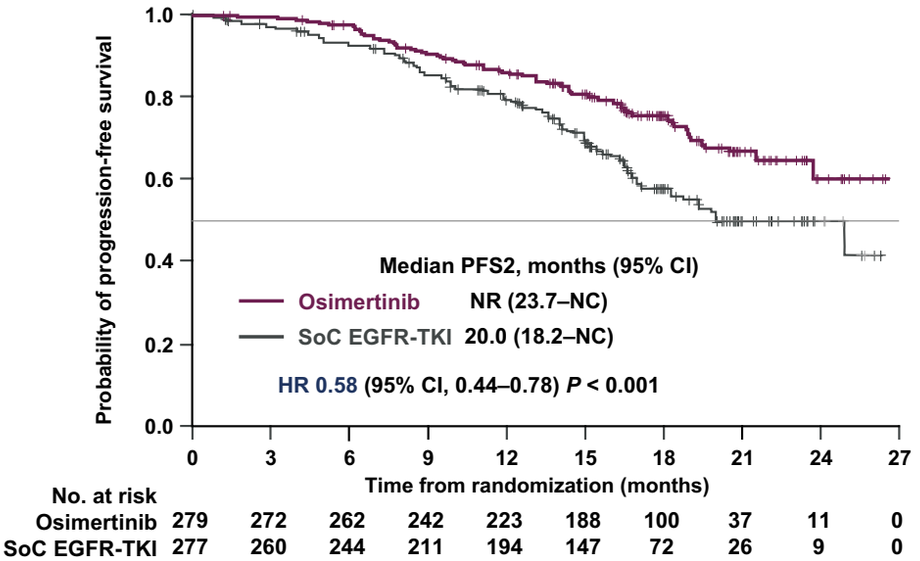

Figure 4.
Kaplan–Meier estimates of PFS2. Tick marks indicate censored data. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NC, not calculable; NR, not reached; PFS2, second progression-free survival; SoC, standard-of-care; TKI, tyrosine kinase inhibitor.

In the osimertinib and SoC arms, respectively, 35% and 33% received another EGFR-TKI–containing therapy as their second-line therapy. This unusual treatment sequence may have occurred because the crossover criteria prevented them receiving second-line osimertinib, and/or in the absence of aggressive or systemic progression or after an intervening therapy, such as chemotherapy or radiotherapy, an investigator may have judged that a patient could still benefit from another EGFR-TKI or prevent a disease flare. Alternatively, some patients who discontinued study treatment early due to an adverse event may have been offered an alternative EGFR-TKI, or refused or been too unhealthy for chemotherapy.

TDTKI was employed as a surrogate endpoint for time to chemotherapy, which was not statistically analyzed due to potential bias; that is, time to chemotherapy analysis would not have distinguished between patients eligible for therapy from those too unwell to receive chemotherapy, thus time to chemotherapy would appear longer for patients who delayed chemotherapy due to receiving other treatments (e.g., radiotherapy for other lesions), even though they were very unwell. TDTKI was longer for the osimertinib arm than the SoC EGFR-TKI arm, indicating that first-line osimertinib may delay initiation of chemotherapy for longer. This observation is particularly notable considering the most common second-line therapy in the osimertinib arm was platinum-based chemotherapy, which was not included in TDTKI, while in the SoC EGFR-TKI arm it was osimertinib, which would be included in the TDTKI, representing sequential EGFR-TKI therapies. Therefore, TDTKI was longer in the osimertinib arm despite fewer patients receiving 2 lines of EGFR-TKI therapy.

The European Medicines Agency recommends PFS2 as a surrogate endpoint for OS (2). PFS2 encompasses PFS on both the initial treatment and the second-line therapy and, therefore, indicates the impact of the first-line treatment on the efficacy of the subsequent therapy (6). The risk of PFS2 was reduced by 42% for patients in the osimertinib arm, relative to those in the SoC EGFR-TKI arm, of whom 43% received osimertinib as their second-line therapy. Median PFS2 with osimertinib was not reached at data cutoff, with a lower 95% CI of 23.7 months (vs. 20.0 months in the SoC EGFR-TKI arm). This shows osimertinib preserves clinical benefit beyond first progression, and that patients still benefited from subsequent therapies. These data, together with preliminary resistance mechanisms data from the FLAURA study showing evidence for heterogeneous mechanisms of acquired resistance with first-line osimertinib (7), suggest first-line osimertinib does not cause any biological changes and/or resistance to subsequent anticancer therapies that would lead to more aggressive disease or rapid disease progression. PFS2 subgroup analysis by second-line therapy for both treatment arms was not possible as this patient subgroup was not predefined. Further analysis of the molecular mechanisms of resistance to first-line osimertinib is ongoing in the FLAURA study; additionally, the ELIOS trial (NCT03239340) will assess the tumor genetic and proteomic markers at the point of disease progression in patients with EGFRm NSCLC who receive first-line osimertinib.

Conclusion

Clinically meaningful improvements with osimertinib versus SoC EGFR-TKI in each of the exploratory postprogression endpoints reported here advocate first-line use of osimertinib in patients with EGFRm-advanced NSCLC and provide further confidence in the encouraging interim OS data of the FLAURA study.

Disclosure of Potential Conflicts of Interest

D. Planchard is a consultant/advisory board member for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, MedImmune, Novartis, Pfizer, prIME Oncology, Peer CME, and Roche. M.J. Boyer reports receiving other commercial research support from AstraZeneca, Genentech/Roche, Boehringer Ingelheim, Pfizer, Amgen, Merck Sharpe & Dohme, and Bristol-Myers Squibb, and is a consultant/advisory board member for Merck Sharpe & Dohme, AstraZeneca, Bristol-Myers Squibb, and Genentech/Roche. P.K. Cheema is a consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Roche, Takeda, Genomic Health, and Pfizer. T. Takahashi reports receiving speakers' bureau honoraria from AstraZeneca KK, Chugai Pharmaceutical Co., Ltd., and Boehringer Ingelheim Japan, Inc. J.E. Gray reports receiving commercial research grants from AstraZeneca, Genentech, and Boehringer Ingelheim. M. Tiseo is a consultant/advisory board member for AstraZeneca. S. Ramalingam reports receiving commercial research grants from AstraZeneca, speakers' bureau

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Authors' Contributions

Conception and design: D. Planchard, S.S. Ramalingam, A. McKeown, Y. Rukazenkov

Development of methodology: D. Planchard, S.S. Ramalingam, A. McKeown

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Planchard, M.J. Boyer, J.-S. Lee, A. Dechaphunkul, P.K. Cheema, T. Takahashi, J.E. Gray, M. Tiseo, S.S. Ramalingam

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Planchard, J.E. Gray, S.S. Ramalingam, A. Todd, A. McKeown, Y. Rukazenkov

Writing, review, and/or revision of the manuscript: D. Planchard, M.J. Boyer, A. Dechaphunkul, P.K. Cheema, T. Takahashi, J.E. Gray, M. Tiseo, S.S. Ramalingam, A. Todd, A. McKeown, Y. Rukazenkov, Y. Ohe

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Todd, A. McKeown

Study supervision: D. Planchard, J.E. Gray, S.S. Ramalingam, Y. Rukazenkov, Y. Ohe

Other (reviewed statistical content and wording): A. Todd

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