Supplementary Appendix

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

Supplement to: Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum–pemetrexed in *EGFR* T790M–positive lung cancer. N Engl J Med 2017;376:629-40. DOI: 10.1056/NEJMoa1612674

Osimertinib or Platinum-Pemetrexed in EGFR T790M Positive Lung Cancer

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Contents

List of AURA3 Investigators

Australia: Thomas John, Arman Hasani, Chee Lee, Rachel Dear, Kenneth O'Byrne

Canada: Paul Wheatley-Price, Frances Shepherd, Quincy Chu, Janessa Laskin, Normand Blais, Wojciech Morzycki

China: Qing Zhou, Li Zhang, Jie Wang, Caicun Zhou, Shun Lu, Baohui Han, Jianying Zhou, Ying Cheng, Xiangdong Zhou, Wei Zhang, Gongyan Chen, Yuankai Shi, Yong He, Cheng Zhuang, Yanqiu Zhao, Li Shan, Liyan Jiang, Kai Li

France: Jacques Cadranel, Patrick Merle, Elisabeth Quoix, David Planchard, Fabrice Barlesi, Eric Dansin, Julien Mazieres, Bruno Coudert

Germany: Martin Schuler, Barbara Deschler-Baier, Frank Griesinger, Christian Schulz, Martin Sebastian, Martin Kimmich

Hong Kong: Tony Mok, James Ho, Oscar Siu Hong Chan, Victor Ho Fun Lee, Yu Chung Li

Hungary: Gyula Ostoros

Italy: Angelo Delmonte, Silvia Novello, Giuseppe Tonini, Marina Garassino, Cesare Gridelli

Japan: Norihiko Ikeda, Hiroshi Sakai, Akimasa Sekine, Toshiaki Takahashi, Yasuhito Fujisaka, Hiroaki Akamatsu, Hiroshige Yoshioka, Tadasuke Shimokawaji, Hiroshi Tanaka, Toyoaki Hida, Kazuo Kasahara, Fumio Imamura, Shinji Atagi, Koji Takeda, Nobuyuki Katakami, Miyako Satouchi, Naoyuki Nogami, Isamu Okamoto, Ryo Koyama, Kazuhiko Nakagawa, Takashi Yokoi, Katsuyuki Kiura, Makoto Maemondo, Shuji Murakami, Young Hak Kim

Mexico: Jorge Alatorre Alexander, Carlos Hernández Hernández

Netherlands: Wilhelmina Engelsman-Theelen, Adrianus de Langen, Dr. Hendricus Groen

Russian Federation: Irina Bulavina, Artem Poltoratskiy, Konstantin Laktionov, Galina Statsenko, Sergey Orlov

South Korea: Myung-Ju Ahn, Jin Hyoung Kang, Jong Seok Lee, Hye Ryun Kim, Ji-Youn Han, Sang-We Kim, Eun Kyung Cho, Young Joo Min, Ki Hyeong Lee, Jin-Hyuk Choi, Gyeong-won Lee, Sung Sook Lee, Jin-Soo Kim

Spain: Enriqueta Felip Font, Dolores Isla Casado, Jesus Corral Jaime, Santiago Ponce Aix, Pilar Garrido López, Manuel Cobo Dols

Sweden: Ronny Öhman, Bengt Bergman, Karl-Gustaf Kölbeck

Taiwan: Chih-Hsin Yang, Wu-Chou Su, Te-Chun Hsia, Chun-Ming Tsai, Gee-Chen Chang, Cheng-Ta Yang, Chin-Chou Wang, Ming-lin Ho, Ruay-Sheng Lai, Yu-Feng Wei, Jen-Chung Ko

United Kingdom: Fiona Blackhall, Adam Dangoor, Pek Koh, Nicola Steele, Allan Price, Marianne Nicolson, Hendrik-Tobias Arkenau, Thomas Newsom-Davis, Vanessa Potter, Alastair Greystoke, Nick Brown

United States of America: Kathryn Gold, Naiyer Rizvi, Suresh Ramalingam, Sai-Hong Ou, Thomas Cosgriff, Richard Frank, Nasser Hanna, Konstantin Dragnev, Tarek Mekhail, Smitha Menon, Veena Charu, Frederic Kaye, John Wrangle, Frederick Smith, Apurv Agrawal, Ian Anderson, Robert Hirsch, Navkiranjit Gill, Michael Harris, Xingwei Sui, Chandra Belani

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. The study sponsor was permitted a period of 30 days for review of the proposed final manuscript to allow for filing of any relevant patent applications. Responsibility for opinions, conclusion, and interpretation of the data lies with the authors.

Stratification by ethnicity

The site investigator asked the patient to provide information to indicate their ethnicity on the electronic study case report form (crf). This information from the patient was recorded on the crf and used in the randomization system to classify the patient as Asian or non-Asian.

Pemetrexed maintenance treatment

Patients whose disease had not progressed after four cycles of platinum-pemetrexed could continue maintenance pemetrexed according to the approved label; premedication regimen was indicated in adherence with US Food and Drug Administration approved toxicity management guidelines or, where appropriate, local practice guidelines.

Definitions of secondary endpoints

Objective response rate (ORR) was the number of randomized patients with at least one visit response of complete response or partial response. Duration of response (DoR) was defined as time from the date of first documented response until the date of progression or death in the absence of progression. Disease control rate (DCR) was the percentage of patients who had a best overall response of complete response, partial response and stable disease of ≥6 weeks. Tumor shrinkage was calculated from the absolute change and percentage change from baseline in sum of tumor size at each assessment. Overall survival (OS) was defined as the time from the date of randomization until death due to any cause.

Safety assessments

During the treatment period, clinical chemistry, hematology, urinalysis, vital signs, physical examination, weight, digital electrocardiogram and World Health Organization (WHO) performance status were assessed every 3 weeks; left ventricular ejection fraction (LVEF) was assessed every 12 weeks; adverse events (AEs; graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0]) were

monitored continuously throughout the treatment period and during the 28-day follow-up period.

Progression free-survival – HR derivation

The hazard ratio (HR) and confidence interval (CI) were obtained directly from the U and V statistics as follows:[1,2]

$$HR = \exp(U/V)$$

$$95\%\ CI\ for\ HR = (\exp[U/V - 1.96/\sqrt{V}], \exp[U/V + 1.96\sqrt{V}])$$

Where $U = \sum i(d_{1i} - e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for the stratification variable.

Progression free-survival – subgroups

Subgroup analyses were conducted by comparing progression-free survival (PFS) between treatments in the following groups: ethnicity (Asian vs. Non-Asian), gender (male vs. female), age at screening (<65 vs. ≥65), *EGFR* mutation status prior to start of study (Exon 19 deletion vs. L858R mutation), duration of prior EGFR-TKI (<6 months, ≥6 months), central nervous system (CNS) metastases at entry, smoking history. HRs (osimertinib:platinum-pemetrexed) and CIs were estimated with the use of a Cox proportional hazards model (ties=Efron) containing the treatment term, factor and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals was obtained for each level of the subgroup from this single model. The HRs and 95% CIs are presented on a forest plot (Figure 2 in the article) including the HR and 95% CI from the overall population (and also from the primary analysis from U and V statistics from the stratified log rank test).

Progression free-survival – sensitivity analyses

The possibility of bias in assessment and measurement of PFS by investigators was assessed by comparing the HRs derived from investigator review with the HR derived using the blinded independent central review (BICR) assessment of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST).

In order to assess possible evaluation-time bias, that could occur if scans were not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable RECIST assessment was analyzed using a stratified

log rank test, as described for the primary analysis of PFS. For patients who died in the absence of progression, the date of death was used to derive the PFS time used in the analysis.

The possibility of bias resulting from the rate and nature of censoring (attrition bias) was assessed by repeating the primary PFS analysis, except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two or more non-evaluable tumor assessments were included. In addition, patients who had subsequent therapy prior to progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.

Objective response rate, duration of response and expected duration of response

The ORR was compared between treatment using logistic regression models adjusting for the covariate ethnicity (Asian/non-Asian). Descriptive data are provided for the duration of response in responding patients. In order to analyze the secondary outcome variable of duration of response between groups (reported in the supplementary results section below), the expected duration of response (EDoR) were derived for each treatment group.[3] The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients, and provides an estimate based on all randomized patients. Treatments were compared by calculating the ratio of EDoRs using the log Normal probability distribution for duration of response in responding patients. Refer to the statistical analysis plan (available at NEJM.org) for information on the choice of probability distribution. The analysis of DoR was stratified by the same covariates as the primary analysis, weighting each stratum inversely proportional to the within stratum variance of the log of the ratio of EDoRs.

Overall survival

Overall survival will be analyzed as per PFS. Three OS analyses are planned: a) approximately 4 months after the data cut-off for the primary analysis of PFS; b) at approximately 50% maturity and c) at approximately 70% maturity. The first data cut-off for OS occurred on September 2, 2016, and results will be reported separately.

Patient reported outcomes – mixed model for repeated measures

Patient reported outcomes (PROs) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30) and EORTC QLQ – Lung Cancer 13 items (LC13) questionnaire. The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after

progression. The C30 was assessed every 6 weeks before and after progression. Change from baseline in the primary PRO symptom scores of dyspnea, cough, chest pain, fatigue and appetite loss were analyzed using a mixed model for repeated measures analysis, with covariates for baseline score, visit, and a treatment-by-visit interaction.

Rationale for change in planned analyses

In Amendment 2 to AURA3 CSP (dated May 6, 2015), the number of patients to be randomized in the study was reduced from 610 to 410. Although the primary endpoint was PFS, the study had been sized to compare OS formally and thus was overpowered for PFS (>95% power to detect a difference in PFS assuming the true HR is 0.67 at a 5% 2-sided significance level). Due to the necessity of introducing crossover to osimertinib for patients who progressed in the platinum-pemetrexed group, the interpretation of OS was compromised and, therefore, the study was re-sized to focus on the primary endpoint of PFS, resulting in a sample size reduction. After Amendment 2, the study had 90% power to demonstrate a statistically significant PFS assuming the original hypothesized treatment effect of PFS HR of 0.67 at a 5% 2-sided significance level. In Amendment 3 (dated March 21, 2016, before the data cut-off for PFS of April 15, 2016), the Sponsor made a reduction in power to detect a statistically significant difference for the primary analysis of PFS from 90% to 80% (assuming an HR of 0.67 and 5% 2-sided significance level). The decision to change the power was based on the compelling results from the most recent (November 1, 2015 data cut-off) PFS data from the phase 2 osimertinib monotherapy studies (AURA extension and AURA2) (data on file).

Based on Amendment 3, if the assumed treatment effect were still an HR of 0.67 (which translates to approximately 3 months of improvement on an estimated median PFS of 6 months in the control group, assuming proportional hazards), then 221 progression events would provide 80% power to demonstrate a statistically significant difference in PFS at the 5% 2-sided significance level (as compared with the 295 progression events required for assuring the originally planned 90% power to demonstrate a statistically significant PFS for a hypothesized treatment effect of PFS HR of 0.67 at a 5% 2-sided significance level).

Additionally, in order to maximize the maturity of the OS data at the time of the first analysis, the data cut-off for the first OS analysis occurred approximately 4 months after the data cut-off for the primary PFS analysis (OS data cut-off: September 2, 2016). At the time of the primary PFS analysis, OS was summarized and not analyzed. A summary of the frequency of deaths and primary cause of death were provided for safety purposes, and no additional summaries were performed in order to protect the integrity of the first OS analysis. The

approach to control the overall Type I error at 5% (2-sided) for OS was modified to the Lan DeMets approach that approximates the O'Brien and Fleming spending function.

The statistical analysis changes made by the Sponsor, and supported by principal investigators, in Amendments 2 and 3 to the protocol before PFS data cut-off, are considered to be reasonable and constitute a sound approach to the interpretation of the study.

The study protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

Supplementary Results

Median cycles of chemotherapy

The median number of cycles was 4.0 for both cisplatin and carboplatin, and 6.0 for pemetrexed. The median duration of pemetrexed maintenance was 3.1 months (i.e. 4 cycles).

Dose modifications

Two hundred and three (73%) patients in the osimertinib group did not have dose modifications (defined as interruptions or reduction to 40 mg) during the study. Of the 76 (27%) patients with dose interruptions, most were due to an AE (38 [14%] patients). Eight (3%) patients in the osimertinib group had dose reductions from 80 mg to 40 mg, all due to AEs. Of these eight, only one patient subsequently discontinued osimertinib due to the same AE (cardiac failure).

In the platinum-pemetrexed group, 57 (42%) patients had a delay in pemetrexed administration, 16 (38%) patients had a delay in cisplatin administration, and 28 (30%) patients had a delay in carboplatin administration. Delays in administration of pemetrexed, cisplatin and carboplatin due to AEs were reported in 28 (21%) patients, five (12%) patients, and 15 (16%) patients, respectively. Nineteen (14%) patients had reductions in the dose of pemetrexed, 12 (29%) patients had reductions in the dose of cisplatin, and 17 (18%) patients had reductions in the dose of carboplatin. The most frequent reason for dose reductions were AEs for all three drugs (pemetrexed, 17 [13%] patients; cisplatin, 12 [29%] patients; carboplatin, 10 [11%] patients).

Prior treatment in patients with central nervous metastases at study entry

A total of 144 (34%) patients (93 [33%] in the osimertinib group and 51 [36%] in the platinum-pemetrexed group) had CNS metastases at study entry, determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy. In these patients with CNS metastases, 43% (40/93) in the osimertinib group and 57% (29/51) in the platinum-pemetrexed group had received prior treatment for CNS metastases.

Sensitivity analysis of progression-free survival by blinded independent central review and assessment of concordance

The sensitivity analysis of PFS by BICR on the intent-to-treat population was consistent with the investigator-based analysis. At data cut-off, a total of 219 (52%) progression events or

deaths in the absence of RECIST progression had occurred based on BICR (116 patients [42%] in the osimertinib group compared to 103 patients [74%] in the platinum-pemetrexed group). The median PFS was 11.0 months in the osimertinib group vs. 4.2 months in the platinum-pemetrexed group (HR 0.28 [95% CI: 0.20 to 0.38] p<0.001) (Figure S5). Based on a KM analysis, the estimated proportion of patients alive and progression-free at 6 months was 70% (95% CI: 64 to 75) in the osimertinib group vs. 34% (95% CI: 26 to 43) in the platinum-pemetrexed group; at 12 months: 47% (95% CI, 39 to 54) vs. 11% (95% CI, 6 to 19).

The overall concordance between the BICR and investigator-assessed disease progression was 83%; there was disagreement in the assessment of disease progression status for 73 patients (Table S2). The concordance was 78% in the osimertinib group, with disagreement for 62 patients. The concordance was 92% in the platinum-pemetrexed group, with disagreement for 11 patients. The difference in concordance between treatment groups may be due in part to the mandatory BICR confirmatory review of scans at the time of disease progression for platinum-pemetrexed patients before cross-over to osimertinib was allowed. The true positive rates in the osimertinib and platinum-pemetrexed groups are 0.84 and 0.98, respectively, and the true negative rates in the osimertinib and platinum-pemetrexed groups are 0.74 and 0.76, respectively.

There was no evidence of evaluation-time bias; the HR of 0.29 (95% CI, 0.22, 0.40; p<0.001) was consistent with the primary analysis.

Progression-free survival sensitivity analysis: attrition bias

A sensitivity analysis to evaluate attrition bias (censoring the five patients who received subsequent anti-cancer therapy prior to progression at the start of that subsequent therapy, and using the date of objective progression or death for the one patient who progressed or died in the absence of progression following two or more non-evaluable RECIST assessments prior to progression or death) was also performed. The results of this sensitivity analysis indicated that the censoring rules applied did not affect the outcome of the primary analysis of PFS; the HR was 0.30 (95% CI, 0.22 to 0.40; p<0.001) (Figure S6).

Analysis of duration of response

There was a statistically significant improvement in expected duration of response for patients on osimertinib compared to patients on platinum-pemetrexed (ratio of EDoR: 6.22; 95% CI, 4.04 to 9.57; p<0.001).

New lesions

At data cut-off, 26% of patients (n=73) on osimertinib had progressed due to new lesions by investigator assessment compared to 45% (n=63) on platinum-pemetrexed, mostly driven by CNS (5% and 14%) and lung new lesions (9% and 18%) respectively (Table S3).

Possibly causally-related adverse events leading to osimertinib discontinuation

The AURA3 protocol mandated discontinuation of patients with the following specific events: corneal ulceration, interstitial lung disease (ILD), and QTc interval prolongation with signs/symptoms of serious arrhythmia. Ten (4%) patients in the osimertinib group reported a possibly causally-related AE leading to treatment discontinuation. Reported AEs were as follows: pneumonitis (n=5); ILD (n=3); cardiac failure (n=2); non-cardiac chest pain and pneumonia (n=1 each). A single patient had discontinuation recorded next to more than one AE.

Cardiac effects

In AURA3, LVEF decreased ≥10% and a drop to <50% occurred in 14/258 (5%) patients on osimertinib with a baseline and at least one follow-up LVEF assessment. The majority of these patients (12/14 [86%]) had asymptomatic LVEF decreases that did not require dose interruption or supportive cardiac concomitant medication. Time to onset of the first LVEF decrease (LVEF decrease ≥10 percentage points from baseline to a LVEF value of <50%) was 5.5 months, with a median exposure in the platinum-pemetrexed group of 4 months (approximately half of the median exposure in the osimertinib group).

Cardiac effects (cardiac failure) were reported in nine (3%) patients in the osimertinib group (including six patients with ejection fraction decrease) and no patients in the platinum-pemetrexed group. A small decrease in the median maximum change from baseline in LVEF was reported in both osimertinib and platinum-pemetrexed groups at 27 weeks: −2.0% (range: −45% to +16%) and −1.5% (range: −14% to +11%) respectively. Based on the available clinical trial data, a causal relationship between changes in cardiac contractility and osimertinib has not been established.

In the osimertinib group, seven patients reported QT prolongation AEs possibly causally-related to treatment (as assessed by the investigator), all grade 1 or 2 in severity. Osimertinib was interrupted for five of the seven patients, but none of these QT prolongation events required treatment. In all cases, the event was reported as resolved, with no further recurrence. In the platinum-pemetrexed group, one patient reported a QT prolongation AE (grade 2 in severity) possibly causally-related to cisplatin. The event was not treated, but

was reported as resolved. AE reporting is at investigator's discretion, not based on QTcF lab data alone.

Analysis of QTcF by lab data was as follows. A change from baseline in QTcF was observed in the osimertinib group, in line with previous osimertinib studies, with the median increasing to 12.45 msec at Cycle 3, after which it remained stable. No clinically significant change from baseline in median QTcF was observed in the platinum-pemetrexed group. Changes from baseline of >30 msec in mean QTcF were observed in 86 (31%) patients in the osimertinib group and seven (5%) patients in the platinum-pemetrexed group, with five patients in the osimertinib group having QTcF increases >60 msec during the study. Four (1%) patients in the osimertinib group had a mean QTcF of >500 msec at any time during study, compared with none in the platinum-pemetrexed group.

Serious adverse events

Fifty (18%) patients in the osimertinib group and 35 (26%) patients in the platinum-pemetrexed group had serious AEs (SAEs; including events with an outcome of death). Possibly causally-related SAEs (including deaths) were reported in 3% (n=8) of patients in the osimertinib group and 13% (n=17) in the platinum-pemetrexed group.

The most frequently reported SAEs in the osimertinib group (≥1% of patients) were pulmonary embolism (four [1%] patients vs. two [1%] patients in the platinum-pemetrexed group); pneumonia (three [1%] vs. zero on platinum-pemetrexed); and dyspnea (three [1%] vs. zero on platinum-pemetrexed). The most frequently reported SAEs in the platinum-pemetrexed group (≥1% of patients) were deep vein thrombosis (four [3%] patients vs. zero on osimertinib); anemia (three [2%] vs. zero on osimertinib); epilepsy (three [2%] vs. zero on osimertinib); pulmonary embolism (two [1%] vs. four [1%] on osimertinib); pyrexia (two [1%] vs. two [1%] on osimertinib); nausea (two [1%] vs. one [<1%] on osimertinib); non-cardiac chest pain (two [1%] vs. one [<1%] on osimertinib); and decreased appetite (two [1%] vs. zero on osimertinib).

In the osimertinib group, pulmonary embolism was reported in seven (3%) patients, and was Grade 3 in four (1%) patients, with all four AEs classified as SAEs. In the platinum-pemetrexed group, pulmonary embolism was reported in five (4%) patients, and classified as Grade 3 in three (2%) patients, with two classified as an SAE. One report of Grade 3

pulmonary embolism in the osimertinib group was possibly causally-related to treatment according to the investigator.

Safety summary for patients who crossed over from platinum-pemetrexed group to osimertinib after progression.

In cross-over patients, AEs occurred in 69 (84%) patients and were considered possibly related to osimertinib in 54 (66%) patients. Grade ≥3 AEs were reported in 17 (21%) patients and were considered to be possibly related to osimertinib in six (7%) patients. A total of nine (11%) patients had SAEs, which were considered to be possibly related to osimertinib in two (2%) patients. Fatal AEs occurred in two (2%) patients, of which one (1%) was considered by the investigator to be possibly related to osimertinib (respiratory failure). Adverse events infrequently led to permanent discontinuation of osimertinib (two [2%] cross-over patients); AEs leading to discontinuation were considered to be possibly related to osimertinib in one (1%) cross-over patient.

Treatment beyond progression

In AURA3, 129 patients in the osimertinib group were still alive after radiological progression, of whom 82 (64%) continued osimertinib treatment for more than 7 days post-progression for a median of 4.1 months. In the platinum-pemetrexed group, 104 patients were still alive after radiological progression, of whom 12 (12%) continued treatment for more than 7 days (only five patients continued carboplatin/cisplatin) post-progression for a median of 1.6 months.

Supplementary Tables

Table S1. Baseline demographics and clinical characteristics

	Osimertinib (N=279)	Platinum-pemetrexed (N=140)
Age, years		
Median (range)	62 (25–85)	63 (20–90)
Female sex, n (%)	172 (62)	97 (69)
Country, n (%)		
South Korea	45 (16)	27 (19)
Japan	41 (15)	22 (16)
China	34 (12)	14 (10)
Taiwan	35 (13)	13 (9)
Italy	20 (7)	5 (4)
USA	10 (4)	11 (8)
Canada	12 (4)	8 (6)
Australia	11 (4)	5 (4)
Russia	13 (5)	3 (2)
Germany	12 (4)	3 (2)
United Kingdom	12 (4)	3 (2)
Netherlands	10 (4)	4 (3)
Spain	7 (3)	7 (5)
Hong Kong	8 (3)	4 (3)
France	4 (1)	6 (4)
Mexico	3 (1)	2 (1)
Sweden	2 (1)	2 (1)
Hungary	0	1 (1)
Race, n (%)		
White	89 (32)	45 (32)
Asian	182 (65)	92 (66)
Other*	8 (3)	3 (2)

Smoking status, n (%)		
Never	189 (68)	94 (67)
Current	14 (5)	8 (6)
Former	76 (27)	38 (27)
WHO performance status, n (%)		
0	102 (37)	56 (40)
1	177 (63)	84 (60)
Histology, n (%)		
Adenocarcinoma NOS	232 (83)	122 (87)
Squamous cell carcinoma NOS	3 (1)	0
Other†	44 (16)	18 (13)
Overall disease classification, n (%)		
Metastatic‡	266 (95)	138 (99)
Locally advanced¶	13 (5)	2 (1)
CNS metastases§, n (%)	93 (33)	51 (36)
No CNS metastases§, n (%)	186 (67)	89 (64)
Extrathoracic visceral metastases, n (%)**	145 (52)	80 (57)
No extrathoracic visceral metastases, n (%)**	134 (48)	60 (43)
***EGFR* mutations††, n (%)**		
T790M mutation‡‡	275 (99)	138 (99)
Exon 19 deletion	191 (68)	87 (62)
Exon 21 L858R	83 (30)	45 (32)
G719X	4 (1)	2 (1)
S768I	1 (<1)	1 (1)
Exon 20 insertion	1 (<1)	2 (1)
Number of previous anti-cancer regimens for advanced disease, n (%)¶¶		
1	269 (96)	134 (96)

2	9 (3)	6 (4)
3[§§]	1 (<1)	0
Previous EGFR-TKI therapy, n (%)	279 (100)	139 (99)
Gefitinib	166 (59)	87 (62)
Erlotinib	96 (34)	49 (35)
Afatinib	20 (7)	4 (3)
Prior adjuvant/neo-adjuvant therapy,* n (%)**	25 (9)	10 (7)

There were no notable differences in baseline demographics and clinical characteristics between the groups. CNS, central nervous system; *EGFR*, epidermal growth factor receptor; NOS, not otherwise specified; TKI, tyrosine kinase inhibitor.

*Race was self-reported. The category of "other" race includes black, American Indian, and Alaska Native.

†Including: adenocarcinoma: acinar, papillary, bronchiolo-alveolar, solid with mucous formation, bronchiolo-alveolar and papillary; non-small cell carcinoma; adenosquamous carcinoma.

‡Metastatic disease: Patient had any metastatic site of disease.

¶Locally advanced: Patient had only locally advanced sites of disease.

§CNS metastases were determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy. One patient was identified as having locally advanced disease in the brain.

**Extra-thoracic visceral metastases were determined programmatically from baseline data where the disease site was "Adrenal," "Ascites," Brain/CNS," "Gastrointestinal," "Genitourinary," "Hepatic (including gallbladder)," "Liver," "Other CNS," "Pancreas," "Peritoneum," or "Spleen", and/or those "Other metastatic sites" such as "Eye" and "Thyroid" as identified as extra-thoracic visceral sites by AstraZeneca Physicians.

††*EGFR* mutation identified by the cobas® EGFR Mutation Test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).

‡‡Six patients (four in the osimertinib group and two in the platinum-pemetrexed group) did not have centrally confirmed T790M mutation-positive status documented in the study database. Three patients (two in the osimertinib group and one in the platinum-pemetrexed group) were subsequently found to be tumor T790M mutation-positive; therefore, three patients (two in the osimertinib group and one in the platinum-pemetrexed group) were tumor T790M negative and were randomized in error. One of the three patients who was tumor T790M negative was plasma ctDNA T790M positive.

¶¶Patients were classified as having received more than one previous line of therapy if they received any of the following: adjuvant or neoadjuvant chemotherapy administered less than 6 months before the start of EGFR-TKI therapy; more than one EGFR-TKI (switching from a first-generation EGFR-TKI to a second-generation EGFR-TKI, or restarting EGFR-TKI after >12 months off treatment) administered sequentially; or the addition of anticancer agents such as cytotoxic chemotherapy or a c-Met monoclonal antibody toward the end of a previous monotherapy EGFRTKI regimen.

§§Patient treated with fulvestrant then letrozole before starting EGFR-TKI.
***Initial treatment received for early disease at initial diagnosis, prior to advanced disease.

Table S2. Concordance between investigator-assessed and blinded-independent central review (BICR)-assessed disease progression (intent-to-treat set)

N (%)		Disease progression per BICR	
	Disease progression per investigator	**Progressive disease**	**No progression**
Overall (N=419)	Progressive disease	198 (47)	52 (12)
	No progression	21 (5)	148 (35)
Osimertinib (N=279)	Progressive disease	97 (35)	43 (15)
	No progression	19 (7)	120 (43)
Platinum-pemetrexed (N=140)	Progressive disease	101 (72)	9 (6)
	No progression	2 (1)	28 (20)

Table S3. New lesions by investigator assessment (intent-to-treat population)

New lesion site	Osimertinib (n=279), n (%)	Platinum-pemetrexed (n=140), n (%)
Patients with no new lesions	206 (74)	77 (55)
Patients with new lesions	73 (26)	63 (45)
Adrenal gland	1 (<1)	0
Bone	9 (3)	6 (4)
Breast	1 (<1)	0
Central nervous system	13 (5)	20 (14)
Distant lymph nodes	1 (<1)	3 (2)
Head and neck	3 (1)	2 (1)
Kidney	0	1 (1)
Liver	10 (4)	7 (5)
Lung	24 (9)	25 (18)
Other	3 (1)	2 (1)
Pancreas	0	1 (1)
Pericardium	0	1 (1)
Peritoneum	0	2 (1)
Pleura	10 (4)	5 (4)
Regional lymph node	3 (1)	5 (4)
Spleen	1 (<1)	0

Table S4. Mixed model repeated measures analysis of key lung cancer symptoms; mean change from baseline in patients treated with osimertinib compared with platinum-pemetrexed.

	Appetite loss		Cough		Chest pain		Dyspnea		Fatigue	
Groups	Osimertinib (n=279)	Platinum-pemetrexed (n=140)	Osimertinib (n=279)	Platinum-pemetrexed (n=140)	Osimertinib (n=279)	Platinum-pemetrexed (n=140)	Osimertinib (n=279)	Platinum-pemetrexed (n=140)	Osimertinib (n=279)	Platinum-pemetrexed (n=140)
N (%)	239 (86)	97 (69)	228 (82)	113 (81)	228 (82)	113 (81)	228 (82)	113 (81)	239 (86)	97 (69)
Adjusted mean	-5.51	2.73	-12.22	-6.69	-5.15	0.22	-5.61	1.48	-5.68	4.71
Estimated difference (95%CI)	-8.24 (-12.88–3.60)		-5.53 (-8.89–-2.17)		-5.36 (-8.20–-2.53)		-7.09 (-9.86–-4.33)		-10.39 (-14.55–-6.23)	
P-value	p<0.001		p=0.001		p<0.001		p<0.001		p<0.001	

Adjusted mean and estimated differences obtained from a mixed model repeated measures analysis. The model included patient, treatment, visit, treatment by visit interaction baseline symptom score and baseline symptom score by visit interaction and used an unstructured covariance matrix. N = number of patients included in the analysis. A difference < 0 favors osimertinib. Results are restricted to patients who provided baseline and at least one follow-up assessment. The proportion of patients with missing data for the endpoints from the LC13 questionnaire (cough, chest pain and dyspnea) was similar in the osimertinib group (18%) compared to the platinum-pemetrexed group (19%). There was a greater proportion of patients with missing data for the endpoints from the C30 questionnaire (appetite loss and fatigue) in the platinum-pemetrexed group (31%) compared to the osimertinib group (14%).

Table S5. Grade ≥3 adverse events reported in at least three patients in either treatment group*

N (%)	Osimertinib (N=279)	Platinum-pemetrexed (N=136)
Pulmonary embolism	4 (1)	3 (2)
Neutropenia†	4 (1)	16 (12)
Asthenia	3 (1)	6 (4)
Decreased appetite	3 (1)	4 (3)
Diarrhea	3 (1)	2 (1)
Fatigue	3 (1)	1 (1)
Alanine aminotransferase increased	3 (1)	1 (1)
Aspartate aminotransferase increased	3 (1)	1 (1)
Dyspnea	3 (1)	0
Anemia†	2 (1)	16 (12)
Nausea	2 (1)	5 (4)
Thrombocytopenia†	1 (<1)	10 (7)
Hyperglycemia	1 (<1)	3 (2)
Hyponatremia	1 (<1)	3 (2)
Vomiting	1 (<1)	3 (2)
Leukopenia†	0	5 (4)
Hypokalemia	0	3 (2)
Epilepsy	0	3 (2)

*Safety analyses included all patients who received at least one dose of study drug (safety analysis set). Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomized treatment or the day before first administration of cross-over treatment.
†Grouped term. If a patient has multiple preferred term level events within a specific grouped term adverse event, then the maximum CTCAE grade across those events is counted.

Table S6. Most common possibly causally-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or platinum-pemetrexed*

N (%)	Osimertinib (N=279)		Platinum-pemetrexed (N=136)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	231 (83)	16 (6)	121 (89)	46 (34)
Diarrhea	82 (29)	2 (1)	8 (6)	1 (1)
Rash†	79 (28)	1 (<1)	6 (4)	0
Paronychia†	57 (20)	0	1 (1)	0
Dry skin†	52 (19)	0	2 (1)	0
Stomatitis	34 (12)	0	19 (14)	2 (1)
Pruritus	30 (11)	0	4 (3)	0
Nausea	21 (8)	0	64 (47)	4 (3)
Decreased appetite	20 (7)	1 (<1)	43 (32)	4 (3)
Anemia†	9 (3)	1 (<1)	35 (26)	13 (10)
Fatigue	19 (7)	0	32 (24)	1 (1)
Neutropenia†	15 (5)	0	27 (20)	15 (11)
Vomiting	11 (4)	0	25 (18)	3 (2)
Thrombocytopenia†	21 (8)	0	22 (16)	9 (7)
Leukopenia†	14 (5)	0	17 (13)	5 (4)
Constipation	7 (3)	0	21 (15)	0
Asthenia	7 (3)	0	15 (11)	4 (3)
Malaise	0	0	14 (10)	0
Selected adverse events				
Interstitial lung disease†	9 (3)	1 (<1)	1 (1)	1 (1)
QT prolongation	7 (3)	0	1 (1)	0

*Safety analyses included all patients who received at least one dose of study drug (safety analysis set). Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following discontinuation of randomized treatment or the day before first administration of cross-over treatment. Some patients had more than one adverse event.

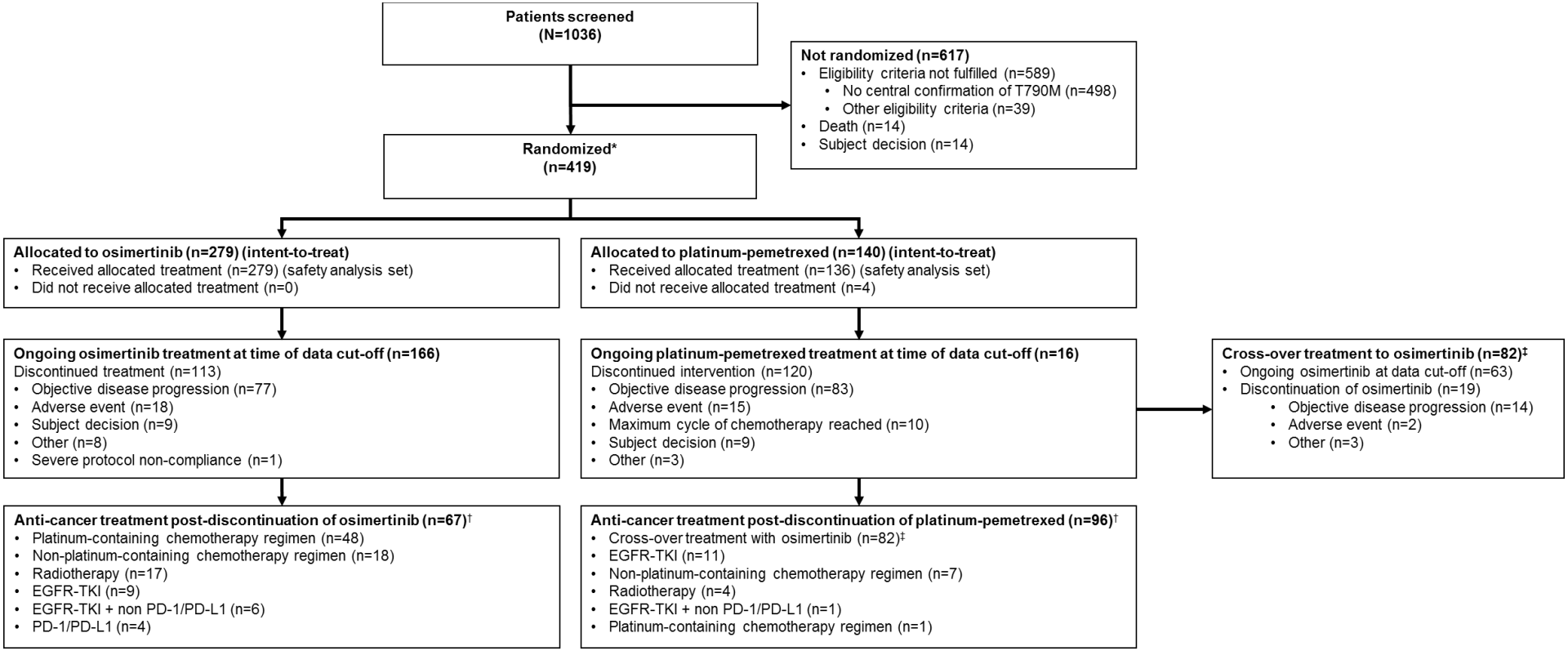
†Grouped term. If a patient has multiple preferred term level events within a specific grouped term adverse event, then the maximum CTCAE grade across those events is counted.

Table S7. *EGFR* genotyping for three patients with Exon 20 insertion and their response to treatment

	Treatment	*EGFR* mutations detected	Tumor best response (days from randomization)	Disease progression (days from randomization)
Patient 1	Osimertinib	T790M, L858R, Exon 20 insertion	Stable Disease (169)	No, stable disease ongoing
Patient 2	Platinum-pemetrexed	T790M, Exon 19 deletion, Exon 20 insertion	Partial response (79)	Yes (128)
Patient 3	Platinum-pemetrexed	T790M, L858R, Exon 20 insertion	Stable Disease (56)	Yes (91)

Supplementary Figures

Figure S1. Patient disposition



*Six patients (four in the osimertinib group and two in the platinum-pemetrexed group) did not have centrally confirmed T790M mutation-positive status documented in the study database. Three patients (two in the osimertinib group and one in the platinum-pemetrexed group) were subsequently found to be tumor T790M mutation positive; therefore, three patients (two in the osimertinib group and one in the platinum-pemetrexed group) were tumor T790M negative and were randomized in error. One of the three patients who was tumor T790M negative was plasma ctDNA T790M positive.

†Patients could have more than one line of therapy post discontinuation of randomized treatment

‡Post-confirmation of objective disease progression by blinded independent central review
EGFR, epidermal growth factor receptor; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; TKI, tyrosine kinase inhibitor

Figure S2. Disposition of screened patients included in the plasma circulating tumor DNA analysis for the detection of *EGFR* T790M. ctDNA, circulating tumor DNA

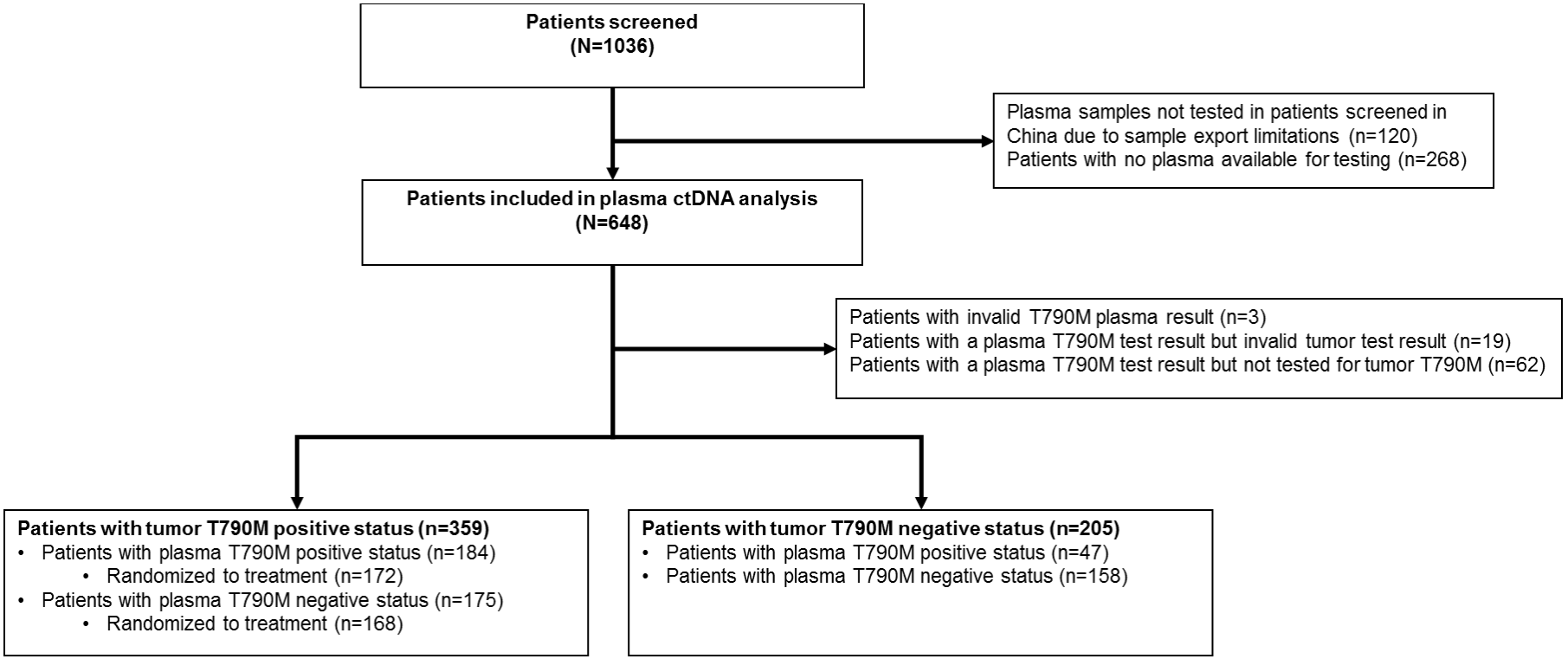


Figure S3. Kaplan-Meier estimates of progression-free survival (investigator assessed) in patients without central nervous system metastases at study start. The tick marks indicate censored data. CI, confidence interval

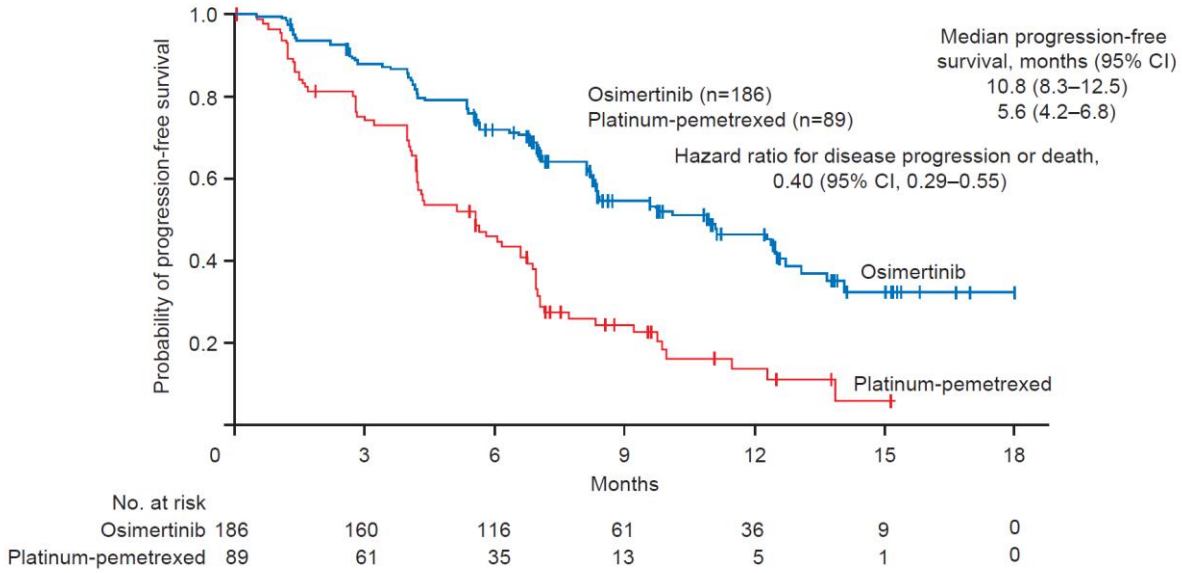
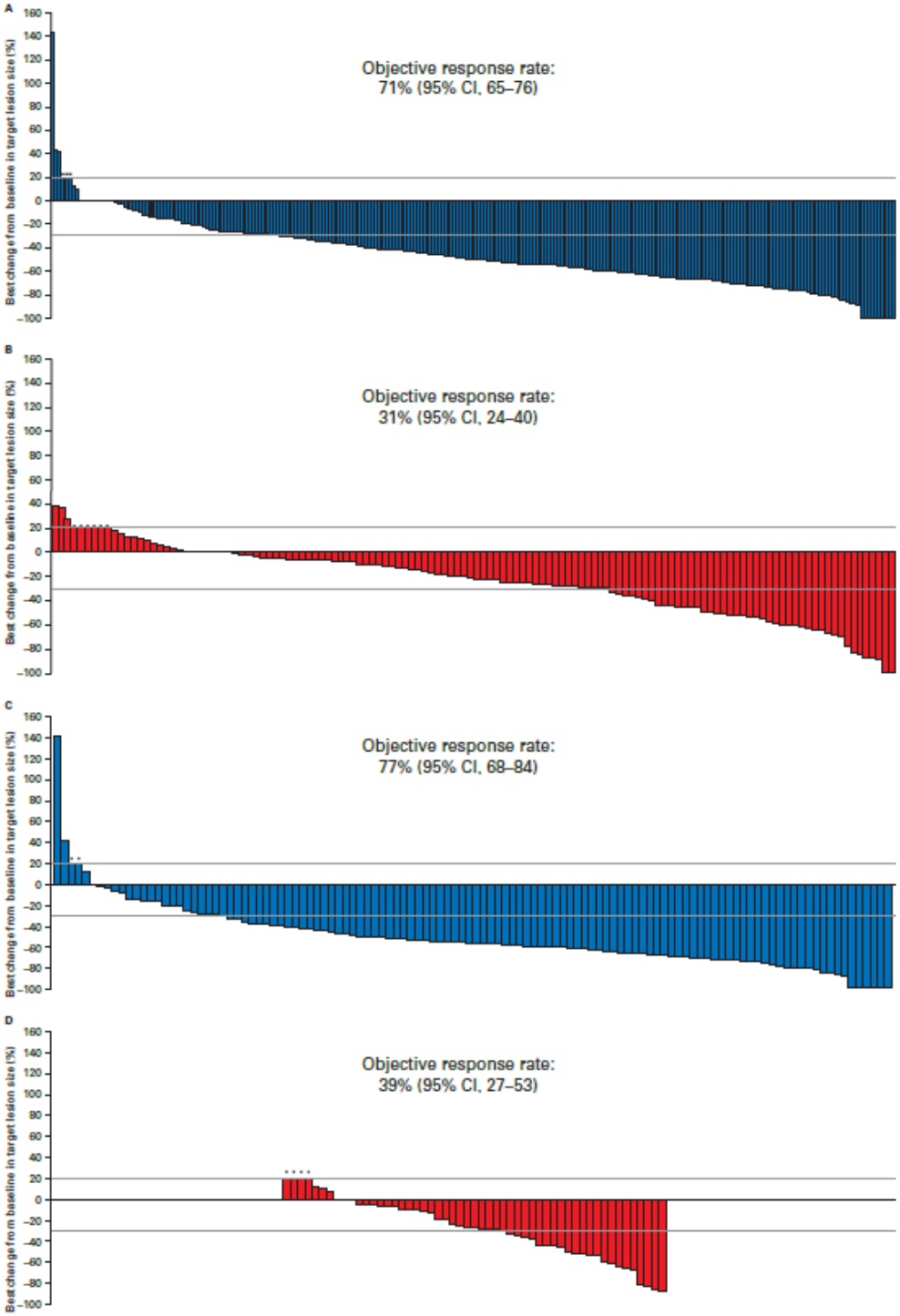


Figure S4. Waterfall plots for best percentage change in target-lesion size are shown for the intent-to-treat osimertinib group (Panel A) and platinum-pemetrexed group (Panel B). For those patients with plasma *EGFR* T790M-positive status, the waterfall plots are shown by osimertinib (Panel C) and platinum-pemetrexed (Panel D) treatment.



The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at -30% represents the boundary for determination of partial response. In the intent-to-treat population, there was a greater mean percentage tumor shrinkage from baseline in patients on osimertinib vs platinum-pemetrexed: unadjusted mean −46 (standard deviation [SD] 30) vs. −24 (SD 29); the difference in least square means between the treatment groups was −22% (95% CI, −28 to −16; p<0.001). *represents imputed values: if it is known that the patient has died, has new lesions or progression of assessments, best change will be imputed as 20%.

Figure S5. Kaplan-Meier estimates of progression-free survival by blinded independent central review in the intent-to-treat population. Tick marks indicate censored data. CI, confidence interval; NC, non-calculable.

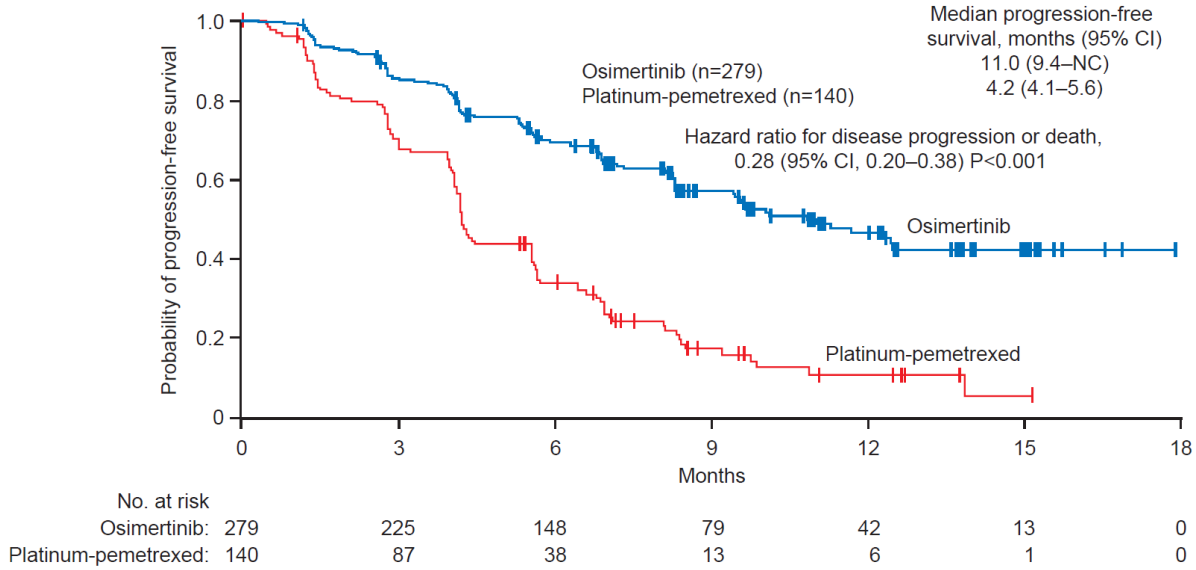
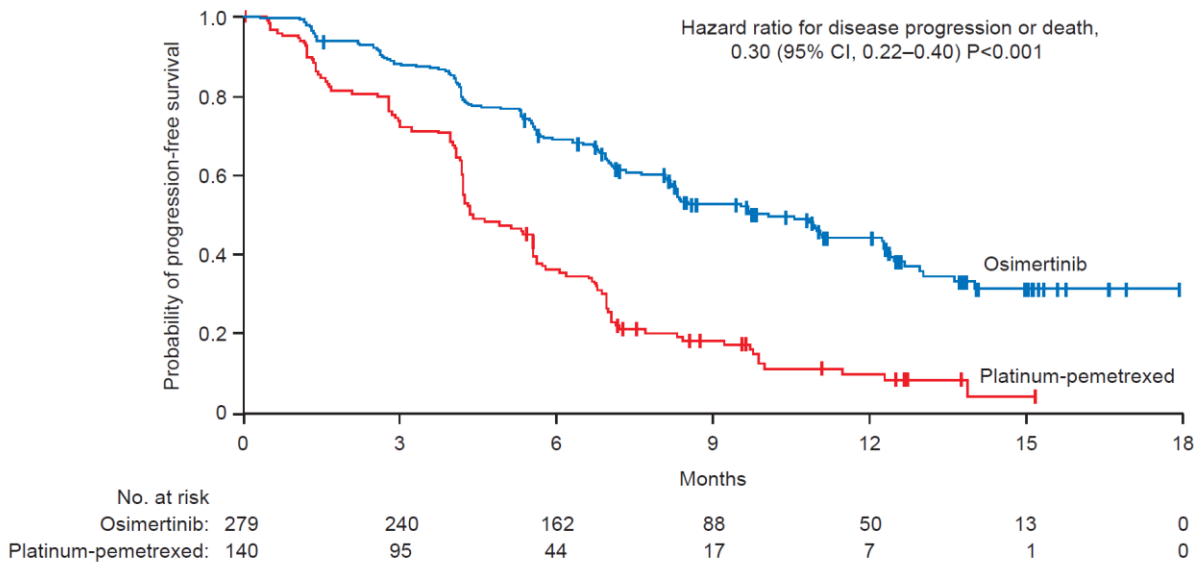


Figure S6. Kaplan-Meier estimates of progression-free survival (investigator assessment) in the intent-to-treat population to assess possible attrition bias. The tick marks indicate censored data. CI, confidence interval; NC, non-calculable



References

1. Selke T and Siegmund D. Sequential Analysis of the Proportional Hazards Model. Biometrika 1983;70:315-26.
2. Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Stat Med 1991;10:749-55.
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