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ORIGINAL ARTICLE

Osimertinib versus platinum—pemetrexed for patients with *EGFR* T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis

V. A. Papadimitrakopoulou[1], T. S. Mok[2], J.-Y. Han[3], M.-J. Ahn[4], A. Delmonte[5], S. S. Ramalingam[6], S. W. Kim[7], F. A. Shepherd[8,9], J. Laskin[10], Y. He[11], H. Akamatsu[12], W. S. M. E. Theelen[13], W.-C. Su[14], T. John[15], M. Sebastian[16], H. Mann[17], M. Miranda[17], G. Laus[18], Y. Rukazenkov[18] & Y.-L. Wu[19*]

[1]Department of Thoracic Head and Neck Medical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, USA; [2]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong, People's Republic of China; [3]Center for Lung Cancer, National Cancer Center, Goyang; [4]Department of Hematology and Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, Meldola, Italy; [6]Department of Hematology and Medical Oncology, Emory University School of Medicine Winship Cancer Institute, Atlanta, USA; [7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Ontario; [9]Department of Medical Oncology and Hematology, The University of Toronto, Ontario; [10]Department of Medicine, BC Cancer Agency, Vancouver, British Columbia, Canada; [11]Department of Respiratory Disease, Daping Hospital, Chongqing, People's Republic of China; [12]Internal Medicine III, Wakayama Medical University Hospital, Wakayama, Japan; [13]Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [14]Department of Oncology, National Cheng Kung University Hospital, Tainan, Taiwan; [15]Department of Medical Oncology, Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia; [16]Department of Medicine, Hematology and Oncology, University Hospital Frankfurt, Frankfurt, Germany; [17]Oncology R&D, AstraZeneca, Cambridge; [18]Global Medicines Development, AstraZeneca, Cambridge, UK; [19]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, People's Republic of China

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Background: In AURA3 (NCT02151981), osimertinib, a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), significantly prolonged progression-free survival and improved response in patients with *EGFR* T790M advanced non-small-cell lung cancer (NSCLC) and progression on prior EGFR-TKI treatment. We report the final AURA3 overall survival (OS) analysis.

Patients and methods: Adult patients were randomized 2 : 1 to osimertinib (80 mg orally, once daily) or pemetrexed plus carboplatin/cisplatin (platinum—pemetrexed) intravenously, every 3 weeks ($\leq$6 cycles). Patients could crossover to osimertinib on progression confirmed by blinded independent central review. OS and safety were secondary end points.

Results: A total of 279 patients were randomly assigned to receive osimertinib and 140 to platinum—pemetrexed (136 received treatment). At data cut-off (DCO; 15 March 2019), 188 patients (67%) receiving osimertinib versus 93 (66%) receiving platinum—pemetrexed had died. The hazard ratio (HR) for OS was 0.87 [95% confidence interval (CI) 0.67—1.12; $P = 0.277$]; the median OS was 26.8 months (95% CI 23.5—31.5) versus 22.5 months (95% CI 20.2—28.8) for osimertinib and platinum—pemetrexed, respectively. The estimated 24- and 36-month survival was 55% versus 43% and 37% versus 30%, respectively. After crossover adjustment, there was an HR of 0.54 (95% CI 0.18—1.6). Time to first subsequent therapy or death showed a clinically meaningful advantage toward osimertinib (HR 0.21, 95% CI 0.16—0.28; $P < 0.001$). At DCO, 99/136 (73%) patients in the platinum—pemetrexed arm had crossed over to osimertinib, 66/99 (67%) of whom had died. The most common adverse events possibly related to study treatment were diarrhea (32%; grade $\geq$3, 1%) and rash (grouped term; 32%; grade $\geq$3, $<$1%) in the osimertinib arm, versus nausea (47%; grade $\geq$3, 3%) in the platinum—pemetrexed arm.

Conclusions: In patients with T790M advanced NSCLC, no statistically significant benefit in OS was observed for osimertinib versus platinum—pemetrexed, which possibly reflects the high crossover rate of patients from platinum—pemetrexed to osimertinib.

Clinical trials number: ClinicalTrials.gov NCT02151981; https://clinicaltrials.gov/ct2/show/NCT02151981.

Key words: AURA3, osimertinib, epidermal growth factor receptor-tyrosine kinase inhibitor, non-small-cell lung cancer, overall survival

*Correspondence to: Prof. Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, 510080, People's Republic of China. Tel: +86-008620-83877855

E-mail: syylwu@live.cn (Y.-L. Wu).

INTRODUCTION

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are standard of care for patients with *EGFR* mutation-positive (*EGFRm*) advanced non-

small-cell lung cancer (NSCLC).[1,2] Despite high response rates to EGFR-TKI therapy, most patients develop resistance, with the *EGFR* T790M mutation detectable in ~50% of patients treated with first-/second-generation EGFR-TKIs.[3,4]

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI-sensitizing and T790M-resistance mutations and has demonstrated efficacy in NSCLC, including central nervous system (CNS) metastases.[5-10] The AURA3 (NCT02151981) phase III trial compared the efficacy and safety of osimertinib versus platinum-based doublet chemotherapy in patients with T790M NSCLC and disease progression on first-line EGFR-TKI therapy.[6] The primary analysis [data cut-off (DCO); 15 April 2016] demonstrated that treatment with osimertinib was associated with superior clinical efficacy versus platinum chemotherapy: investigator-assessed progression-free survival (PFS; primary end point) hazard ratio (HR) 0.30, 95% confidence interval (CI) 0.23—0.41 ($P < 0.001$), and median PFS 10.1 versus 4.4 months, respectively.[6] At the time of reporting the primary analysis, overall survival (OS) data were not mature (15% maturity). Here we report results from the final OS analysis (67% maturity).

METHODS

Patients and trial design

Detailed methodology of the AURA3 trial has been published previously.[6] Briefly, adult patients with centrally confirmed *EGFR* T790M-positive locally advanced/metastatic NSCLC and radiological evidence of progression following treatment with a first-line EGFR-TKI were stratified according to race (Asian versus non-Asian) and randomized 2 : 1 to receive either 80 mg osimertinib orally (once daily) or intravenous pemetrexed 500 mg/m^2 of body surface area plus either carboplatin (target area under the curve, 5) or 75 mg/m^2 cisplatin every 3 weeks for up to six cycles, until investigator-assessed disease progression per RECIST v1.1. All patients were required to provide a blood sample at screening to test for T790M in plasma circulating tumor DNA on the cobas® EGFR Mutation Test v2 (Roche Molecular Systems Inc., Pleasanton, CA). Concordance between tumor and plasma testing has been reported previously.[11]

Patients whose disease had not progressed after four cycles of platinum-based chemotherapy could receive pemetrexed maintenance therapy. Patients who had crossed over to osimertinib were not permitted to continue on pemetrexed monotherapy. Treatment beyond progression was allowed if the investigator deemed the patient to be receiving clinical benefit. According to a protocol amendment (22 December 2014), patients who had been assigned to receive platinum—pemetrexed could crossover to the osimertinib group after objective disease progression (per RECIST v1.1) confirmed by investigator assessment and blinded independent central review.

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 prior to study enrollment. Study protocols were designed by the sponsor and the investigators. The sponsor was responsible for collecting and analyzing data. The authors had full access to all data and are responsible for the accuracy of the data.

Trial end points

The primary end point for AURA3 was PFS (RECIST v1.1), by investigator assessment. OS and safety data are reported here as secondary end points. Subgroup analyses of OS were *post hoc* and in line with the prespecified PFS subgroup analyses, previously reported by Mok et al.[6] These analyses were performed to ensure consistency between subgroups and the overall population, with regard to treatment effect on survival. The DCO reported here is 15 March 2019. Please refer to the primary publication for additional secondary and exploratory end points.[6] RECIST v1.1 events were not collected following the DCO for the primary PFS analysis, and so there were no updates to PFS or other secondary end points.

Trial assessments

All randomized patients were included in the full analysis set, which was used for efficacy analyses. The safety analysis included all patients in the full analysis set who had received at least one dose of study treatment.

OS was defined as the time from the date of randomization until death due to any cause. Assessments for survival were performed every 6 weeks following disease progression and then, following a protocol amendment (21 March 2016), increased to a 12-weekly frequency after the first OS DCO (performed ~4 months after the primary analysis of PFS).

Time to first subsequent therapy (TFST) or death, time to second subsequent therapy (TSST) or death, and adverse events (AEs) are defined in further detail in the supplementary File, available at https://doi.org/10.1016/j.annonc.2020.08.2100.

Statistical analysis

This was a protocol-defined, preplanned final OS analysis to be performed when OS data reached ~70% maturity (287 death events). To provide strong control of the type I error rate (5% two sided), PFS, objective response rate, and OS were tested in sequential order. If any previous analysis in the sequence was not statistically significant, the alpha spending was not transferred to subsequent analyses. Previous OS analyses were immature and have not been reported; the ~70% maturity reported herein represents the

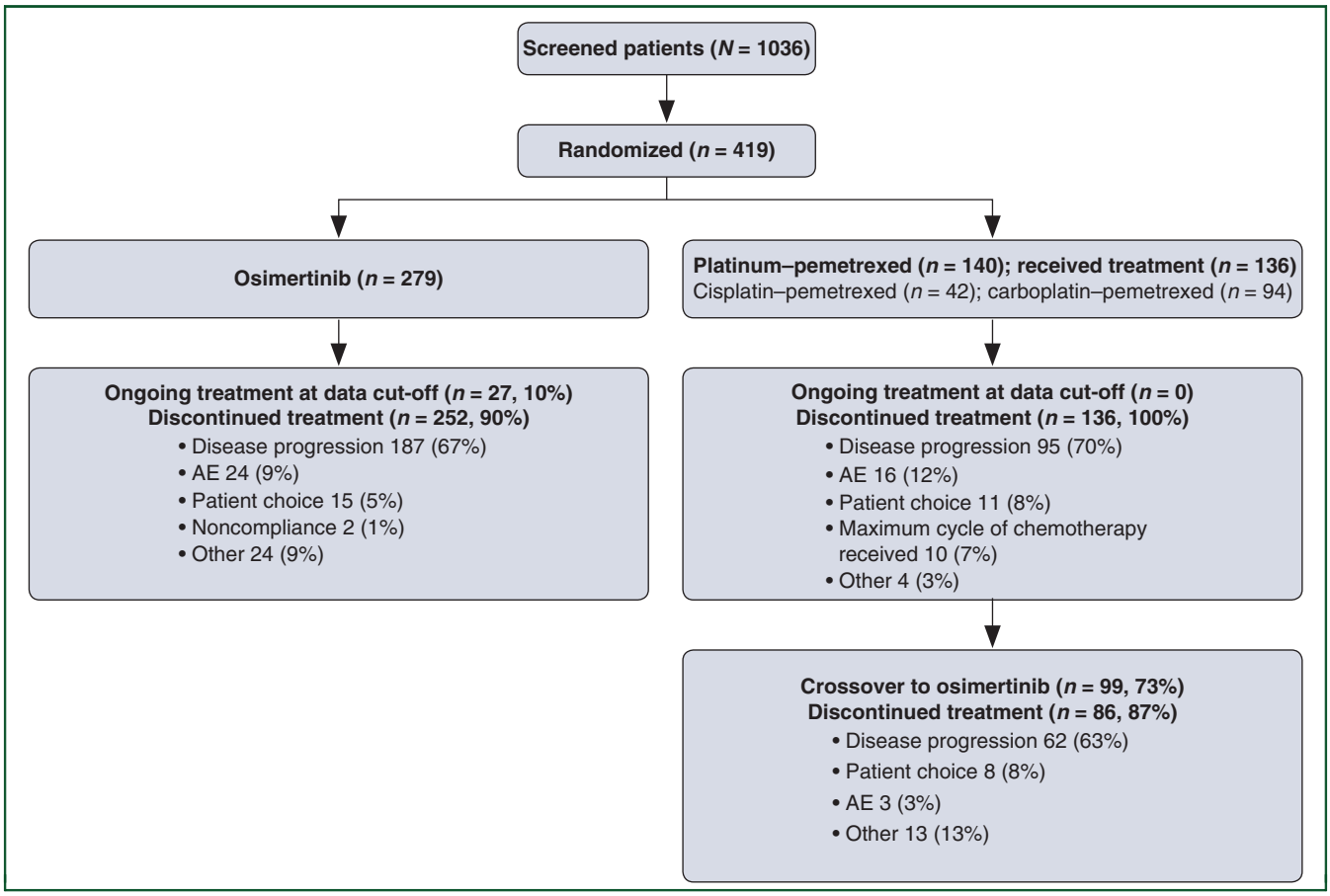

Figure 1. Patient disposition.
For patients who discontinued treatment and crossed over to osimertinib, percentages are calculated based on the crossover population ($n = 99$). For the osimertinib and platinum—pemetrexed arms, percentages are calculated based on the overall populations for those respective arms ($n = 279$ and $n = 136$).
AE, adverse event.

first published OS data from AURA3. Refer to the supplementary File, available at https://doi.org/10.1016/j.annonc.2020.08.2100 for more details.

A rank preserving structural failure time model (RPSFTM) exploratory analysis was performed to adjust for treatment switching and to estimate a relative OS effect of osimertinib treatment compared with platinum—pemetrexed treatment. For further details on RPSFTM methodology and assumptions made in this model, please refer to the supplementary File, available at https://doi.org/10.1016/j.annonc.2020.08.2100.

RESULTS

Demographics and treatment

At the final DCO, 415 patients had received one or more doses of study treatment (osimertinib, 279; platinum—pemetrexed, 136; Figure 1); 99 patients (73%) treated with platinum—pemetrexed crossed over to receive osimertinib (Figure 1). As previously reported, patient demographics and baseline characteristics were balanced between arms and reflective of the patient population. Demographics were broadly consistent with the total population for those patients who crossed over from platinum—pemetrexed to osimertinib (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.08.2100).

The median duration of total treatment exposure in the osimertinib arm was 13.8 months (range 0.2-52.2) and 4.3 months (range 0.4-38.8) in the platinum—pemetrexed arm. The median duration of treatment exposure to osimertinib in patients who crossed over was 11.0 months (range 0.1-44.0). At the final DCO, 27 patients (10%) in the osimertinib arm remained on treatment, whereas all patients in the platinum—pemetrexed arm had discontinued treatment. Of the 99 patients who received crossover osimertinib, 13 patients (13%) remained on treatment.

At the time of OS final analysis, 188 patients (67%) in the osimertinib arm had died compared with 93 patients (66%) in the platinum—pemetrexed arm, including 66 (67%) of 99 patients who crossed over; 58 (21%) and 27 (19%) patients were still in survival follow-up, respectively. The remaining patients had terminated study prior to death; the most common reason was voluntary discontinuation [osimertinib, 23 (8%); platinum—pemetrexed, 16 (11%)]. Other reasons included lost to follow-up [osimertinib, seven (3%), platinum—pemetrexed, one (1%)] and other [osimertinib, three (1%); platinum—pemetrexed three (2%)]. Median follow-up for OS was 23.5 months in the osimertinib arm versus 20.3 months in the platinum—pemetrexed arm.

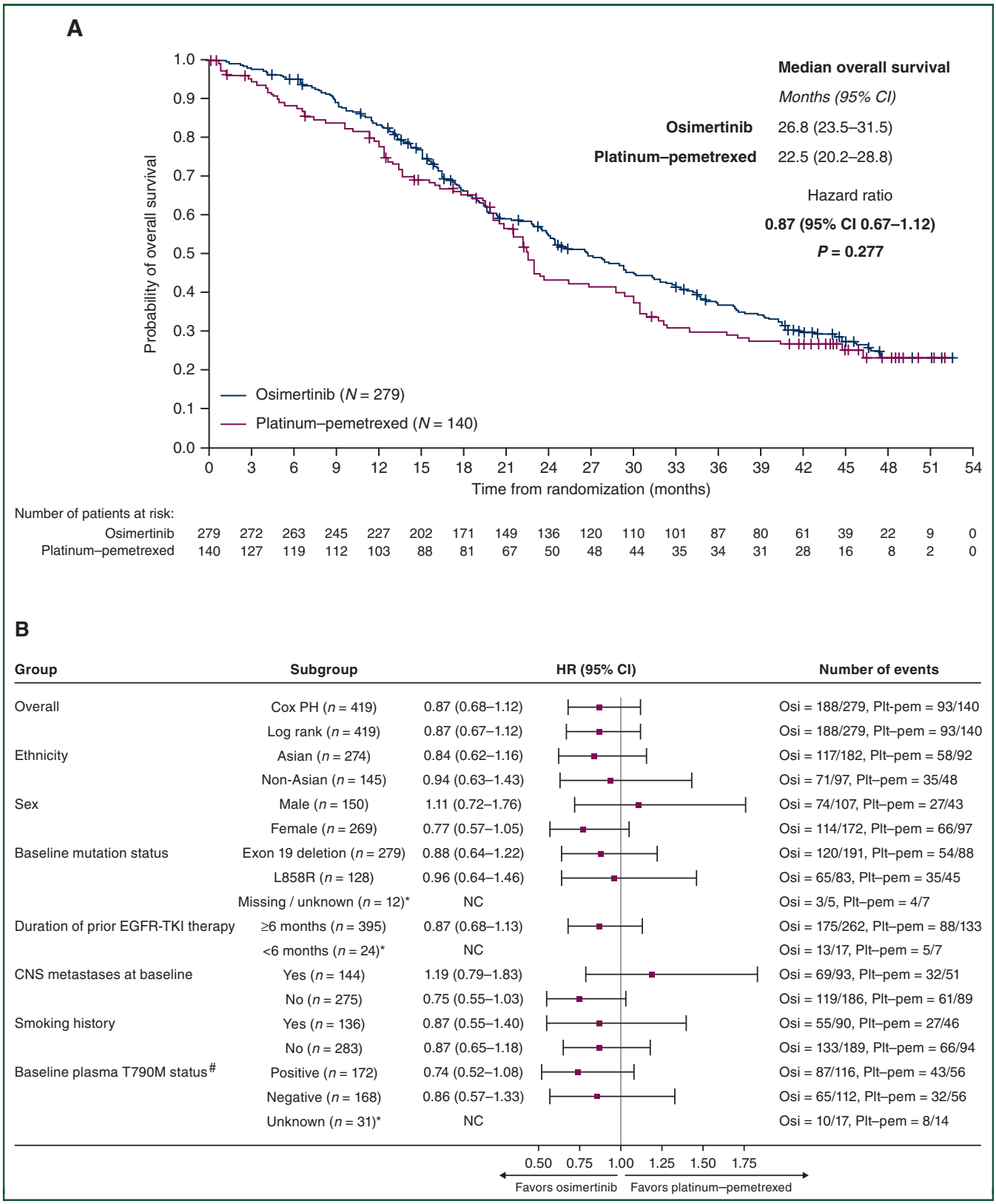

Figure 2. Overall survival in patients treated with osimertinib versus platinum—pemetrexed.

(A) Kaplan—Meier curve for overall survival in patients treated with osimertinib versus platinum—pemetrexed (full analysis set). Patients not known to have died at the time of analysis are censored at the last recorded date that the patient was known to be alive. Crosses represent censored observations. (B) Subgroup analysis of overall survival. Data cut-off: 15 March 2019. Each subgroup analysis was performed using a single Cox PH containing the treatment, the subgroup covariate of interest, and the treatment by subgroup interaction, and using the Efron approach for handling ties. The CI was calculated using a profile likelihood approach. The statistical analysis was performed using a log-rank test stratified by ethnicity. * If there were <20 events in at least one treatment of a subgroup, then the analysis was not performed. # Baseline plasma T790M mutation status subgroup analysis is performed on the full analysis set population, excluding patients enrolled in China.

CI, confidence interval; CNS, central nervous system; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; NC, not calculated; Osi, osimertinib; PH, proportional hazards model; Plt—pem, platinum—pemetrexed.

Efficacy

The HR for OS was 0.87 (95% CI 0.67—1.12; 95.564% CI 0.67—1.13; $P = 0.277$), with a median OS of 26.8 months (95% CI 23.5—31.5) in the osimertinib arm and 22.5 months (95% CI 20.2—28.8) in the platinum—pemetrexed arm (Figure 2A). The estimated survival rates at 12, 24, and 36 months in the osimertinib arm were 83%, 55%, and 37%, respectively, and 78%, 43%, and 30%, respectively, in the platinum—pemetrexed arm. OS subgroup analyses showed similar results with the exception of the subgroups of male patients and patients with CNS metastases at baseline, where a nonsignificant higher risk of death in the osimertinib arm was observed (Figure 2B). A numerically longer median OS for osimertinib was observed in patients with negative baseline plasma T790M status compared with patients with positive baseline plasma T790M status: 34.9 months (95% CI 25.4—44.3) and 23.9 months (95% CI 18.7—29.4), respectively (supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.08.2100).

An exploratory analysis of OS adjusted for crossover (RPSFTM on treatment method) showed an HR of 0.54 (95% CI 0.18—1.60; supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.08.2100). Median OS in the platinum—pemetrexed arm, adjusting for the effect of crossover, was 15.9 months (95% CI 13.4—19.1) versus 26.8 months (95% CI 23.5—31.5) in the osimertinib arm.

At the time of first subsequent treatment, platinum chemotherapy and pemetrexed were the most commonly received anticancer therapies in patients randomized to osimertinib [108 (65%) and 109 (66%) of 165 patients receiving first subsequent therapy, respectively] (Table 1), compared with EGFR inhibitor [111 (97%) of 114 patients] in the platinum—pemetrexed arm, the majority of which was osimertinib crossover [98 (86%) of 114 patients]. For details on any line of subsequent treatment, and subsequent treatment by region, please refer to supplementary Tables S3 and S4, available at https://doi.org/10.1016/j.annonc.2020.08.2100.

For TFST or death, 230 (82%) versus 128 (91%) of patients had events in the osimertinib and platinum—pemetrexed arms, respectively; median TFST was 16.0 months (95% CI 13.8—18.4) and 6.0 months (95% CI 5.2—6.9), respectively (HR 0.21; 95% CI 0.16—0.28; $P < 0.001$; Figure 3A). For TSST or death, 214 (77%) versus 105 (75%) patients had events in the osimertinib and platinum—pemetrexed arms, respectively (HR 0.87; 95% CI 0.69—1.11; $P = 0.263$; Figure 3B), with a median TSST of 20.0 months (95% CI 17.2—23.2) and 19.0 months (95% CI 16.5—22.0), respectively.

Table 1. Post-treatment anticancer therapies at the time of first subsequent therapy[a]

Therapy	Osimertinib ($n = 165$), n (%)	Platinum—pemetrexed ($n = 114$), n (%)	Total ($n = 279$), n (%)
EGFR inhibitor	24 (15)	111 (97)	135 (48)
Osimertinib crossover	0 (0)	98 (86)[b]	98 (35)[b]
EGFR protein kinase inhibitors (other than osimertinib)	18 (11)	9 (8)	27 (10)
Pemetrexed	109 (66)	2 (2)	111 (40)
Cytotoxic chemotherapy platinum compounds	108 (65)	1 (1)	109 (39)
Cytotoxic chemotherapy taxanes	14 (8)	1 (1)	15 (5)
Antibody against VEGF	14 (8)	0 (0)	14 (5)
Cytotoxic chemotherapy podophyllotoxin derivative	5 (3)	0 (0)	5 (2)
MET inhibitor	5 (3)	0 (0)	5 (2)
Cytotoxic chemotherapy (vinca alkaloids and analogs)	3 (2)	0 (0)	3 (1)
Radiotherapy	1 (1)	1 (1)	2 (1)
MEK inhibitor	2 (1)	0 (0)	2 (1)
Unknown	2 (1)	0 (0)	2 (1)
Antibody against PD-1	2 (1)	0 (0)	2 (1)
Antibody against EGFR	1 (1)	0 (0)	1 (<1)
Antibody against HER2	1 (1)	0 (0)	1 (<1)
Cytotoxic chemotherapy	1 (1)	0 (0)	1 (<1)

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase; MET, hepatocyte growth factor receptor; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor.

[a] Patients may have received more than one subsequent anticancer therapy.

[b] 98 patients rather than 99 patients were reported as having osimertinib crossover as one patient had a >21-day interruption between chemotherapy cycles and was therefore classified as having discontinued chemotherapy as per protocol; however, the patient received one further cycle of chemotherapy before crossing over to osimertinib after disease progression and was classified as having received a first subsequent therapy after discontinuation of platinum-based chemotherapy.

Safety

The safety profile of osimertinib was consistent with the primary analysis, with no new safety signals. For proportion of AEs reported in both arms, please refer to supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2020.08.2100. AEs considered by the investigator as possibly related to study treatment were observed in 237 patients (85%) in the osimertinib arm and 121 (89%) in the platinum—pemetrexed arm. Fewer patients in the osimertinib arm reported grade ≥3 AEs possibly related to study treatment (24 [9%]), versus those in the platinum—pemetrexed arm (46 [34%]). In patients who crossed over from platinum—pemetrexed to osimertinib, 75 (76%) of 99 reported an AE possibly related to osimertinib, with nine (9%) of these being grade ≥3. The rate of discontinuations of osimertinib versus platinum—pemetrexed due to possibly related AEs was 14 (5%) versus 12 (9%), respectively, and one (1%) in patients who crossed over from platinum—pemetrexed to osimertinib.

The most common (possibly treatment-related) AEs reported in the osimertinib arm were diarrhea and rash and acnes [grouped term; 89 (32%) and 88 (32%) patients, respectively], compared with nausea and decreased appetite [64 (47%) and 43 (32%) patients, respectively], in the platinum—pemetrexed arm (supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.08.2100). All-cause AEs are summarized in supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.08.2100. In the osimertinib arm, interstitial lung disease (ILD) and pneumonitis AEs were reported in five patients (2%) and eight patients (3%), respectively; four (1%) and seven (2%) AEs were considered by the investigator as possibly related to treatment. All cases of ILD and

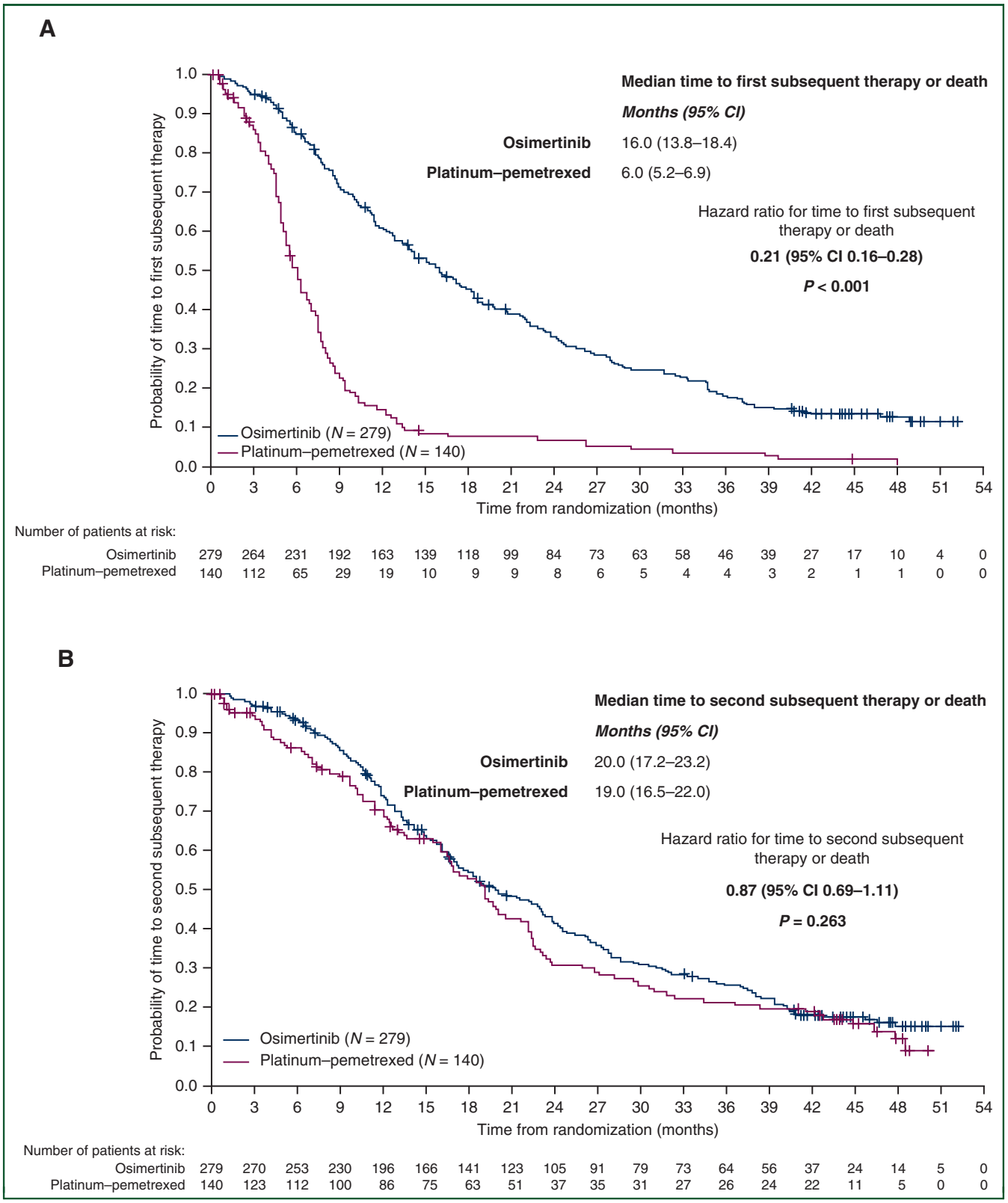

Figure 3. Time to subsequent therapies or death.
Crosses represent censored observations. (A) Time to first subsequent therapy* or death. * One patient in the osimertinib 80-mg arm and another patient in the platinum—pemetrexed arm received radiotherapy at the time to first subsequent therapy date. (B) Time to second subsequent therapy# or death. # One patient in the osimertinib 80-mg arm received radiotherapy at the time to second subsequent therapy date.
CI, confidence interval.

pneumonitis were grade 1 or 2 in severity, apart from two (1%) reports of grade 5 pneumonitis, deemed possibly related to treatment. In the platinum—pemetrexed arm, there was one (1%) ILD AE of grade 1 and one (1%) pneumonitis AE of grade 3; both were deemed possibly related to treatment.

AEs leading to death occurred in 12 patients (4%) in the osimertinib arm and two (1%) in the platinum—pemetrexed arm, prior to crossover. In addition, five of 99 (5%) patients who crossed over from platinum—pemetrexed to osimertinib subsequently reported an AE that led to death. In the osimertinib arm, two deaths (1%, both pneumonitis) were deemed possibly related to treatment. In addition, one of the deaths in patients who crossed over to osimertinib (1%; respiratory failure) was deemed possibly related to treatment. Both of the AEs leading to death in the platinum—pemetrexed arm (1%) prior to crossover were deemed possibly related to treatment.

DISCUSSION

We report mature OS data from the AURA3 phase III study in patients with T790M NSCLC after one line of EGFR-TKI treatment. The PFS benefit previously seen with osimertinib versus platinum—pemetrexed in AURA3 did not result in a statistically significant improvement in OS with an HR of 0.87 (95% CI 0.67—1.12; $P = 0.277$) and median OS of 26.8 months for osimertinib versus 22.5 months for platinum—pemetrexed. The lack of survival benefit is possibly due to the high proportion of patients (73%) who crossed over from the platinum—pemetrexed arm to receive osimertinib. An exploratory RPSFTM analysis adjusting for crossover demonstrated an HR of 0.54 (95% CI 0.18—1.60). Among patients receiving subsequent anticancer therapy in the osimertinib arm, platinum-based chemotherapy was most common (65% of first subsequent treatments). In patients who have not already received chemotherapy for advanced disease (i.e. AURA3 osimertinib patients), platinum—pemetrexed would be considered a standard of care. Delaying platinum-based chemotherapy to later line could impede a patient's ability to receive such treatment, as overall performance status decreases.

Confounded OS analyses due to substantial levels of crossover have been reported in phase III studies of first-line first- and second-generation EGFR-TKI versus chemotherapy in *EGFRm* NSCLC,[12—15] although a pooled analysis of phase III trials of afatinib versus chemotherapy noted an OS benefit in patients with tumors harboring *EGFR* exon 19 deletions.[16] More recently, the FLAURA phase III trial of first-line osimertinib versus comparator EGFR-TKI showed a statistically significant improvement in survival (HR 0.80, 95.05% CI 0.64—1.00; $P = 0.046$), despite 31% (85 of 277) of patients crossing over to osimertinib.[10]

The median OS with osimertinib reported here (26.8 months) is in line with the pooled AURAext/AURA2 dataset (26.8 months), supporting the consistent efficacy profile observed with osimertinib.[17] The median OS with osimertinib is also impressive when placed into the context of first- and second-generation EGFR-TKIs in the first-line setting for *EGFRm* NSCLC, where a similar length of median OS was observed.[12-15,18] It is notable that patients in the platinum—pemetrexed arm achieved a median OS of 22.5 months, which is consistent with previous reports in chemotherapy arms in first-line *EGFRm* NSCLC randomized studies that allowed for crossover.[12-15]

Contrary to the other subgroups reported, male patients and those with CNS metastases at baseline showed nonsignificant OS HRs favoring platinum—pemetrexed; however, the 95% CIs were wide and overlapped with the female and no CNS metastases groups at baseline, respectively, suggesting that there was no difference in OS between the subgroups. Furthermore, previous investigation into the efficacy of osimertinib versus platinum—pemetrexed in patients with CNS metastases has demonstrated higher CNS objective response rate and longer CNS PFS with osimertinib.[8]

Consistent with the PFS analysis by T790M plasma status,[11] osimertinib was associated with a numerically longer OS in patients with negative baseline plasma T790M compared with patients with positive baseline plasma T790M. In a previous analysis from AURA3, plasma T790M detection was associated with a larger median baseline tumor size and the presence of extrathoracic disease (58% for M1b positive versus 39% for M0-1a positive; $P = 0.002$). This is in line with previous findings that circulating tumor DNA shedding correlates with tumor burden,[19] and a lack of detectable circulating tumor DNA following treatment with EGFR-TKIs correlates with a better overall prognosis.

Patients in the osimertinib arm reported fewer grade $\geq$3 AEs possibly related to study treatment compared with platinum—pemetrexed, despite patients in the osimertinib arm having a longer duration of total treatment exposure. Seven patients in the osimertinib arm and one patient in the platinum—pemetrexed arm had an AE of possibly treatment-related pneumonitis. Reassuringly, no new safety signals were reported by patients receiving osimertinib as crossover treatment.

The clinical implications of these results should be considered in light of data from the FLAURA trial, which demonstrated a statistically significant and clinically relevant OS benefit for first-line osimertinib versus comparator EGFR-TKIs in patients with *EGFRm* advanced NSCLC.[10] The median OS with first-line osimertinib (38.6 months) is broadly comparable to the cumulative outcome expected with first-line first- or second-generation EGFR-TKIs (median PFS 9.2-14.7 months) in global, randomized controlled trials,[10,20-22] plus second-line osimertinib median OS from AURA3 (26.8 months). However, in global randomized controlled trials of first-line EGFR-TKIs, up to 50%[10,18,23,24] of patients who discontinued EGFR-TKI did not receive a subsequent anticancer treatment, a finding supported by real-world evidence studies (36%-40%).[25,26] Furthermore, approximately 50% of patients following first- or second-generation EGFR-TKIs harbor T790M,[3,4] further diminishing the second-line patient population eligible to receive osimertinib. Presently, there is no way to confidently predict which patients who start first-

or second-generation EGFR-TKIs will progress with T790M disease. In view of this, and the clinical benefit reported from FLAURA, using osimertinib as first-line treatment, provides more patients the opportunity to receive the associated OS benefit of osimertinib versus comparator first-line EGFR-TKI.

In conclusion, no statistically significant benefit in OS was observed for osimertinib versus platinum—pemetrexed in AURA3, possibly reflecting the high crossover rate of patients from the platinum—pemetrexed arm to receive osimertinib. The continued tolerable safety profile reported here for osimertinib, together with superior PFS,[6] improved patient quality of life, and longer time to symptom deterioration, versus platinum—pemetrexed,[27] reinforces osimertinib as standard-of-care second-line treatment for patients with T790M advanced NSCLC and disease progression on a prior EGFR-TKI.

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DISCLOSURES

VAP has declared honorarium from F Hoffman-La Roche; advisory or consultancy fees from Nektar Therapeutics, Astra Zeneca Pharmaceuticals, Arrys Therapeutics, Merck & Co, LOXO Oncology, Araxes Pharma, F. Hoffman—LaRoche Ltd, Janssen Research Foundation, Bristol-Myers Squibb, Clovis Oncology, Eli Lilly & Co, Novartis Pharmaceuticals Corp., Takeda Pharmaceuticals, AbbVie, TRM Oncology, Tesaro, Exelixis, Gritstone, Leeds Biolabs, IDEAYA, Bolt Therapeutics, and G2 Innovation; and research funding from Eli Lilly & Co, Novartis, Merck, Astra Zeneca Pharmaceuticals, F Hoffman-La Roche, Nektar Therapeutics, Janssen, Bristol-Myers Squibb, Checkmate, and Incyte. TSM has declared honoraria from ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Blueprint Medicines Corporation, Bristol-Myers Squibb, Celgene, CStone Pharmaceuticals, Eli Lilly, Fishawack Facilitate, Hengrui Therapeutics, Ignyta, Incyte Corporation, InMed Medical Communication, IQVIA, Janssen, Loxo Oncology, Merck Serono, MSD, MORE Health, Novartis, OncoGenex Pharmaceuticals, OrigiMed, PeerVoice, Pfizer, PrIME Oncology, Roche/Genentech, Sanofi-Aventis R&D, SFJ Pharmaceutical, Takeda Pharmaceuticals HK, Vertex Pharmaceuticals, and Yuhan Corporation; advisory or consultancy fees from ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Blueprint Medicines Corporation, Bristol-Myers Squibb, Celgene, Cirina, CStone Pharmaceuticals, Eli Lilly, Fishawack Facilitate, GeneDecode, Hengrui Therapeutics, Ignyta, Incyte Corporation, InMed Medical Communication, IQVIA, Janssen, Loxo-Oncology, Merck Serono, MSD, MORE Health, Novartis, OncoGenex Pharmaceuticals, OrigiMed, PeerVoice, Pfizer, PrIME Oncology, Roche/Genentech, Sanofi-Aventis R&D, SFJ Pharmaceutical, Takeda Pharmaceuticals HK, Vertex Pharmaceuticals, and Yuhan Corporation; leadership roles for AstraZeneca and Hutchison Chi-Med; research funding from AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, MSD, Novartis, Pfizer, Roche, SFJ, and Xcovery; shareholdings in Hutchison Chi-Med, and Sanomics; stock options in Clearbridge BioMedics (now Biolidics), Loxo-Oncology, OrigiMed, and Virtus Medical Group; and officer or director for AstraZeneca, Hutchison Chi-Med (remunerated), American Society of Clinical Oncology (ASCO), Asian Thoracic Oncology Research Group (ATORG), Chinese Lung Cancer Research Foundation Limited (CLCRF), Chinese Society of Clinical Oncology (CSCO), Hong Kong Cancer Fund (HKCF), Hong Kong Cancer Therapy Society (HKCTS), and International Association for the Study of Lung Cancer (IASLC; term ended on 30/4/19 [non-remunerated]). J-YH has declared honoraria from Roche, AstraZeneca, Bristol-Myers Squibb, MSD, and Takeda; advisory or consultancy fees from AstraZeneca, Bristol-Myers Squibb, MSD, Takeda, Pfizer, Novartis, and Lilly; research funding from Roche, Pfizer, Ono Pharmaceutical, and Takeda. M-JA has declared advisory or consultancy fees from AstraZeneca, MSD, Ono Pharmaceutical, and Lilly; and speaker fees from AstraZeneca, MSD, Ono Pharmaceutical, Lilly, Roche, Alpha Pharmaceutical, and Takeda. SSR has declared honoraria from AstraZeneca, Amgen, Bristol-Myers Squibb, Merck, Roche/Genentech, Loxo, Nektar, and Tesaro; advisory or consultancy fees from AstraZeneca, Amgen, Bristol-Myers Squibb, Merck, Roche/Genentech, Loxo, Nektar, and Tesaro; and research funding from AstraZeneca, Amgen, Bristol-Myers Squibb, Merck, Tesaro, Advaxis, and Takeda. SWK has declared advisory or consultancy fees from AstraZeneca; and research funding from AstraZeneca. FAS has declared advisory or consultancy fees from AstraZeneca; research funding from AstraZeneca; and shareholdings in AstraZeneca. JL has declared honoraria from Roche, AstraZeneca, and Pfizer; and research funding from Roche, Boehringer Ingelheim, Pfizer, and AstraZeneca. HA has declared honoraria from AstraZeneca, Chugai, Pfizer, and Boehringer Ingelheim; and advisory or consultancy fees from AstraZeneca and Pfizer. W-CS has declared travel, accommodation, or expenses from Bristol-Myers Squibb and Boehringer Ingelheim. TJ has declared advisory or consultancy fees from Roche, Bristol-Myers Squibb, Merck, Ignyta, AstraZeneca, Takeda, Boehringer Ingelheim, and Pfizer. MS has declared honoraria from AstraZeneca, Pfizer, Roche, Boehringer Ingelheim, Novartis, Celgene, Takeda, Lilly, Bristol-Myers Squibb, and MSD; advisory or consultancy fees from AstraZeneca, Pfizer, Roche, Boehringer Ingelheim,

Novartis, Celgene, Takeda, Lilly, Bristol-Myers Squibb, and MSD; and speaker fees from AstraZeneca, Pfizer, Roche, Boehringer Ingelheim, Novartis, Celgene, Takeda, Lilly, Bristol-Myers Squibb, and MSD. Y-LW has declared honoraria from AstraZeneca, Roche, Eli Lilly, Pfizer, MSD, Bristol-Myers Squibb, and Boehringer Ingelheim; advisory or consultancy fees from AstraZeneca and Roche; and research funding from AstraZeneca and Roche. HM, MM, GL, and YR are employees of and have shareholdings in AstraZeneca. AD, YH, and WSMET have declared no conflicts of interest.

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