Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC

Overall Survival with Osimertinib in Previously Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer

Suresh S. Ramalingam, M.D.,[1] Johan Vansteenkiste, M.D., Ph.D.,[2] David Planchard, M.D., Ph.D.,[3] Byoung Chul Cho, M.D., Ph.D.,[4] Jhanelle E. Gray, M.D.,[5] Yuichiro Ohe, M.D., Ph.D.,[6] Caicun Zhou, M.D., Ph.D.,[7] Thanyanan Reungwetwattana, M.D.,[8] Ying Cheng, M.D.,[9] Busyamas Chewaskulyong, M.D.,[10] Riyaz Shah, M.D.,[11] Manuel Cobo Dols, M.D.,[12] Ki Hyeong Lee, M.D., Ph.D.,[13] Parneet Cheema, M.D.,[14] Marcello Tiseo, M.D., Ph.D.,[15] Thomas John, M.D., Ph.D.,[16] Meng-Chih Lin, M.D.,[17] Fumio Imamura, M.D., Ph.D.,[18] Takayasu Kurata, M.D., Ph.D.,[19] Alexander Todd, M.Sc.,[20] Rachel Hodge, M.Sc.,[20] Matilde Saggese, M.D., M.D. (Res),[21] Yuri Rukazenkov, M.D., Ph.D.,[21] Jean-Charles Soria, M.D., Ph.D.[3,22,23]

Authors' affiliations:

1. Emory University School of Medicine, Winship Cancer Institute, Atlanta, USA
2. Respiratory Oncology Unit, Department of Respiratory Medicine, University Hospital KU Leuven, Leuven, Belgium
3. Gustave Roussy, Department of Medical Oncology, Thoracic Unit, Villejuif, France
4. Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea
5. Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
6. Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo
7. Pulmonary Hospital of Tongji University, Shanghai
8. Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
9. Jilin Provincial Cancer Hospital, Changchun, China
10. Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand

11. Kent Oncology Centre, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK
12. Hospital Regional Universitario Málaga, IBIMA, Málaga, Spain
13. Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, South Korea
14. William Osler Health System, University of Toronto, Toronto, ON, Canada
15. Department of Medicine and Surgery, University of Parma and Medical Oncology Unit, University Hospital of Parma, Parma, Italy
16. Department of Medical Oncology, Austin Health, Melbourne, Australia
17. Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan
18. Department of Thoracic Oncology, Osaka International Cancer Institute, Japan
19. Department of Thoracic Oncology, Kansai Medical University Hospital, Japan
20. Late Oncology Statistics, AstraZeneca, Cambridge, UK
21. Oncology R&D, AstraZeneca, Cambridge, UK
22. Early Oncology R&D, AstraZeneca, Gaithersburg, Maryland
23. University Paris Sud, Orsay, France

Corresponding author:

Suresh S. Ramalingam, Winship Cancer Institute of Emory University, 1365 Clifton Rd. NE, C-4014E, Atlanta, GA 30322, ssramal@emory.edu.

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Abstract (249/250 words)

Background:

Osimertinib is a third-generation, irreversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations. The Phase III FLAURA study investigated first-line osimertinib versus comparator EGFR-TKI in patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). Here we report the final overall survival analysis.

Methods:

We randomly assigned (1:1 ratio) patients with previously untreated, EGFR mutation-positive (Ex19del/L858R) advanced NSCLC to receive osimertinib (80 mg once daily [qd]) or comparator EGFR-TKI (gefitinib 250 mg qd/erlotinib 150 mg qd). Overall survival was a key secondary endpoint. Data cutoff: 25 June 2019.

Results:

Globally, 556 patients were randomized to osimertinib (n=279) or comparator EGFR-TKI (n=277). Osimertinib statistically significantly improved overall survival vs comparator EGFR-TKI (hazard ratio for death 0.799; 95.05% confidence interval [CI], 0.641 to 0.997; P=0.046). Median overall survival in the osimertinib and comparator EGFR-TKI arms were 38.6 months (95% CI, 34.5 to 41.8) and 31.8 months (95% CI, 26.6 to 36.0), respectively. At the 3-year time point, 28% of patients in the osimertinib arm and 9% of patients in the comparator arm remained on study drug. 85 patients (31%) received osimertinib as a second-line treatment. Median total treatment exposure times were 20.7 months and 11.5 months, respectively. Adverse events of grade 3 or higher were numerically lower in the osimertinib arm (42% vs 47%).

Conclusions:

Osimertinib improved overall survival in a clinically and statistically significant manner versus comparator EGFR-TKI in the first-line treatment of patients with EGFR-mutation positive advanced NSCLC.

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Introduction

For patients with advanced non–small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)–sensitizing mutations (Exon 19 deletions [Ex19del]/ exon 21 codon 858 [L858R] point mutations), current guidelines recommend treatment with an EGFR-TKI; per the National Comprehensive Cancer Network guidelines, osimertinib is the preferred EGFR-TKI in this setting.[1-4]

Osimertinib is a third-generation, irreversible, oral EGFR-TKI, that potently and selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations, and has demonstrated efficacy in NSCLC central nervous system (CNS) metastases.[5-9] The FLAURA trial (ClinicalTrials.gov: NCT02296125) was a double-blind phase 3 trial to assess the efficacy and safety of osimertinib in patients with previously untreated EGFR mutation–positive advanced NSCLC versus comparator EGFR-TKIs, gefitinib or erlotinib.[9] The primary analysis (data cutoff June 12, 2017) showed osimertinib produced a statistically significant improvement in progression-free survival versus comparator EGFR-TKIs (median 18.9 vs. 10.2 months; hazard ratio 0.46, P<0.001). At the time of the primary analysis, overall survival data were immature (data maturity, 25%), and did not reach formal statistical significance for osimertinib; however, there was a trend towards improved overall survival with osimertinib (hazard ratio for death, 0.63; P=0.007).[9] A nominally statistically significant benefit in CNS progression-free survival was also demonstrated with osimertinib in the FLAURA study, however, formal significance testing could not be completed due to the immature overall survival data not being statistically significant.[8] Both treatment arms had a similar overall safety profile, with a lower rate of Grade 3 or higher adverse events in the osimertinib arm.[9] Based on these efficacy and safety data, osimertinib received an extension of indication to include first-line treatment of patients with advanced NSCLC whose tumors have activating EGFR mutations.[10,11] Here, we report the pre-planned final overall survival analysis.

Methods

Trial patients

Full details of the FLAURA trial have been published previously and are provided in the protocol, available with the full text of this article at NEJM.org.[9] In brief, eligible patients were over 18 years old (≥20 years in Japan), had EGFR mutation–positive (Ex19del, L858R) locally advanced or metastatic NSCLC, had not previously received treatment for advanced disease, and were eligible to receive first-line treatment with gefitinib or erlotinib. Patients with known or suspected CNS metastases whose condition was neurologically stable were eligible.

Trial oversight

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 and human biologic samples of the trial sponsor, AstraZeneca. All patients provided written informed consent. This trial was funded by the sponsor and was designed by the principal investigators (first and last authors) and the sponsor. The sponsor was responsible for collection and analysis of data and had a role in data interpretation. The manuscript was written by the authors, with medical writing support funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. The authors vouch for the completeness and accuracy of the data and the data analyses and adherence to the protocol, and had full access to all data. The protocol and statistical analysis plan are available at NEJM.org.

Trial design and treatment

In this double-blind, phase 3 trial, patients were stratified according to tumor EGFR mutation status (Ex19del or L858R) and race (Asian or non- Asian) and were randomly assigned in a

1:1 ratio to receive either oral osimertinib (80 mg once daily) or a comparator oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients randomly assigned to comparator EGFR-TKI were eligible for crossover to open label-osimertinib following confirmed objective disease progression by blinded independent central review (or by investigator assessment if disease progression occurred after the primary data cutoff), and post-progression documentation of T790M-positive mutation status by local or central testing.

Trial endpoints

Overall survival was a key secondary endpoint. Per protocol, following the primary progression-free survival analysis (data cutoff June 12, 2017) progression events according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) were no longer centrally collected.

Trial assessments

Following the primary data cutoff, tumor assessments were performed in accordance with clinical practice and scans were no longer centrally collected. Assessments for survival were made every 6 weeks following objective disease progression up to the time of final overall survival analysis.

Overall survival was defined as time from randomization to death due to any cause. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Final overall survival analysis was planned when approximately 318 death events had occurred in the full analysis set. Overall survival was analyzed for pre-defined subgroups (Supplementary Appendix). Survival was estimated with Kaplan–Meier methodology with a

log-rank test, stratified according to race (Asian vs. non-Asian) and mutation type (Ex19del vs. L858R), used to compare overall survival between treatment arms; the Breslow approach was used to handle tied events. Data for patients with an unconfirmed survival status or confirmed status of alive were censored based on the last recorded date on which the patient was known to be alive.

Based on 318 death events, approximately 72% power would be obtained to demonstrate a hazard ratio <0.75 (improvement in overall survival from 25 to 33.3 months) with a two-sided 5% significance level. The Lan DeMets approach that approximates the O'Brien and Fleming spending function was used to maintain an overall 2-sided 5% type I error across the interim and final analysis of overall survival. The p-value observed at the interim overall survival analysis was not statistically significant. This did not preclude further planned testing of overall survival, and per the Lan DeMets approach, there was a significance level of 0.0495 (2-sided) remaining for the final overall survival analysis.

Per the planned hierarchic procedure used to adjust for multiplicity in testing, if statistical significance is achieved on the final overall survival analysis, the CNS progression-free survival analysis conducted at the time of the primary analysis could be formally tested for statistical significance.

The final overall survival analysis data cutoff was June 25, 2019.

Results

Patients and treatment

From December 2014 through March 2016, a total of 556 patients were randomly assigned to, and received at least one dose of, trial treatment (279 to osimertinib and 277 to a comparator EGFR-TKI). Baseline patient demographics were previously reported.[9] Patient disposition is presented in Figure S1 in the Supplementary Appendix. At the time of data cutoff, the median duration of treatment exposure was 20.7 months (range, 0.1–49.8) for patients receiving osimertinib and 11.5 months (range, 0.0–50.6) for those receiving

comparator EGFR-TKI therapy. In the osimertinib and comparator EGFR-TKI arms 61 (22%) and 13 (5%) patients were ongoing randomized study treatment at the time of data cutoff.

Efficacy

At the time of data cutoff, 321 (58%) death events had occurred, representing the planned number of events and maturity. All patients had the opportunity to have a follow-up of 43 months; the median follow-up for overall survival in the osimertinib and comparator EGFR-TKI arms were 35.8 months and 27.0 months, respectively.

There was a statistically significant improvement in overall survival in the osimertinib arm versus the comparator EGFR-TKI arm (hazard ratio for death 0.799; 95.05% CI, 0.641 to 0.996; P=0.046; Figure 1). The median overall survival was 38.6 months (95% CI, 34.5 to 41.8) in the osimertinib arm and 31.8 months (95% CI, 26.6 to 36.0) in the comparator EGFR-TKI arm. Survival rates, and the number of patients remaining on their first-line therapy (study drug), were consistently higher in the osimertinib arm than the comparator EGFR-TKI arm at 12, 24 and 36 months (Table 2). As a result of the multiple testing strategy, the CNS progression-free survival analysis previously published is now formally statistically significant.[8]

Overall survival benefit with osimertinib over comparator EGFR-TKIs was generally consistent across pre-defined subgroups, with some variation in the magnitude of benefit (Figure 2). Of note, numerical differences in the hazard ratios for overall survival between treatment arms were observed between Asian and non-Asian patients, and between those patients with the ex19del and L858R mutations; however, their confidence intervals were overlapping. Conducting a global interaction test for heterogeneity indicates a potential difference in magnitude of benefit for these 2 subgroups (quantitative test) with the direction of the benefit (qualitative test) consistently favoring osimertinib.

In total, 133 patients (48%) in the osimertinib arm and 180 patients (65%) in the comparator EGFR-TKI arm started a first subsequent anticancer therapy following discontinuation of

their randomized treatment. Of the patients in the comparator EGFR-TKI arm, 47% (85/180) received osimertinib as first subsequent therapy (Figure 3A), which is 31% (85/277) of all patients in the comparator EGFR-TKI arm. In the osimertinib and comparator EGFR-TKI arms, 72 patients (26%) and 92 patients (33%) received a second subsequent therapy, respectively (Figure 3B). Further data on subsequent therapies is reported in the Results section and Table S1 of the Supplementary Appendix. Osimertinib extended the time to first and second subsequent therapies or death versus the comparator EGFR-TKI arm (HR 0.48; 95% CI 0.39, 0.58; and HR 0.69; 95% CI 0.56, 0.84, respectively; Figure S2 in the Supplementary Appendix).

Safety

The safety profile of osimertinib in the present analysis was consistent with the safety profile in the primary analysis. Overall, 98% of patients in the osimertinib arm and comparator EGFR-TKI arm had at least one adverse event (Table 1). Adverse events possibly causally-related to study treatment are listed in Table S2 of the Supplementary Appendix. Adverse events of grade 3 or higher were reported in 42% of patients in the osimertinib arm and 47% of patients in the comparator EGFR-TKI arm (not significant; Table S3 of the Supplementary Appendix). Serious adverse events were reported in 27% of patients in each treatment arm (Table S4 of the Supplementary Appendix). Cardiac effects (changes in QT interval) of Grade 3 or higher were reported in 5 patients (2%) and 4 patients (1%) in the osimertinib and comparator EGFR-TKI arms, respectively. There were no new cases of interstitial lung disease reported since the primary data cut.

Fatal adverse events occurred in 9 patients (3%) in the osimertinib arm, none of which were considered possibly causally related to treatment. In the comparator EGFR-TKI arm, fatal events occurred in 10 patients (4%), two of which were considered possibly causally-related to treatment.

Dose interruptions, dose reductions and permanent discontinuation of treatment due to adverse events occurred in 120 (43%), 14 (5%), and 41 (15%) patients in the osimertinib arm and in 113 (41%), 10 (4%), and 50 (18%) patients in the comparator EGFR-TKI arm (Table S4 of the Supplementary Appendix).

Further details on safety are provided in the Results section of the Supplementary Appendix.

Discussion

FLAURA is the first global, randomized phase 3 trial to show a statistically significant and clinically meaningful improvement in the overall survival of one EGFR-TKI over another in untreated patients with EGFR mutation–positive advanced NSCLC. Both the primary and key secondary efficacy endpoints were met, with much of the progression-free survival benefit maintained through to overall survival.[9] With an opportunity for follow up of at least 43 months across both arms, median overall survival for the osimertinib arm was extended by 6.8 months relative to the comparator EGFR-TKI arm, with a 20% reduction in the risk of death, even in the presence of crossover from the comparator EGFR-TKI arm to osimertinib. Furthermore, three times as many patients were continuing on study treatment in the osimertinib arm at 36 months versus the comparator EGFR-TKI arm.

The overall survival benefit was generally consistent across the predefined subgroups. The magnitude of benefit was variable, with both the Asian and L858R EGFR mutation type subgroups showing hazard ratio point estimates of near 1.00. As a secondary endpoint, this study was not powered for a subgroups analysis of overall survival. Consequently, variability in overall survival across the subgroups is expected and should be interpreted with caution. The confidence intervals for these two subgroups were wide and overlapped with the non-Asian and ex19del EGFR mutation type subgroups, respectively, suggesting that it is unlikely there is a statistical difference between them. Progression-free survival is the most direct measure of treatment effect, and in the primary analysis there was a consistent progression-free survival benefit with osimertinib across all pre-defined subgroups.[9]

Previous clinical trials of first- and second-generation EGFR-TKIs have reported median overall survival results ranging from approximately 18 to 28 months.[12-17] The comparator EGFR-TKI arm in our study outperformed these previous analyses with a median overall survival of 31.8 months, which may be at least in part due to the significant crossover of patients from the comparator EGFR-TKI arm to osimertinib. Osimertinib is more efficacious in pretreated patients who acquire the T790M EGFR resistance mutation than other earlier-generation EGFR-TKIs;[6,18,19] therefore, crossover from the comparator EGFR-TKI arm to osimertinib in FLAURA likely contributed to the better than expected overall survival of the comparator EGFR-TKI arm. More recently, the ARCHER 1050 trial reported a median overall survival for gefitinib of 26.8 months and 34.1 months for dacomitinib; however, unlike the FLAURA trial, the ARCHER 1050 trial excluded patients with CNS metastases, which is associated with shorter survival.[20]

In the FLAURA study, patients with documentation of a T790M-positive mutation status following disease progression were eligible for crossover from the comparator EGFR-TKI arm to receive second-line osimertinib. Approximately 50% of patients on earlier generation EGFR-TKIs develop the EGFR T790M resistance mutation on disease progression,[21,22] thus creating a biologically driven limit to the number of patients eligible to receive osimertinib as a second-line therapy. In the real-world evidence setting, it has been reported that only 25% to 39% of patients who receive first- or second-generation EGFR-TKIs go on to receive osimertinib as a second-line therapy, in line with the 31% crossover rate observed in FLAURA.[23-25] Using osimertinib in the first-line setting would provide all patients with the opportunity to benefit from the improved efficacy, both systemically and within the CNS. Subsequent therapies received on each arm were consistent with expectations, based on the treatment guidelines for this patient population.[1,2] The majority of patients in the osimertinib arm received chemotherapy as their second-line treatment, while crossover to osimertinib was the most common second-line therapy in the comparator EGFR-TKI arm. The proportion of patients who received another EGFR-TKI containing regimen (other than osimertinib) was comparable across both treatment arms. Similar proportions of patients

received a second subsequent therapy in both treatment arms, and the type of therapies received were comparable. In both arms of the FLAURA study approximately 30% of those patients who had reached time to first subsequent therapy had died before receiving a second-line therapy, which is likely attributable to decline in overall patient condition that parallels disease progression. This proportion is comparable to results from prior studies conducted in EGFR mutated patients with TKI therapy.[23-25] This observation has been the basis for use of the most effective therapies in the first-line treatment for patients with advanced stage malignancies.

CNS metastases is a common complication in patients with EGFR mutation-positive NSCLC, occurring in up to 40% of patients over the course of their disease.[26] Per the protocol, as overall survival data are statistically significant, we are able to report that osimertinib has a statistically significant benefit versus comparator EGFR-TKI for CNS progression-free survival, as well as an overall survival benefit regardless of presence or absence of CNS metastases.

Understanding resistance mechanisms following first-line treatment and determining appropriate therapies based on molecular resistance profiles remain important considerations. Reassuringly, no unexpected resistance mechanisms have been observed with first-line osimertinib;[27] however, further research is ongoing (phase 2 ELIOS NCT03239340). Research to understand optimal treatment based on resistance patterns following progression on first-line osimertinib therapy is also ongoing (phase 2 ORCHARD, NCT03944772 and SAVANNAH, NCT03778229).

In our trial, osimertinib had a predictable and manageable tolerability profile consistent with the primary analysis and with previous studies, with regards to the number of events, and with no new signals identified.[6,28-30] Toxicities of Grade 3 or higher occurred at a lower rate with osimertinib compared with comparator EGFR-TKIs, and rates of dose reductions and interruptions were comparable between treatment arms, despite a near two-fold higher

duration of exposure in the osimertinib arm. Overall, osimertinib presented a favorable and consistent toxicity profile.

In conclusion, first-line treatment with osimertinib was associated with a statistically significant and clinically meaningful improvement in overall survival versus comparator EGFR-TKIs in patients with EGFR mutation–positive locally advanced or metastatic NSCLC, despite the crossover rate. Together with its favorable tolerability profile and established systemic and CNS efficacy, this further substantiates the role of osimertinib as the preferred first-line treatment option for EGFR mutation–positive advanced NSCLC.

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Tables

Table 1. Adverse Events*

Adverse Event	Osimertinib (N=279)						Comparator EGFR-TKI (N=277)						
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Ur
Diarrhea	167 (60)	119 (43)	41 (15)	7 (3)	0	0	162 (58)	118 (43)	35 (13)	7 (3)	0	1 (<1)	1
Rashes and acnes†	164 (59)	132 (47)	29 (10)	3 (1)	0	0	219 (79)	111 (40)	88 (32)	20 (7)	0	0	
Nail effects†	108 (39)	61 (22)	45 (16)	2 (1)	0	0	95 (34)	58 (21)	35 (13)	2 (1)	0	0	
Dry skin†	106 (38)	89 (32)	16 (6)	1 (<1)	0	0	102 (37)	78 (28)	21 (8)	3 (1)	0	0	
Paronychia	89 (32)	43 (15)	45 (16)	1 (<1)	0	0	84 (30)	48 (17)	34 (12)	2 (1)	0	0	
Stomatitis	82 (29)	66 (24)	14 (5)	1 (<1)	1 (<1)	0	60 (22)	51 (18)	8 (3)	1 (<1)	0	0	
Anorexia†	66 (24)	32 (11)	27 (10)	7 (3)	0	0	58 (21)	29 (10)	24 (9)	5 (2)	0	0	
Cough	60 (22)	42 (15)	18 (6)	0	0	0	50 (18)	33 (12)	17 (6)	0	0	0	
Nausea	55 (20)	37 (13)	18 (6)	0	0	0	55 (20)	31 (11)	23 (8)	0	0	0	1
Constipation	51 (18)	42 (15)	9 (3)	0	0	0	39 (14)	29 (10)	10 (4)	0	0	0	
Pruritus†	50 (18)	41 (15)	8 (3)	1 (<1)	0	0	47 (17)	33 (12)	14 (5)	0	0	0	

Renal†	50 (18)	32 (11)	13 (5)	3 (1)	1 (<1)	1 (<1)	32 (12)	24 (9)	7 (3)	1 (<1)	0	0	
Fatigue	45 (16)	25 (9)	17 (6)	3 (1)	0	0	35 (13)	23 (8)	10 (4)	2 (1)	0	0	
Anemia	44 (16)	22 (8)	15 (5)	7 (3)	0	0	27 (10)	19 (7)	5 (2)	3 (2)	0	0	
Dyspnoea	42 (15)	28 (10)	12 (4)	2 (1)	0	0	22 (8)	10 (4)	9 (3)	3 (1)	0	0	
Vomiting	41 (15)	32 (11)	9 (3)	0	0	0	32 (12)	24 (9)	4 (1)	4 (1)	0	0	
Headache	39 (14)	29 (10)	8 (3)	2 (1)	0	0	25 (9)	17 (6)	8 (3)	0	0	0	
Back pain	36 (13)	22 (8)	14 (5)	0	0	0	29 (10)	15 (5)	14 (5)	0	0	0	
Upper respiratory tract infection	36 (13)	20 (7)	16 (6)	0	0	0	23 (8)	12 (4)	11 (4)	0	0	0	
Cardiac effects (QT)†	36 (13)	16 (6)	15 (5)	5 (2)	0	0	15 (5)	8 (3)	3 (1)	4 (1)	0	0	
Pyrexia	32 (11)	28 (10)	4 (1)	0	0	0	12 (4)	9 (3)	2 (1)	1 (<1)	0	0	
Insomnia	31 (11)	23 (8)	8 (3)	0	0	0	21 (8)	12 (4)	9 (3)	0	0	0	
Nasopharyngitis	31 (11)	17 (6)	14 (5)	0	0	0	16 (6)	11 (4)	5 (2)	0	0	0	
Aspartate aminotransferase increased	28 (10)	19 (7)	7 (3)	2 (1)	0	0	69 (25)	39 (14)	18 (6)	12 (4)	0	0	
Musculoskeletal pain	28 (10)	19 (7)	9 (3)	0	0	0	14 (5)	8 (3)	6 (2)	0	0	0	

Alopecia	22 (8)	18 (6)	4 (1)	0	0	0	35 (13)	31 (11)	4 (1)	0	0	0	
Alanine aminotransferase increased	19 (7)	11 (4)	6 (2)	2 (1)	0	0	74 (27)	30 (11)	19 (7)	21 (8)	4 (1)	0	

*Listed are adverse events that were reported in at least 10% of the patients in either treatment arm. Safety analyses included all the patients who received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event.
†Grouped term

Table 2. Survival rates and proportion of patients remaining on first-line study treatment

		12 months	24 months	36 months
Survival rate, % (95% CI)	Osimertinib (n=279)	89 (85, 92)	74 (69, 79)	54 (48, 60)
	Comparator EGFR-TKI (n=277)	83 (77, 87)	59 (53, 65)	44 (38, 50)
Remaining on first-line study treatment, n (%)	Osimertinib (n=279)	195 (70)	117 (42)	78 (28)
	Comparator EGFR-TKI (n=277)	130 (47)	44 (16)	24 (9)

Figures

Figure 1. Overall Survival.

Shown is the Kaplan–Meier estimate of overall survival in the full analysis set.

Censored data are indicated by tick marks. Data for patients who had not died at the time of the analysis were censored based on the last recorded date on which the patient was known to be alive.

CI denotes confidence interval, EGFR-TKI epidermal growth factor receptor tyrosine kinase inhibitor, and NC could not be calculated.

Overall Survival in Full Analysis Set

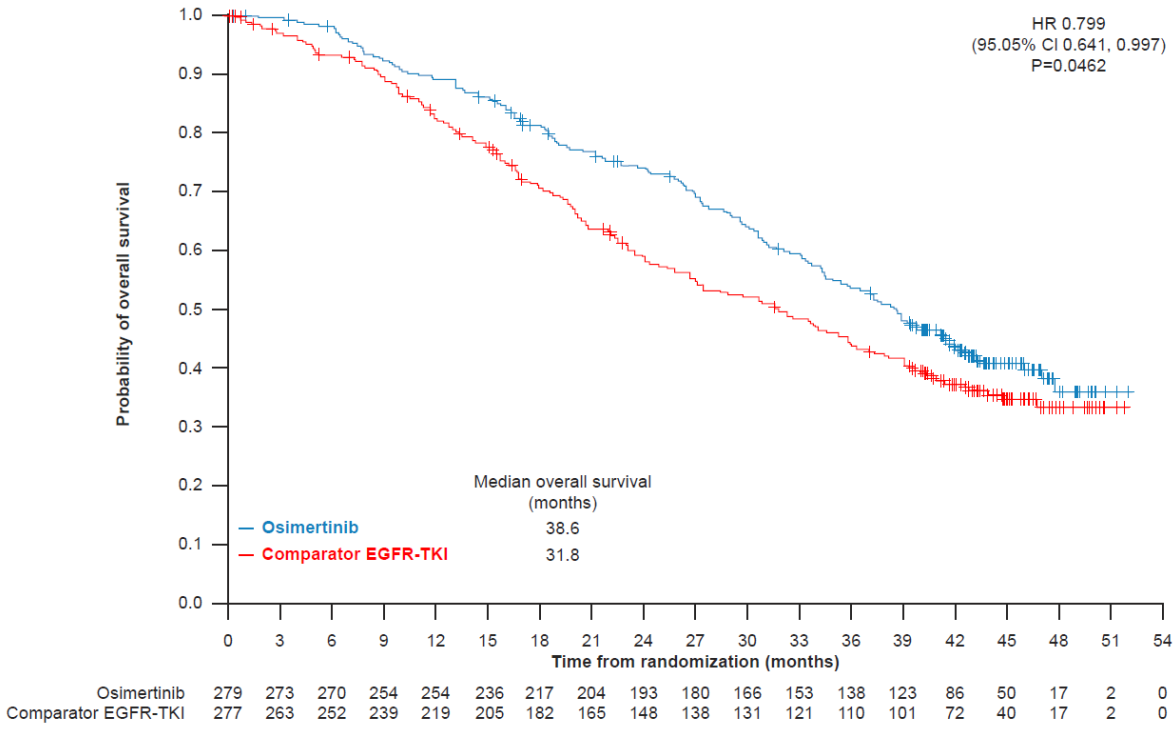


Figure 2. Subgroup analyses of overall survival. A hazard ratio of less than 1 implies a lower risk of death with osimertinib than with comparator EGFR-TKIs. The Cox proportional-hazards model includes randomly assigned treatment, the subgroup covariate of interest, and the treatment-by-subgroup interaction. The size of the circles is proportional to the number of events. Overall population analyses are presented from both a Cox proportional-hazards model and the primary analysis (U and V statistics from a log-rank test stratified according to EGFR mutation type and race). If there were fewer than 20 events in a subgroup, then the analysis was not performed. The shaded area indicates the 95% CI for the overall hazard ratio (all patients). EGFR mutation status at randomization was determined by a local or central test.

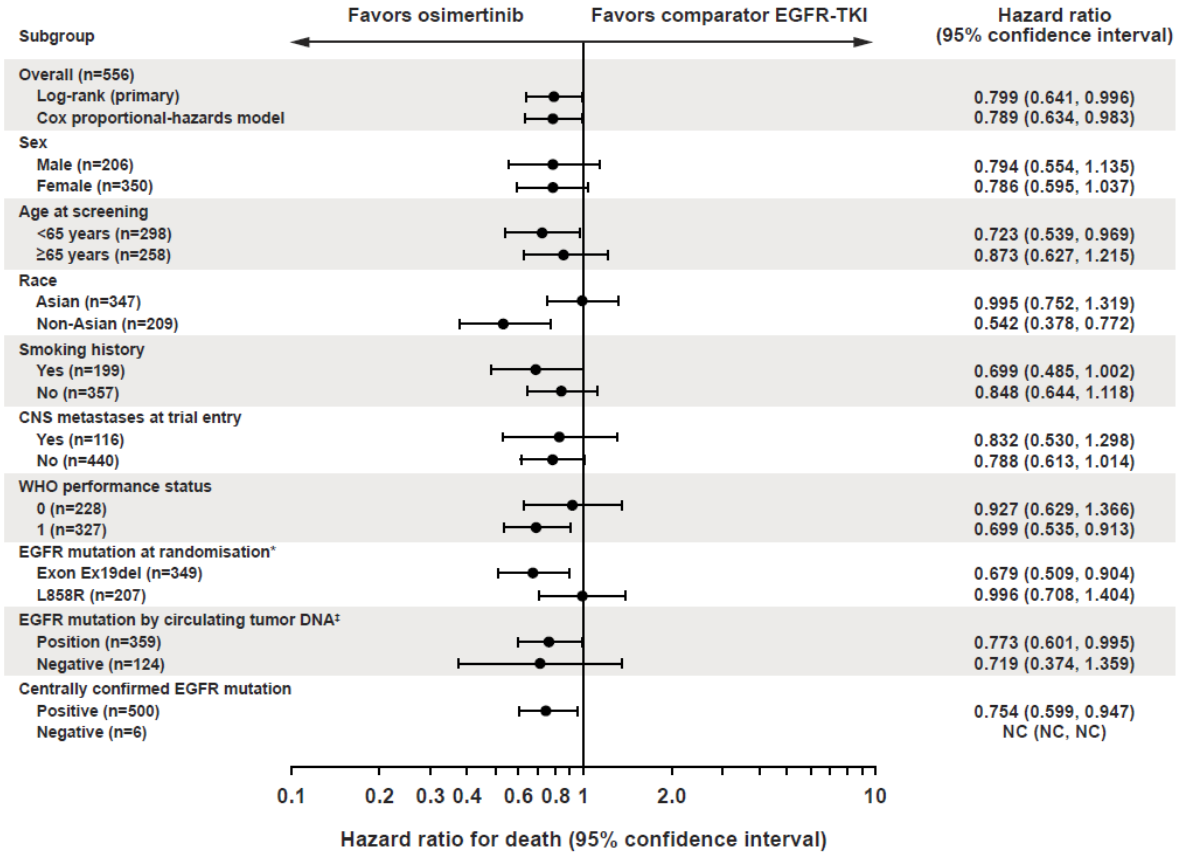
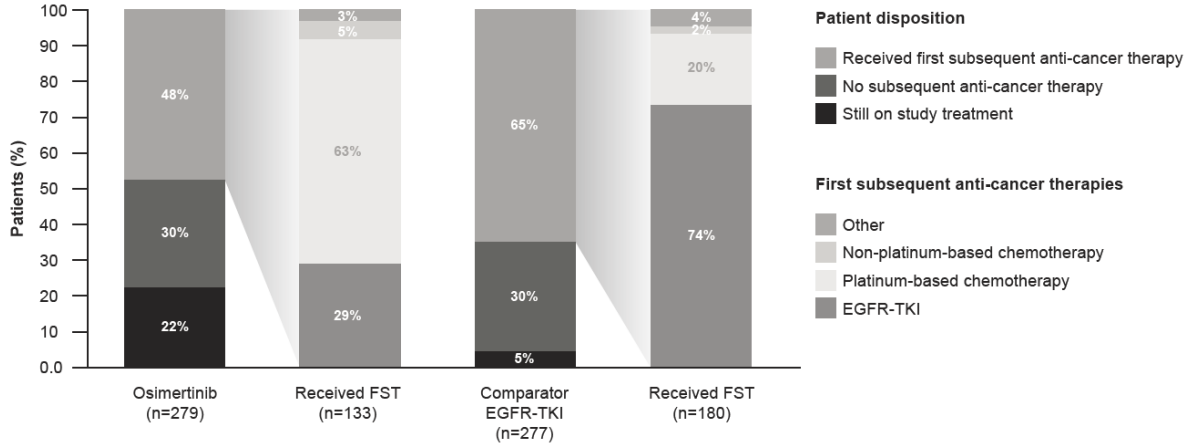


Figure 3. First subsequent therapies received



FST, first subsequent therapy.

<<Second subsequent therapy plot to be added>>

Overall Survival with Osimertinib in Previously Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer

SUPPLEMENTARY APPENDIX

This appendix is provided by the authors to give readers additional information about their work.

Supplement to: Ramalingam SS, Vansteenkiste J et al. Overall Survival with Osimertinib in Previously Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer

Contents

LIST OF FLAURA INVESTIGATORS

Australia: Michael Boyer, Chee Lee, Brett Hughes, Kenneth O'Byrne, Peter Briggs, Michael Milward, Thomas John

Belgium: Ingel Demedts, Johan Vansteenkiste, Frédérique Bustin

Brazil: Carlos Henrique Barrios

Bulgaria: Constanta Timcheva

Canada: Charles Butts, Glenwood Goss, Rosalyn Juergens, Natasha Leighl, Susanna Cheng, Ronald Burkes

China: Caicun Zhou, Helong Zhang, Yongqian Shu, Ying Cheng, Qing Zhou, Wei Li, Guosheng Feng, Yong He, Buhai Wang, Hongjun Gao, Kejun Nan, Xiangdong Zhou, Yun Fan, Jian an Hunag, Yi Hu, Yun-Peng Liu, Chunling Liu, Yiping Zhang, Bo Zhu

Czech Republic: Tomas Bartek

France: Isabelle Monnet, Claude El Kouri, Maurice Perol, Henri Berard, David Planchard, Jeannick Madelaine

Germany: Joachim von Pawel, Christian Grohe, Sabine Bohnet, Helge Bischoff, Christian Meyer zum Büschenfelde, Anja Rückert

Hungary: Lazlo Urban, Zsolt Papi-Szekely, Eszter Csánky, Csaba Böcskei, Sándor Tehenes

Israel: Maya Gottfried, Jair Bar, Nir Peled, Mirjana Wollner

Italy: Alessandro Bertolini, Antonio Ardizzoia, Caterina Accettura, Michele Mitella, Rodolfo Passalacqua, Silvia Novello, Fausto Roila, Marcello Tiseo

Japan: Akimasa Sekine, Fumio Imamura, Yuichiro Ohe, Naoyuki Nogami, Toshiaki Takahashi, Takayasu Kurata, Kazuo Kasahara, Isamu Okamoto, Kiyotaka Yoh, Shunichi Sugawara, Nobuaki Kobayashi, Tsuneo Shimokawa, Chiyuki Okuda, Tatsuo Fukuhara, Masafumi Sata, Kazuhiko Nagakawa, Shinji Atagi, Yoshiro Nakahara

Republic of Korea: Byoung Chul Cho, Jong-Seok Lee, Kye Young Lee, Sang Won Shin, Ki Hyeong Lee, Eun Kyung Cho, Jin-Hyoung Kang

Malaysia: Soon Hin How, Pei Jye Voon, Yong Kek Pang

Philippines: Jemela Anne Osorio-Sanchez, Guia Elena Imelda Ladrera

Poland: Piotr Serwatowski, Aleksandra Szczesna, Katarzyna Zajda, Rodryg Ramlau, Dariusz Sawka

Portugal: Maria Encarnação Teixeira, Teresa Almodovar, Marta Soares, Amélia Almeida, Ana Barroso

Romania: Michael Schenker, Alexandru Calin Girgorescu, Polixenia Iorga

Russian Federation: Sergey Orlov, Nina Karaseva, Vladimir Moiseenko

Spain: Rosario Garcia Campelo, Maria Dolores Isla Casado, Manuel Cobo Dols, Ernest Nadal, Marc Campayo Guillaumes, Jose Luis González Larriba, Margarita Majem Tarruella, Sergio Vázquez Estévez, José Fuentes Pradera¸ Diego Márquez Medina

Sweden: Anders Vikstrom

Switzerland: Oliver Gautschi, Christian Britschgi, Andreas Mueller

Taiwan: Ying-Huang Tsai, Ming-Fang Wu, Cheng-Ta Yang, Meng Chih Lin, Chao-Hsun Chen, Wu-Chou Su

Thailand: Busyamas Chewaskulong, Thanyanan Reungwetwattana, Vichien Srimuninnimit, Arunee Dechaphunkul, Sudsawat Laohavinij, Virote Sriuranpong

Turkey: Ramazan Yildiz

Ukraine: Igor Bondarenko, Ihor Vynnychenko, Hryhoriy Adamchuk, Yaroslav Shparyk

United Kingdom: Siow Ming Lee, Allan Price, Yvonne Summers, Riyaz Shah

Unites States of America: Konstantin Dragnev, Ajit Maniam, Steven McCune, Jimmy Ruiz, Suresh Ramalingam, Pasi Jänne, Trevor Feinstein, John Hamm, Ian Anderson, Farrah Khan, Ralph Boccia, Jhanelle Gray

Vietnam: Ngoc Tran, Nhung Nguyen

SUPPLEMENTARY METHODS

Study oversight

All authors signed a confidentiality agreement with the sponsor. An agreement was in place between the study sponsor and the authors, which established the authors' rights to publish the study and access the data. Responsibility for opinions, conclusion, and interpretation of the data lies with the authors.

Trial design and treatment

A protocol amendment on April 13, 2015, allowed patients randomly assigned to a standard EGFR-TKI to cross over to open-label osimertinib after confirmation of disease progression (during trial treatment or within 28 days of trial treatment cessation with no intervening therapy).

Statistical methods

Overall survival was analyzed using a log rank test stratified by race (Asian versus non-Asian) and mutation type (Ex19del versus L858R) for generation of the P-value and the Breslow approach was used for handling ties. The hazard ratio and confidence intervals were obtained directly from the U and V statistics (Berry, et al.,1991; Selke & Siegnumd, 1983).

The covariates in the statistical modelling were based on the values entered into the interactive voice recognition system at randomization, even if it subsequently discovered that these values were incorrect.

Overall survival was analyzed for pre-defined subgroups. Each subgroup required at least 20 overall survival events per subgroup level for the data to be included in the analysis. The analysis was performed using a Cox proportional hazards model, including treatment, subgroup, and a treatment-by-subgroup interaction term for each subgroup to provide the hazard ratio and 95% confidence interval this was then presented on a forest plot.

Global interaction test

A global interaction test was used to assess whether there is a consistent treatment effect across the predefined subgroups. This test was performed using the overall population. The fit of the Cox proportional hazards model, including treatment, covariates for race (Asian versus non-Asian) and mutation type (Ex19del versus L858R), and all covariate by treatment interaction terms, was compared with a model that excluded the interaction terms. This comparison was assessed at the 2-sided 10% significance level. If the Cox proportional hazards model was not significantly improved it would be concluded that the treatment effect is consistent across subgroups. If the global interaction test was statistically significant, a step-wise backwards selection would be performed on the saturated model to attempt to determine the cause and type of interaction. Throughout this process, all the main effects remain in the model regardless of whether the corresponding interaction term is present, with the least significant interactions excluded one-by-one. Any newly significant interactions are re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. This enables identification of the factors that potentially alter the treatment effect. Any quantitative interactions identified using this procedure are then tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail & Simon, 1985).

SUPPLEMENTARY RESULTS

Safety

The most commonly reported adverse events due to any cause (treatment-related or not) were diarrhea (60% in the osimertinib arm and 58% in the comparator EGFR-TKI arm), rashes and acnes (grouped term; 59% and 79%, respectively), and nail effects (grouped term; 39% and 28%, respectively) (Table 1). Adverse events that were considered by the investigator to be causally-related were reported by 91% and 92% of patients in the osimertinib and comparator EGFR-TKI arms, respectively (Table S2). Overall, serious adverse events were reported in 74 patients (27%) in the osimertinib arm and 76 patients (27%) in the comparator EGFR-TKI arm (Table S4).

Fatal adverse events occurred in 9 patients (3%) in the osimertinib arm, these included: pneumonia (n=2), sepsis (n=1), respiratory tract infection (n=1), cerebral infarction (n=1), cerebral ischemia (n=1), myocardial infarction (n=1), pulmonary embolism (n=1), intestinal ischemia (n=1), renal failure (n=1). In the comparator EGFR-TKI arm, fatal events occurred in 10 patients (4%): pneumonia (n=2), sepsis (n=2), cognitive disorder (n=1), endocarditis (n=1), pericarditis (n=1), circulatory collapse (n=1), peripheral artery occlusion (n=1), hemoptysis (n=1), respiratory failure (n=1), diarrhea (n=1), gastrointestinal hemorrhage (n=1), and unknown cause of death (n=1); two of these were considered possibly causally-related to treatment: pericarditis (n=1) and diarrhea (n=1).

Adverse events leading to permanent discontinuation, dose interruption or dose reduction

Permanent discontinuation attributed to adverse events occurred less frequently in the osimertinib arm compared with the comparator EGFR-TKI arm (41 patients [15%] and 50 patients [18%], respectively). The most common events leading to permanent discontinuation in the osimertinib arm were interstitial lung disease (n=6), pneumonitis (n=5) and QT prolongation (n=4), while in the comparator EGFR-TKI arm they were alanine and aspartate aminotransferase increases (n=12 and n=8, respectively). The frequency of dose

interruptions (29% in the osimertinib arm and 26% in the comparator EGFR-TKI arm) and dose reductions (4% for both treatment arms) due to adverse events were similar in the two arms. The most frequently experienced adverse events leading to dose interruptions in the osimertinib arm were diarrhea (n=9), decreased appetite (n=9), QT prolongation (n=8), and pneumonia (n=5); in the comparator EGFR-TKI arm they were increased alanine aminotransferase (n=18), increased aspartate aminotransferase (n=12), QT prolongation (n=6) and decreased appetite (n=6). Dose reductions were primarily driven by QT prolongation (5 patients) in the osimertinib arm and by skin disorders (10 patients), in the comparator EGFR-TKI arm.

Cardiac effects

Of those patients with a baseline and at least one follow-up LVEF assessment, LVEF decreased ≥10 percentage points to a value of <50% in 12 of 267 patients (4%) in the osimertinib arm and 4 of 271 patients (1%) in the standard EGFR-TKI arm.

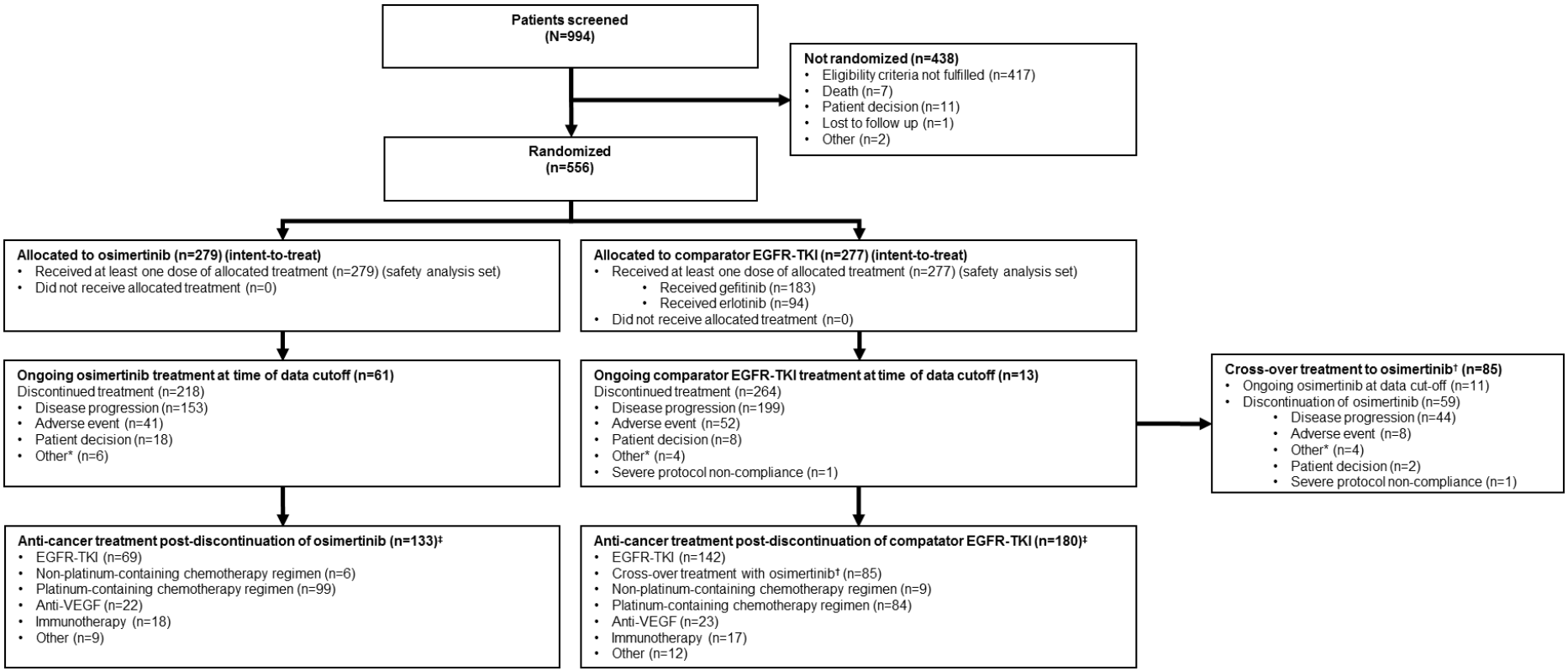
Cardiac effects (cardiac failure) were reported in 16 patients (6%) in the osimertinib arm and 6 patients (2%) in the comparator EGFR-TKI arm. Most adverse events in this category were ejection fraction decrease (14 of 16 patients in the osimertinib arm vs. 5 of 6 patients in the comparator EGFR-TKI arm), with no symptoms reported. This led to dose interruptions in 2 patients (1%) in the osimertinib arm and 2 patients (1%) in the comparator EGFR-TKI arm. There were no reports of dose reduction in the osimertinib arm and 1 report (<1%) in the comparator EGFR-TKI arm. One patient in the osimertinib arm discontinued study treatment after 2 cycles of treatment due to exacerbation of chronic heart failure and QT prolongation event; this patient had a medical history of hypertension, chronic heart failure, valvular heart disease, cerebral infarction, hyperlipidemia and atrial fibrillation. Two patients in the osimertinib arm discontinued treatment due to adverse events of myocardial infarction, one was considered unelated to treatment and the second was an acute case and was considered not to be cardiac failure-related. In the comparator EGFR-TKI arm there was one report of treatment discontinuation due to ejection fraction decrease (to 51%, which was

down from 80% at baseline; no symptoms reported), and one patient had grade 2 event of pericardial effusion reported. Of those patients who crossed over to osimertinib there was one patient who discontinued treatment due to heart failure.

Cardiac effects (QT) adverse events were reported in 49 patients (%) in the osimertinib arm and 18 patients (%) in the comparator arm. Electrocardiogram QT prolongation made up the majority of adverse events in the cardiac effects (QT) category (osimertinib arm: 40 patients [14%]; comparator EGFR-TKI arm: 14 patients [5%]). One report of cardiac arrhythmia was reported in each arm. One patient had a dose interruption due to QT prolongation in the osimertinib arm, and there were no dose reductions. In the comparator EGFR-TKI arm, no dose interruptions or reductions due to cardiac effects (QT) were reported. Three patients (1%) in the osimertinib arm discontinued treatment due to an adverse event of electrocardiogram QT prolongation. Two of these patients had no reported symptoms and their event was grade 2; another patient had a history of hypertension and diabetes mellitus type 2 and had a QTcF of 486 at time of discontinuation. One patient (<1%) in the comparator EGFR-TKI arm and one patient (1%) who crossed over to osimertinib both discontinued due to a QT prolongation event of grade 1, but had no reported symptoms. In addition, one patient (<1%) in the osimertinib arm discontinued due to an adverse event of tachyarrhythmia, considered unrelated to study drug; this patient also had grade 3 asthenia. One patient (<1%) in the osimertinib arm discontinued due to a grade 2 adverse event of conduction disorder (ejection fraction 65%).

SUPPLEMENTARY FIGURES

Figure S1. Patient disposition

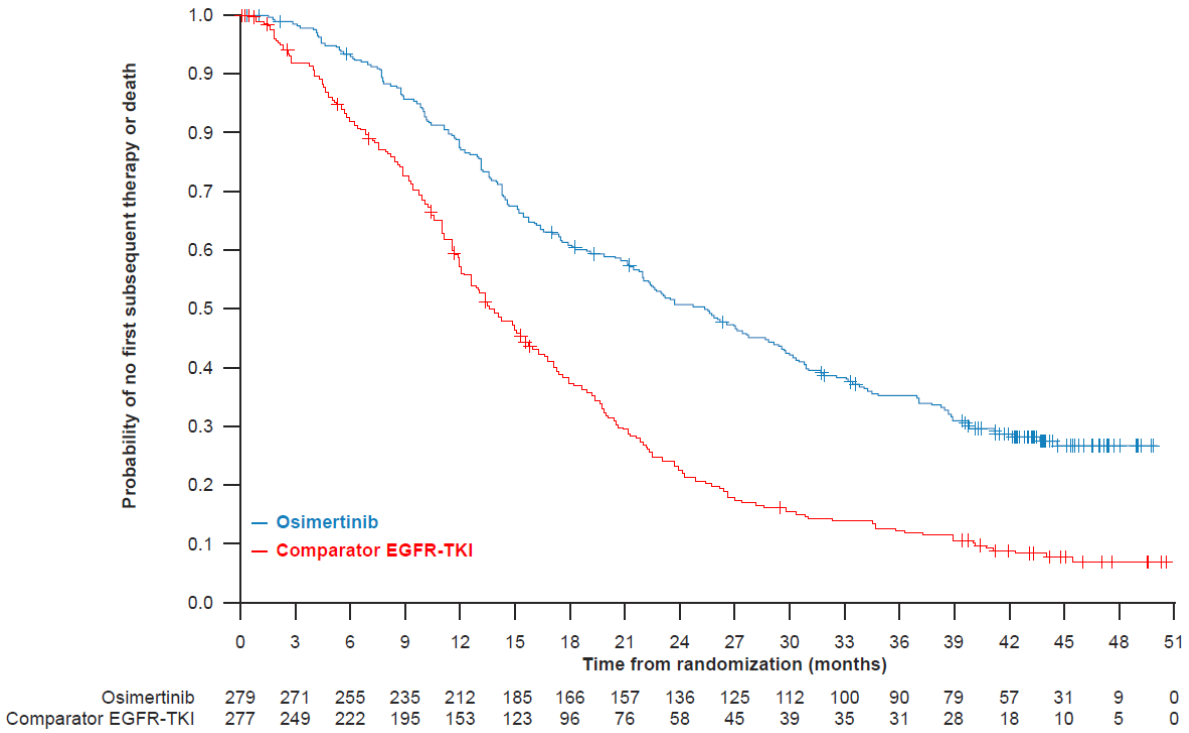


*Any reason not specifically recorded; for example, subject died.
†Crossover patients are patients that crossed over and received at least one dose of open-label osimertinib.
‡Post-treatment anti-cancer therapies are those with a start date on or after the last dose date of randomized study treatment. Patients with no subsequent anti-cancer therapy have discontinued randomized study treatment without starting any other subsequent anti-cancer therapy. Patients may be counted in multiple rows if they received more than one anti-cancer therapy or a combination therapy which contains drug substances from multiple classifications.

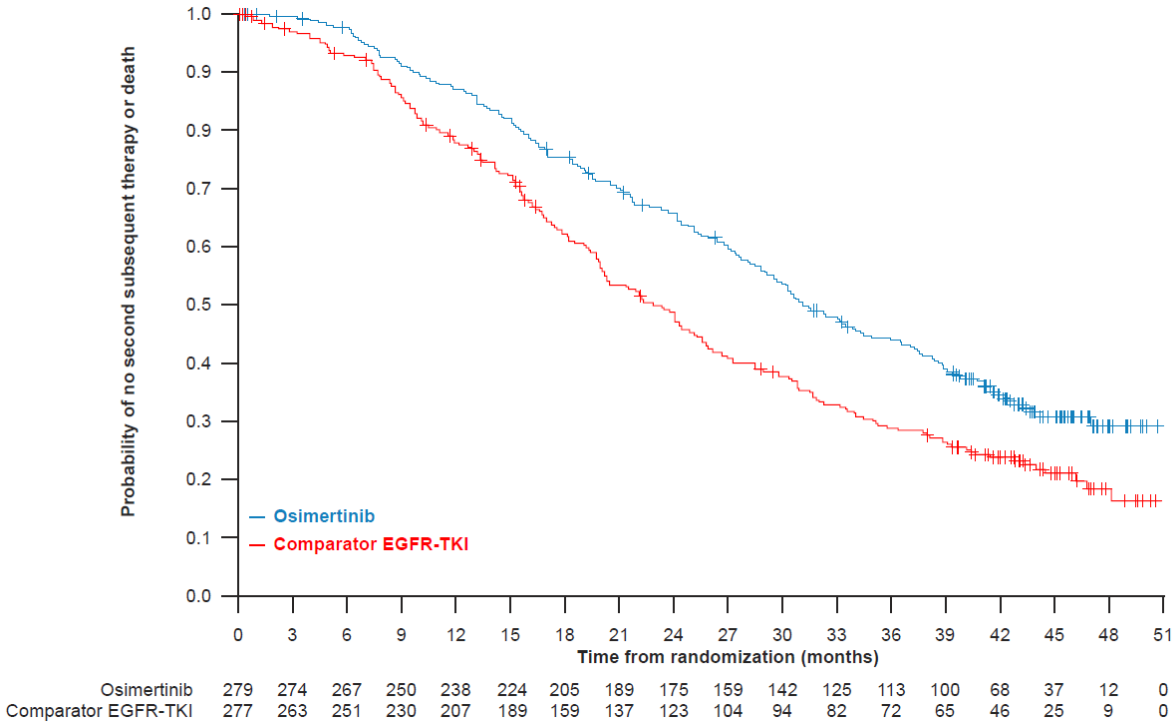
Figure S2. Kaplan-Meier estimates of time to first subsequent therapy (A) and second subsequent therapy (B).

Censored data are indicated by tick marks. Data for patients who had not died at the time of the analysis were censored based on the last recorded date on which the patient was known to be alive.

A.



B.


Probability of no second subsequent therapy or death
1.0
0.9
0.9
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Comparator EGFR-TKI
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time from randomization (months)
Osimertinib 279 274 267 250 238 224 205 189 175 159 142 125 113 100 68 37 12 0
Comparator EGFR-TKI 277 263 251 230 207 189 159 137 123 104 94 82 72 65 46 25 9 0

SUPPLEMENTARY TABLES

Table S1. First and second subsequent therapies*

Subsequent therapy, n (%)	Osimertinib	Comparator EGFR-TKI
First subsequent therapies		
Cytotoxic chemotherapy	90 (32)	39 (14)
Platinum-containing chemotherapy	84 (30)	36 (13)
EGFR-TKI†	38 (14)	49 (18)
Osimertinib	1 (<1)	85 (31)
Immunotherapy	4 (1)	4 (1)
VEGF inhibitor	10 (4)	4 (1)
Other	4 (1)	5 (2)
Second subsequent therapies		
Cytotoxic chemotherapy	38 (14)	56 (20)
Platinum-containing chemotherapy	15 (5)	42 (15)
EGFR-TKI	25 (9)	23 (8)
Immunotherapy	6 (2)	5 (2)
VEGF inhibitor	11 (4)	11 (4)
Other	2 (1)	7 (3)

EGFR, epidermal growth factor receptor; PD1, programmed cell death; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

*The first post-treatment anticancer therapy was the first treatment started on or after the last dose date of randomized trial treatment. The second post-treatment anticancer therapy was the second treatment started on or after the last dose date of randomized trial treatment. Patients with no post-treatment anticancer therapy had discontinued randomized trial treatment without starting any other post-treatment anticancer therapy. Patients may be counted in multiple rows if they received more than one anticancer therapy or a combination therapy that contained drug substances from multiple classifications.

†Excluding osimertinib

Table S2. Adverse events possibly causally-related to study treatment (investigator assessed) reported in at least 10% of the patients treated in either treatment arm

Adverse event, n (%)	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Diarrhea	140 (50)	144 (52)
Paronychia	84 (30)	77 (28)
Dry skin	86 (31)	86 (31)
Stomatitis	70 (25)	48 (17)
Dermatitis acneiform	69 (25)	132 (48)
Pruritus	44 (16)	38 (14)
Decreased appetite	36 (13)	35 (13)
Rash maculo-papular	34 (12)	44 (16)
Aspartate aminotransferase increased	23 (8)	58 (21)
Alanine aminotransferase increased	17 (6)	62 (22)

Table S3. Adverse events of grade 3 or higher by preferred term

Adverse event, n (%)	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Hyponatraemia	9 (3)	4 (1)
Pruritus*	9 (3)	0
Diarrhea	7 (3)	8 (3)
Pneumonia	8 (3)	7 (3)
Decreased appetite	7 (3)	5 (2)
Anemia	7 (3)	3 (1)
Cardiac effects (QT)*	5 (2)	4 (1)
Renal*	5 (2)	1 (<1)
Neutrophil count decreased	5 (2)	1 (<1)
Sepsis	4 (1)	2 (1)
Pulmonary embolism	4 (1)	1 (<1)
Gamma-glutamyltransferase increased	4 (1)	0
Lymphocyte count decreased	4 (1)	0
Rashes and acnes*	3 (1)	20 (7)
Interstitial lung disease	3 (1)	3 (1)
Hypokalemia	3 (1)	3 (1)
Fatigue	3 (1)	2 (1)
Hypertension	3 (1)	1 (<1)
Cataract disorder	3 (1)	1 (<1)
Weight decreased	3 (1)	0
Aspartate aminotransferase increased	2 (1)	12 (4)

Alanine aminotransferase increased	2 (1)	25 (9)
Dyspnoea	2 (1)	3 (1)
Nail effects*	2 (1)	2 (1)
Asthenia	2 (1)	2 (1)
Stomatitis	2 (1)	1 (<1)
Abdominal pain	2 (1)	0
Platelet count decreased	2 (1)	1 (<1)
Urinary tract infection	2 (1)	0
Headache	2 (1)	0
Embolism	2 (1)	0
Urticaria	2 (1)	0
White blood cell count decreased	2 (1)	0
Hemoptysis	1 (<1)	4 (1)
Dry skin*	1 (<1)	3 (1)
Abnormal hepatic function	1 (<1)	3 (1)
Pneumothorax	1 (<1)	2 (1)
Paronychia	1 (<1)	2 (1)
Gastroenteritis	1 (<1)	1 (<1)
Urinary tract infection bacterial	1 (<1)	1 (<1)
Brain edema	1 (<1)	1 (<1)
Cerebral infarction	1 (<1)	1 (<1)
Cognitive disorder	1 (<1)	1 (<1)
Deep vein thrombosis	1 (<1)	1 (<1)

Pleural effusion	1 (<1)	1 (<1)
Procedural pneumothorax	1 (<1)	1 (<1)
Cerebral ischemia	1 (<1)	0
Clostridial infection	1 (<1)	0
Clostridium difficile colitis	1 (<1)	0
Lower respiratory tract infection	1 (<1)	0
Pneumonia mycoplasmal	1 (<1)	0
Pneumonia pseudomonal	1 (<1)	0
Post-procedural infection	1 (<1)	0
Respiratory syncytial virus bronchitis	1 (<1)	0
Respiratory tract infection	1 (<1)	0
Skin infection	1 (<1)	0
Tracheobronchitis	1 (<1)	0
Urethritis	1 (<1)	0
Bladder cancer	1 (<1)	0
Desmoid cancer	1 (<1)	0
Endometrial cancer	1 (<1)	0
Histiocytic necrotizing lymphadenitis	1 (<1)	0
Invasive ductal breast carcinoma	1 (<1)	0
Iron deficiency anemia	1 (<1)	0
Lymphopenia	1 (<1)	0
Neutropenia	1 (<1)	0
Pancytopenia	1 (<1)	0

Inappropriate antidiuretic hormone secretion	1 (<1)	0
Dehydration	1 (<1)	0
Diabetic ketoacidosis	1 (<1)	0
Hyperamylasemia	1 (<1)	0
Hyperkalemia	1 (<1)	0
Hypermagnesemia	1 (<1)	0
Hypochloremia	1 (<1)	0
Type 2 diabetes mellitus	1 (<1)	0
Acute psychosis	1 (<1)	0
Anxiety	1 (<1)	0
Depression	1 (<1)	0
Depressed level of consciousness	1 (<1)	0
Hemorrhagic stroke	1 (<1)	0
Presyncope	1 (<1)	0
Syncope	1 (<1)	0
Transient ischemic attack	1 (<1)	0
Retinal detachment	1 (<1)	0
Vertigo positional	1 (<1)	0
Acute myocardial infarction	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Cardiac arrest	1 (<1)	0
Cardiac failure chronic	1 (<1)	0
Myocardial infarction	1 (<1)	0

Superior vena cava occlusion	1 (<1)	0
Thrombophlebitis	1 (<1)	0
Venous thrombosis	1 (<1)	0
Hypoxia	1 (<1)	0
Abdominal pain upper	1 (<1)	0
Dysphagia	1 (<1)	0
Haemorrhoidal hemorrhage	1 (<1)	0
Intestinal ischemia	1 (<1)	0
Lower gastrointestinal hemorrhage	1 (<1)	0
Pancreatitis	1 (<1)	0
Hepatitis	1 (<1)	0
Skin toxicity	1 (<1)	0
Benign prostatic hyperplasia	1 (<1)	0
General physical health deterioration	1 (<1)	0
Transaminases increased	1 (<1)	0
Fall	1 (<1)	0
Head injury	1 (<1)	0
Procedural pain	1 (<1)	0
Subdural haematoma	1 (<1)	0
Vomiting	0	4 (1)
Drug-induced liver injury	0	3 (1)
Blood alkaline phosphatase increased	0	3 (1)
Hypoalbuminemia	0	2 (1)

Hyperglycemia	0	2 (1)
Cystitis	0	2 (1)
Respiratory failure	0	2 (1)
Mouth ulceration	0	2 (1)
Pathological fracture	0	2 (1)
Sinusitis	0	1 (<1)
Hypocalcemia	0	1 (<1)
Device-related infection	0	1 (<1)
Rectal abscess	0	1 (<1)
Lower respiratory tract infection viral	0	1 (<1)
Perineal abscess	0	1 (<1)
Pharyngotonsillitis	0	1 (<1)
Endocarditis	0	1 (<1)
Clostridium difficile infection	0	1 (<1)
Bronchitis	0	1 (<1)
Bacteremia	0	1 (<1)
Anal abscess	0	1 (<1)
Endometrial adenocarcinoma	0	1 (<1)
Ovarian fibroma	0	1 (<1)
Prostate cancer	0	1 (<1)
Uterine leiomyoma	0	1 (<1)
Hypothyroidism	0	1 (<1)
Hypoglycemia	0	1 (<1)

Hypophosphatemia	0	1 (<1)
Restlessness	0	1 (<1)
Cerebrovascular accident	0	1 (<1)
Epilepsy	0	1 (<1)
Migraine	0	1 (<1)
Parkinsonism	0	1 (<1)
Peripheral motor neuropathy	0	1 (<1)
Seizure	0	1 (<1)
Somnolence	0	1 (<1)
Spinal cord compression	0	1 (<1)
Subarachnoid hemorrhage	0	1 (<1)
Blepharitis	0	1 (<1)
Vitreous detachment	0	1 (<1)
Vertigo	0	1 (<1)
Angina pectoris	0	1 (<1)
Bundle branch block left	0	1 (<1)
Pericardial effusion	0	1 (<1)
Pericarditis	0	1 (<1)
Ventricular extrasystoles	0	1 (<1)
Aortic dissection	0	1 (<1)
Circulatory collapse	0	1 (<1)
Peripheral artery occlusion	0	1 (<1)
Systolic hypertension	0	1 (<1)

Asthma	0	1 (<1)
Pneumonia aspiration	0	1 (<1)
Pneumonitis	0	1 (<1)
Pulmonary hemorrhage	0	1 (<1)
Gastrointestinal hemorrhage	0	1 (<1)
Melena	0	1 (<1)
Esophagitis	0	1 (<1)
Hepatic failure	0	1 (<1)
Skin irritation	0	1 (<1)
Toxic epidermal necrolysis	0	1 (<1)
Erythema nodosum	0	1 (<1)
Musculoskeletal chest pain	0	1 (<1)
Uterine polyp	0	1 (<1)
Condition aggravated	0	1 (<1)
Death	0	1 (<1)
Drug withdrawal syndrome	0	1 (<1)
Necrosis	0	1 (<1)
Pyrexia	0	1 (<1)
Blood bilirubin increased	0	1 (<1)
Protein urine present	0	1 (<1)
Femoral neck fracture	0	1 (<1)

*Grouped term.

Table S4. Serious adverse events by preferred term

Adverse event, n (%)	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Pneumonia	9 (3)	7 (3)
Interstitial lung disease	4 (1)	3 (1)
Pleural effusion	4 (1)	3 (1)
Hyponatremia	4 (1)	1 (<1)
Pulmonary embolism	4 (1)	1 (<1)
Diarrhea	3 (1)	4 (1)
Sepsis	3 (1)	3 (1)
Pyrexia	3 (1)	2 (1)
Asthenia	2 (1)	2 (1)
Decreased appetite	2 (1)	2 (1)
Dyspnoea	2 (1)	2 (1)
Pneumothorax	2 (1)	2 (1)
Gastroenteritis	2 (1)	1 (<1)
Pneumonitis	2 (1)	1 (<1)
Abdominal pain	2 (1)	0
Enterocolitis	2 (1)	0
Acute kidney injury	2 (1)	0
Deep vein thrombosis	2 (1)	0
Vomiting	1 (<1)	5 (2)
Alanine aminotransferase increased	1 (<1)	2 (1)
Injury by fall	1 (<1)	2 (1)

Angina pectoris	1 (<1)	1 (<1)
Aspartate aminotransferase increased	1 (<1)	1 (<1)
Brain edema	1 (<1)	1 (<1)
Cerebral infarction	1 (<1)	1 (<1)
Clostridial difficile infection	1 (<1)	1 (<1)
Cognitive disorder	1 (<1)	1 (<1)
Confusional state	1 (<1)	1 (<1)
Fatigue	1 (<1)	1 (<1)
Platelet count decreased	1 (<1)	1 (<1)
Procedural pneumothorax	1 (<1)	1 (<1)
Abdominal pain upper	1 (<1)	0
Acute myocardial infarction	1 (<1)	0
Acute psychosis	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Back pain	1 (<1)	0
Benign prostatic hyperplasia	1 (<1)	0
Bladder cancer	1 (<1)	0
Cardiac arrest	1 (<1)	0
Cardiac failure chronic	1 (<1)	0
Cardiac tamponade	1 (<1)	0
Cerebral ischemia	1 (<1)	0
Clostridial infection	1 (<1)	0
Dehydration	1 (<1)	0

Depressed level of consciousness	1 (<1)	0
Desmoid tumor	1 (<1)	0
Diabetic ketoacidosis	1 (<1)	0
Electrocardiogram QT prolonged	1 (<1)	0
Embolism	1 (<1)	0
Empyema	1 (<1)	0
Enteritis infectious	1 (<1)	0
Femur fracture	1 (<1)	0
Gastritis erosive	1 (<1)	0
Head injury	1 (<1)	0
Hemorrhagic stroke	1 (<1)	0
Hemorrhoidal hemorrhage	1 (<1)	0
Hepatic function abnormal	1 (<1)	0
Histiocytic necrotizing lymphadenitis	1 (<1)	0
Hypoxia	1 (<1)	0
Inappropriate antidiuretic hormone secretion	1 (<1)	0
Inguinal hernia	1 (<1)	0
Intestinal ischemia	1 (<1)	0
Invasive ductal breast carcinoma	1 (<1)	0
Lower gastrointestinal hemorrhage	1 (<1)	0
Lower respiratory tract infection	1 (<1)	0
Myocardial infarction	1 (<1)	0
Neck pain	1 (<1)	0

Pancreatitis	1 (<1)	0
Pancytopenia	1 (<1)	0
Pneumonia mycoplasmal	1 (<1)	0
Pneumonia pseudomal	1 (<1)	0
Pneumonia viral	1 (<1)	0
Post procedural infection	1 (<1)	0
Renal failure	1 (<1)	0
Respiratory syncytial virus bronchitis	1 (<1)	0
Respiratory tract infection	1 (<1)	0
Rotator cuff syndrome	1 (<1)	0
Spinal cord compression	1 (<1)	0
Stomatitis	1 (<1)	0
Subdural hematoma	1 (<1)	0
Tachyarrhythmia	1 (<1)	0
Thrombophlebitis	1 (<1)	0
Tonsillolith	1 (<1)	0
Tracheobronchitis	1 (<1)	0
Transaminases increased	1 (<1)	0
Transient ischemic attack	1 (<1)	0
Urinary tract infection	1 (<1)	0
Venous thrombosis	1 (<1)	0
Wound complication	1 (<1)	0
Wrist fracture	1 (<1)	0

Hemoptysis	0	4 (1)
Drug-induced liver injury	0	3 (1)
Cystitis	0	2 (1)
Dermatitis acneiform	0	2 (1)
Mouth ulceration	0	2 (1)
Respiratory failure	0	2 (1)
Anemia	0	1 (<1)
Anal abscess	0	1 (<1)
Aortic dissection	0	1 (<1)
Asthma	0	1 (<1)
Bacteremia	0	1 (<1)
Bronchitis	0	1 (<1)
Bundle branch block left	0	1 (<1)
Cerebrovascular accident	0	1 (<1)
Chest pain	0	1 (<1)
Chronic gastritis	0	1 (<1)
Circulatory collapse	0	1 (<1)
Condition aggravated	0	1 (<1)
Death	0	1 (<1)
Device related infection	0	1 (<1)
Diarrhea infectious	0	1 (<1)
Diverticulitis	0	1 (<1)
Dizziness	0	1 (<1)

Drug withdrawal syndrome	0	1 (<1)
Endocarditis	0	1 (<1)
Endometrial adenocarcinoma	0	1 (<1)
Epilepsy	0	1 (<1)
Erythema nodosum	0	1 (<1)
Escherichia urinary tract infection	0	1 (<1)
Febrile infection	0	1 (<1)
Femoral neck fracture	0	1 (<1)
Flank pain	0	1 (<1)
Gastrointestinal hemorrhage	0	1 (<1)
General physical health deterioration	0	1 (<1)
Hyperglycemia	0	1 (<1)
Hypoglycemia	0	1 (<1)
Hypothyroidism	0	1 (<1)
Ischemic stroke	0	1 (<1)
Lower respiratory tract infection viral	0	1 (<1)
Melaena	0	1 (<1)
Migraine	0	1 (<1)
Musculoskeletal chest pain	0	1 (<1)
Oesophagitis	0	1 (<1)
Orthostatic hypotension	0	1 (<1)
Ovarian fibroma	0	1 (<1)
Pathological fracture	0	1 (<1)

Pericarditis	0	1 (<1)
Perineal abscess	0	1 (<1)
Peripheral artery occlusion	0	1 (<1)
Peripheral motor neuropathy	0	1 (<1)
Pharyngotonsillitis	0	1 (<1)
Pleural infection	0	1 (<1)
Prostate cancer	0	1 (<1)
Pulmonary hemorrhage	0	1 (<1)
Rectal abscess	0	1 (<1)
Salmonella bacteremia	0	1 (<1)
Seizure	0	1 (<1)
Sinusitis	0	1 (<1)
Subarachnoid hemorrhage	0	1 (<1)
Toxic epidermal necrolysis	0	1 (<1)
Ureterolithiasis	0	1 (<1)
Uterine leiomyoma	0	1 (<1)
Uterine polyp	0	1 (<1)
Vertigo	0	1 (<1)