Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial

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ABSTRACT

Purpose: In the phase III ADAURA trial, adjuvant treatment with osimertinib versus placebo, with/without prior adjuvant chemotherapy, resulted in a statistically significant and clinically meaningful disease-free survival benefit in completely resected stage IB–IIIA EGFR-mutated (*EGFR*m) non–small cell lung cancer (NSCLC). We report health-related quality of life (HRQoL) outcomes from ADAURA.

Patients and Methods: Patients randomized 1:1 received oral osimertinib 80 mg or placebo for 3 years or until recurrence/discontinuation. HRQoL (secondary endpoint) was measured using the Short Form-36 (SF-36) health survey at baseline, 12, and 24 weeks, then every 24 weeks until recurrence or treatment completion/discontinuation. Exploratory analyses of SF-36 score changes from baseline until week 96 and time to deterioration (TTD) were performed in the overall population (stage IB–IIIA; $N = 682$). Clinically meaningful changes were defined using the SF-36 manual.

Results: Baseline physical/mental component summary (PCS/MCS) scores were comparable between osimertinib and placebo (range, 46–47) and maintained to Week 96, with no clinically meaningful differences between arms; difference in adjusted least squares (LS) mean [95% confidence intervals (CI), −1.18 (−2.02 to −0.34) and −1.34 (−2.40 to −0.28), for PCS and MCS, respectively. There were no differences between arms for TTD of PCS and MCS; HR, 1.17 (95% CI, 0.82–1.67) and HR, 0.98 (95% CI, 0.70–1.39), respectively.

Conclusions: HRQoL was maintained with adjuvant osimertinib in patients with stage IB–IIIA *EGFR*m NSCLC, who were disease-free after complete resection, with no clinically meaningful differences versus placebo, further supporting adjuvant osimertinib as a new treatment in this setting.

See related commentary by Patil and Bunn, p. 2204

Introduction

For patients with NSCLC, approximately 30% will present with resectable disease, for which the primary treatment is surgery with curative intent (1–4). For patients with stage II–IIIA NSCLC, and select patients with stage IB disease, adjuvant cisplatin-based chemotherapy is recommended (4).

However, clinical outcomes remain poor across disease stages. A pooled analysis of data from patients with resected stage I–III NSCLC receiving adjuvant chemotherapy showed rates of disease

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Translational Relevance

In the phase III ADAURA trial, health-related quality of life (HRQoL), as assessed by the Short Form-36 (SF-36) health survey, was maintained during adjuvant osimertinib treatment, with or without prior adjuvant chemotherapy, in patients with completely resected stage IB–IIIA EGFR-mutated non–small cell lung cancer (NSCLC). No clinically meaningful differences with adjuvant osimertinib versus placebo were observed for the SF-36 component summaries or health domains. In addition to improving efficacy outcomes, a key goal of adjuvant treatment is to also maintain HRQoL as patients will be disease-free after surgery and may receive long-term treatment. Together with the previously reported significant disease-free survival (DFS) benefit with adjuvant osimertinib versus placebo and favorable safety profile of osimertinib, these HRQoL data provide further support for the use of adjuvant osimertinib as a new treatment strategy in this patient population.

recurrence following surgery ranging from 45% for stage IB to 76% for stage III disease, irrespective of postoperative chemotherapy use. The analysis also reported an overall HR for overall survival (OS) of 0.89 [95% confidence interval (CI), 0.82–0.96], corresponding to a 5-year absolute benefit of 5.4% with chemotherapy versus no chemotherapy, after a median follow-up time of 5.2 years (5).

In the advanced NSCLC setting, EGFR-tyrosine kinase inhibitors (EGFR-TKI) are standard of care in patients with *EGFR* mutations (refs. 6, 7; *EGFR*m). Osimertinib, a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits EGFR-TKI sensitizing and *EGFR* T790M resistance mutations with proven efficacy in central nervous system metastases (8–12), is now considered the preferred first-line option for patients with *EGFR*m advanced NSCLC (6, 7). Because of this benefit in the advanced setting, adjuvant osimertinib was assessed in patients with resectable stage IB–IIIA *EGFR*m NSCLC in the phase III ADAURA trial and demonstrated a highly statistically significant and clinically meaningful improvement in DFS versus placebo (HR, 0.20; 99.12% CI, 0.14–0.30; $P < 0.001$; ref. 13). The data also demonstrated a safety profile consistent with that known for osimertinib, with a low frequency of dose modifications and discontinuations and no new safety signals reported (13), with or without chemotherapy (14). Subsequently, osimertinib has been approved in the US, China, the EU, the UK, and multiple countries worldwide, for use as an adjuvant treatment in patients with resectable *EGFR*m (Ex19Del/L858R) NSCLC (15–18).

As established in other adjuvant cancer settings, the effect of adjuvant treatment on HRQoL is an important clinical consideration for patients who, following surgery with curative intent, are disease-free and require long-term treatment to reduce the risk of disease recurrence (4, 19–22). The goal of treatment in the adjuvant setting is therefore to improve efficacy outcomes while also maintaining HRQoL (19). However, in the adjuvant NSCLC setting, HRQoL data are limited, and comprise of two studies showing a transient, modest worsening or no impact on HRQoL with different chemotherapy regimens in patients with resected stage IB–III NSCLC (23, 24), and one study reporting significantly improved HRQoL with the EGFR-TKI gefitinib versus chemotherapy in patients with resected stage II–IIIA *EGFR*m NSCLC (25), although comparison between studies is limited because of the application of different QoL instruments and treatments evaluated.

Here, we report HRQoL outcomes from ADAURA, which is the first global, randomized, phase III trial in the adjuvant, resected *EGFR*m NSCLC setting to evaluate HRQoL with an EGFR-TKI versus placebo, with or without prior adjuvant chemotherapy (13, 26–28).

Patients and Methods

Patients, trial design, and treatment

Details of the ADAURA trial design (NCT02511106) have been previously published (13, 29). Briefly, the phase III double-blind, randomized, placebo-controlled, global ADAURA trial enrolled adult patients (≥18 years; ≥20 years in Japan and Taiwan) with histologically confirmed primary non-squamous NSCLC of post-surgical pathological stage IB, II, or IIIA [American Joint Committee on Cancer (AJCC) 7th edition; ref. 30], central confirmation of *EGFR* mutation [exon 19 deletions (Ex19Del) or exon 21 codon p.Leu858Arg (L858R) point mutations], and a World Health Organization performance status of 0 or 1. Complete surgical resection of the primary NSCLC (with negative margins) was required, and postoperative adjuvant chemotherapy before randomization was allowed, but not mandatory, per physician and patient choice. Patients were stratified according to disease stage (IB, II, or IIIA), *EGFR* mutational status (Ex19Del or L858R), and race (Asian or non-Asian), and randomized 1:1 to oral osimertinib 80 mg once daily or placebo following complete resection and adjuvant chemotherapy, if indicated. Treatment continued for 3 years or until disease recurrence or other discontinuation criteria were fulfilled.

The primary endpoint was investigator-assessed DFS in patients with stage II–IIIA disease and secondary endpoints included DFS in the overall population (stage IB–IIIA disease), OS, HRQoL, and safety. An interim analysis of the primary and key secondary endpoints has been reported previously (13). The data cutoff value (DCO) for the previously reported primary analysis and this HRQoL analysis was January 17, 2020.

The study was approved by the institutional review board or independent ethics committee associated with each study center. The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference for Harmonization), applicable regulatory requirements, and policy of the trial sponsor, AstraZeneca, on bioethics and human biologic samples. All patients provided written informed consent.

HRQoL endpoints and data collection

HRQoL was assessed using the SF-36 health survey version 2 (31), which measures a patient's general health status with a recall period of 4 weeks. The SF-36 collects scores from 36 items across eight health domains [Physical Functioning (PF), Role Limitations–Physical (RP), Vitality (VT), General Health Perceptions (GH), Bodily Pain (BP), Social Function (SF), Role Limitations- Emotional (RE), and Mental Health (MH)] and produces two weighted aggregate scores, the physical component summary (PCS) and the mental component summary (MCS). All eight health domains contribute to the PCS and MCS, but the PF, RP, BP, and GH domains contribute most strongly to the PCS, and the VT, SF, RE, and MH domains contribute most strongly to the MCS. SF-36 data were collected at randomization (predose), weeks 12 and 24 after randomization, and then every 24 weeks until disease recurrence, treatment completion (at 3 years), or treatment discontinuation, whichever occurred first. At treatment discontinuation due to disease recurrence or other discontinuation criteria, HRQoL data were collected at the treatment discontinuation visit; however, no further HRQoL data were collected afterwards. To

minimize bias, SF-36 surveys were completed before any investigations or discussions with the clinical staff or physicians on the day of the patient visit, so patients would not have been aware of any changes in their disease status, such as disease progression, before completing the survey.

SF-36 scores were calculated as follows, using a norm-based scoring method. Briefly, 0–100 scores for each of the health domain scales and component summary measures (PCS and MCS) were transformed to T-scores using standard score formulas based on the 2009 US general population's mean values (normative mean): The mean T-score in the 2009 US population is 50, with an SD of 10 (31). Higher T–scores indicate better health (31). T-scores above and below 50 are above and below the average, respectively, of the 2009 US population. With the SD being 10, each 1-point change in T-scores is interpreted as one-tenth of an SD and has an effect size of 0.1 (31). Missing responses in the SF-36 health survey were imputed using the SF-36 Full Missing Score Estimation procedure, which uses a combination of the respondent's available health domain scale and component summary measure scores (31).

The Full Missing Score Estimation procedure was used for imputing missing responses in the SF-36 health survey (31). A given health domain score [except for physical functioning (PF)] can be estimated when the patient provides a response to at least one item in that scale and regression methods are used to estimate component summary measure scores based on the available scales (31). The model assumes that the missing item response(s) in one scale are the same as the response to the scale's single answered item, or the average of all responses, if more than one item has been answered (31). For the PF scale, which comprises items that vary greatly in difficulty across the scale, estimates of missing values were obtained using the item response theory (IRT) method. At least one item within the scale needs to be answered to be able to compute the scale's score. An IRT model generates values that indicate the probability of a respondent selecting a specific response to a given item, based on their responses to previously answered items in the PF scale (31).

The PCS and MCS scores were estimated for a patient who had data for at least seven of the eight health domain scales and was not missing the following required scale scores: PF for calculation of the PCS score and MH for calculation of the MCS score. If a patient had a fully completed MCS (with no domain scales missing from the calculation), then the PCS score was also calculated completely with no missing domains and vice versa, because all eight health domain scales contribute to the scoring of both MCS and PCS with different weighting. If the MCS score was calculated (and it was missing the PF domain only), then the PCS score was not calculated. Vice versa, if the PCS score was calculated (and it was missing the MH domain only), then the MCS score was not calculated. Among 682 randomized patients, only one patient had MCS score but missing PCS score (due to missing PF domain score) at the Week 156 visit.

Both pre-specified and exploratory analyses of HRQoL were conducted. The pre-specified, per-protocol HRQoL analyses included a time to deterioration (TTD) analysis of the SF-36 PCS and MCS in patients with stage II–IIIA disease, using values for clinically meaningful differences defined in the 2nd edition of the SF-36 scoring manual (32).

The exploratory, *post hoc* HRQoL analyses included a mixed model of repeated measures (MMRM) of change from baseline up to Week 96 in SF-36 PCS, MCS, and health domain scores, and a TTD analysis of the SF-36 PCS, MCS, and health domain scores. Both MMRM and TTD analyses were conducted in the overall population (stage IB–IIIA disease) using clinically meaningful differences assigned on the basis of the values defined in the most recent 3rd edition of the SF-36 scoring manual (31). Values of clinically meaningful differences for MMRM and TTD analyses defined in the 2nd and 3rd editions of the SF-scoring manual are reported in Supplementary Table S1. Changes from baseline were only calculated until Week 96 to ensure balanced comparison between the treatment arms, as earlier discontinuations in completing the SF-36 survey were observed in the placebo arm compared with the osimertinib arm due to earlier disease recurrence.

Statistical analysis

The SF-36 compliance over time was calculated for each visit, including baseline, as the number of patients with an evaluable questionnaire (a questionnaire with a completion date and at least one health domain that was non-missing) at that visit, divided by the number of patients still expected to complete the questionnaire.

The MMRM analysis was performed on the change from baseline in SF-36 PCS, MCS, and health domain scores at each visit up to Week 96, which was averaged across visits over 96 weeks for the osimertinib and placebo arms. The MMRM analysis included patient (as a random effect), treatment and visit (as a fixed effect and repeated measure), and treatment-by-visit interaction as explanatory variables, as well as baseline score and baseline score-by-visit interaction as covariates, using an unstructured covariance structure.

TTD was defined as the time from randomization to the first clinically important worsening, confirmed at the subsequent assessment, or death by any cause in the absence of a clinically important worsening, providing that death occurred within two assessment visits from the last HRQoL assessment, and regardless of whether the patient withdrew from study treatment or received another anticancer therapy before symptom deterioration. TTD was analyzed using a log-rank test stratified by stage (II vs. IIIA, for analyses conducted in patients with stage II–IIIA disease; IB vs. II vs. IIIA, for analyses conducted in the overall population), *EGFR* mutation type (Ex19Del vs. L858R), and race (Asian vs. non-Asian). Summary statistics for TTD of SF-36 PCS, MCS, and health domain scores were calculated using the Kaplan–Meier method. The HR and CI were obtained directly from the U and V statistics, as previously described (13, 33, 34). Patients with two missed visits before confirmed deterioration were censored at the last evaluable assessment before the two missed visits.

Data availability statement

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

Results

Patients and treatment

A total of 682 patients with stage IB–IIIA *EGFR*m NSCLC were randomized with 339 receiving osimertinib and 343 receiving placebo (13). Baseline demographics and clinical characteristics for these patients have been previously published by Wu and colleagues (13) and were balanced between treatment arms. At DCO (January 17, 2020) in the osimertinib and placebo arms, respectively, the median (range) duration of treatment exposure was 22.5 (0–38) months and 18.7 (0–36) months, and 12% and 10% of patients had completed the 3-year study treatment (13).

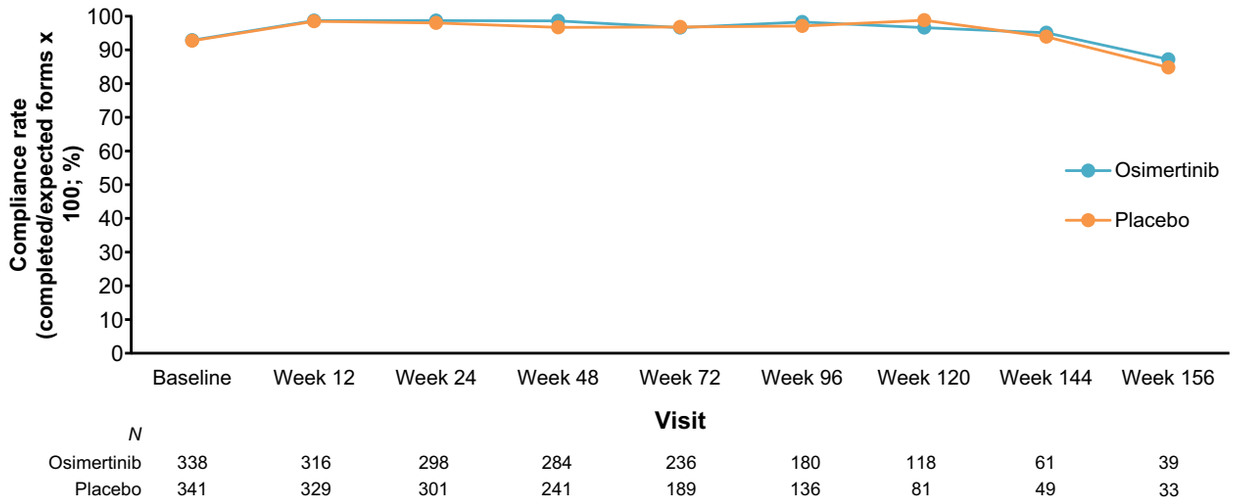

Figure 1.

Compliance rates with the SF-36 survey in the overall population. Compliance rates were calculated as the number of evaluable forms (*n*) divided by the number of expected forms (*N*), multiplied by 100, at 12- or 24-week intervals from baseline to week 156. The expected number of SF-36 forms is shown under each timepoint. SF-36, Short Form-36 health survey.

SF-36 compliance

Compliance with the SF-36 survey ranged from 85% to 99% for the overall population from baseline through to Week 156 (**Fig. 1**). During this period, SF-36 compliance rates were similar with osimertinib (87%–99%) and placebo (85%–99%; **Fig. 1**).

Baseline SF-36 scores

In the overall population, baseline mean (SD) SF-36 PCS and MCS T-scores were comparable between the osimertinib and placebo arms: PCS, 47.09 (7.4) and 46.61 (7.4); MCS, 46.37 (10.4), and 46.82 (10.8), respectively (**Fig. 2**). These T-scores were slightly lower (0.3–0.4 SD below the normative mean) than those in the general population. Individual SF-36 health domain T-scores were also similar between the two treatment arms with the majority being within ±0.3 SD of the normative mean and therefore comparable with the general population. However, greater impairment was observed for the role-physical, social functioning, and role-emotional domains with T-scores 0.5–0.8 SD below the normative mean (**Fig. 2**).

Change in SF-36 scores (MMRM analyses)

In patients receiving osimertinib in the overall population, SF-36 PCS and MCS were maintained from baseline up to Week 96, with no clinically meaningful differences observed compared with the placebo arm (**Fig. 3**). In the osimertinib and placebo arms, from baseline to Week 96, the adjusted least squares (LS) mean for PCS score numerically increased by 1.13 (95% CI, 0.54–1.72) and 2.31 (95% CI, 1.70–2.91), respectively, and the adjusted LS mean for MCS score numerically increased by 1.34 (95% CI, 0.60–2.08) and 2.68 (95% CI, 1.92–3.44), respectively (**Table 1**). The resulting treatment difference for the adjusted LS mean change was −1.18 (95% CI, −2.02 to −0.34) for the

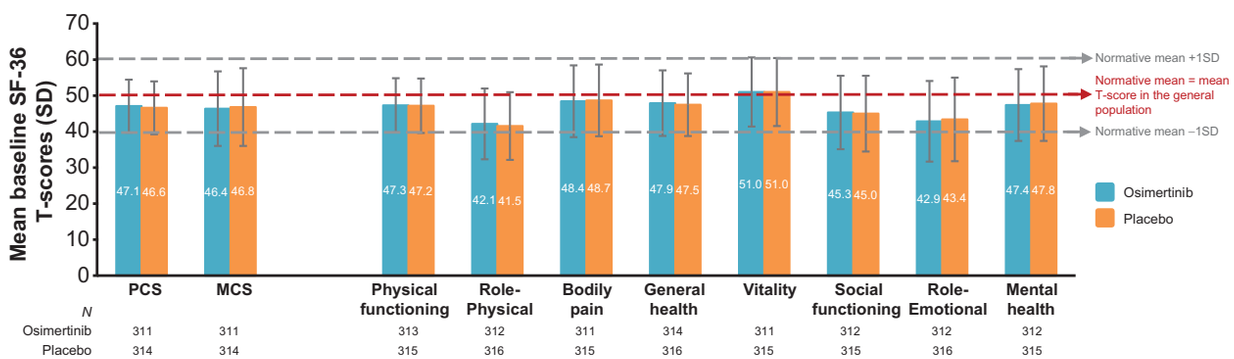

Figure 2.

Baseline T-scores of the SF-36 component summaries and health domains in the overall population. The red dashed line shows the mean 2009 U.S. population SF-36 normative mean calculated from a sample of adults aged ≥18 years, including healthy individuals, and those with chronic conditions (31); normative data are not age-adjusted. The gray dashed lines show this normative mean ± 1SD. The number of patients with data available at each visit is shown below each component summary and health domain. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey.

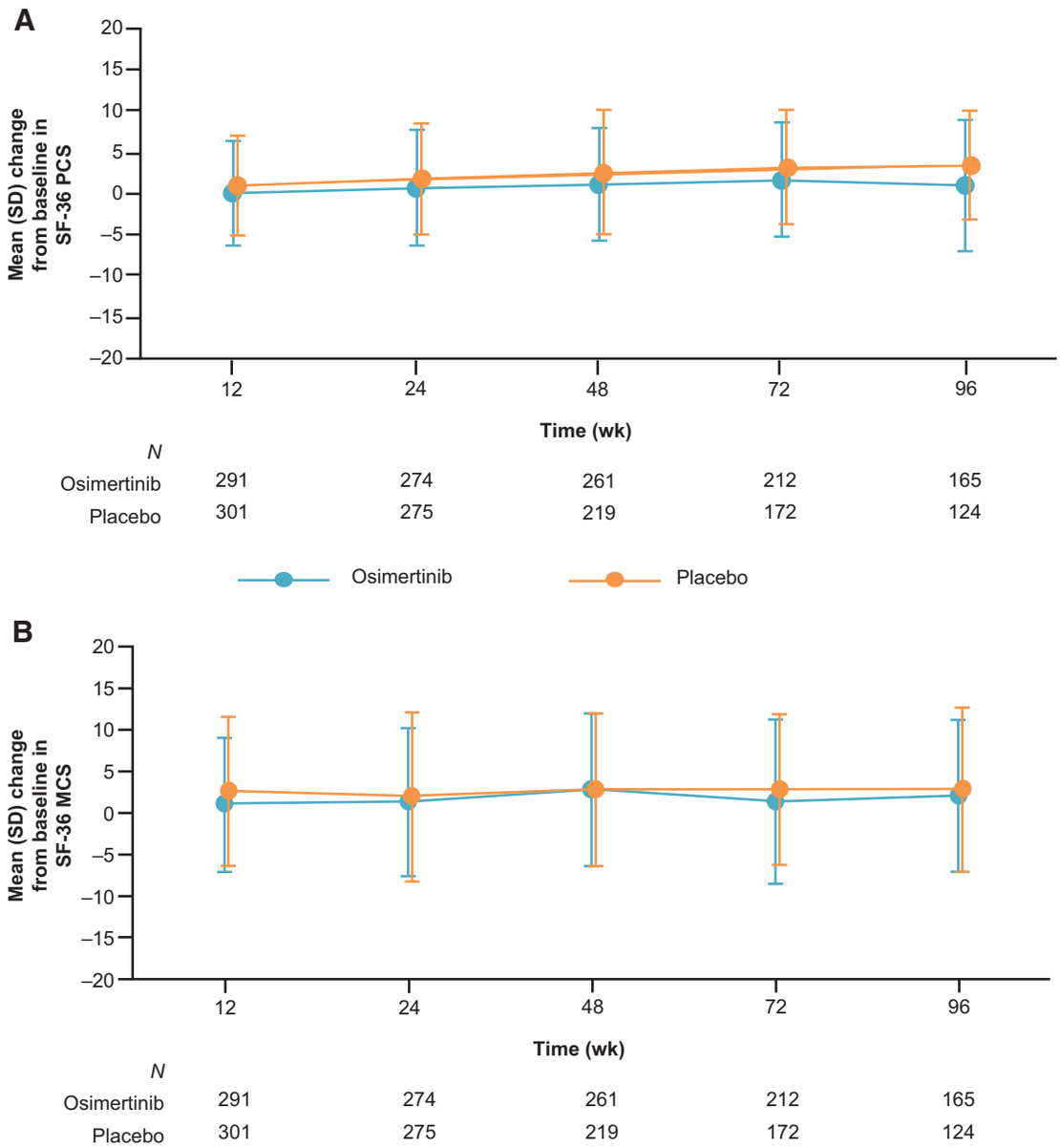

Figure 3.

Change in SF-36 (**A**) PCS and (**B**) MCS T-scores from baseline to week 96 in the overall population. The data shown are mean change from baseline in T-scores with error bars representing the SDs. The number of patients with data available at each visit is shown below each timepoint. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey.

PCS score and −1.34 (95% CI, −2.40 to −0.28) for the MSC score, neither of which represented a clinically meaningful difference between treatment arms, according to the definitions from the 3rd edition of the SF-36 scoring manual (**Table 1**; ref. 31). Similarly, SF-36 health domains T-scores were maintained from baseline to Week 96 with osimertinib treatment, with numerical increases across the majority of domains in both arms (**Table 1**). On the basis of the 3rd edition of the SF-36 scoring manual definitions (31), no clinically meaningful differences were observed for any health domain with osimertinib compared with placebo (**Table 1**).

TTD in SF-36 score analyses

In the overall population during the treatment period, 81% and 84% of patients in the osimertinib and placebo arms, respectively, did not experience a clinically meaningful deterioration in the PCS or death, and 81% in both treatment arms did not experience a clinically meaningful deterioration in the MCS or death; definitions for clinically meaningful differences were based on the 3rd edition of the SF-36 scoring manual (31). In patients who did experience deterioration, there were no differences in TTD of the PCS (HR, 1.17; 95% CI, 0.82–1.67) or MCS (HR, 0.98; 95% CI, 0.70–1.39) between the osimertinib

Table 1. MMRM adjusted LS mean change from baseline up to week 96 in SF-36 component summaries and health domain T-scores in the overall population.

SF-36 component summary or health domain	MMRM adjusted LS mean change from baseline (95% CI)			Clinically meaningful difference[a]
	Osimertinib	Placebo	Osimertinib–placebo	
PCS	1.13 (0.54–1.72) *n* = 293	2.31 (1.70–2.91) *n* = 303	−1.18 (−2.02 to −0.34)	±2
MCS	1.34 (0.60–2.08) *n* = 293	2.68 (1.92–3.44) *n* = 303	−1.34 (−2.40 to −0.28)	±3
Physical functioning	0.53 (−0.10 to 1.16) *n* = 295	1.38 (0.74–2.03) *n* = 303	−0.86 (−1.76 to 0.04)	±3
Role-physical	2.67 (1.91–3.43) *n* = 294	4.47 (3.69–5.25) *n* = 304	−1.80 (−2.90 to −0.71)	±3
Bodily pain	1.66 (0.91–2.40) *n* = 293	2.22 (1.45–2.99) *n* = 303	−0.57 (−1.64 to 0.50)	±3
General health	−0.41 (−1.12 to 0.31) *n* = 296	1.09 (0.36–1.83) *n* = 304	−1.50 (−2.53 to −0.47)	±2
Vitality	0.98 (0.22–1.74) *n* = 293	2.91 (2.13–3.69) *n* = 304	−1.93 (−3.02 to −0.84)	±2
Social functioning	2.77 (2.06–3.49) *n* = 294	3.88 (3.14–4.62) *n* = 303	−1.11 (−2.13 to −0.08)	±3
Role-emotional	1.05 (0.22–1.87) *n* = 294	2.51 (1.66–3.36) *n* = 304	−1.46 (−2.65 to −0.28)	±4
Mental health	1.17 (0.44–1.90) *n* = 294	2.05 (1.30–2.80) *n* = 304	−0.88 (−1.92 to 0.17)	±3

Abbreviations: CI, confidence interval; LS, least squares; MCS, mental component summary; MMRM, mixed model of repeated measures; PCS, physical component summary; SF-36, Short Form-36 health survey.
[a]Clinically meaningful difference based on definitions from the 3rd edition of the SF-36 scoring manual (31).

and placebo arms (**Fig. 4**). There were also no differences between the osimertinib and placebo arms in the TTD for all SF-36 health domains with HRs ranging from 0.68 to 1.19 (**Fig. 5**).

Comparable results were obtained when using clinically meaningful differences as defined by the 2nd edition of the SF-36 scoring manual (31) in the overall patient population and in the pre-specified analysis in patients with stage II–IIIA disease; the pre-specified analysis is presented in Supplementary Figs. S1 and S2. In the overall patient population, the HRs for TTD of the PCS and MCS were 1.25 (95% CI, 0.90–1.73) and 0.95 (95% CI, 0.69–1.30), respectively (Supplementary Fig. S3), and the HRs for TTD of the eight health domains ranged from 0.93 to 1.19 (Supplementary Fig. S4).

Discussion

Previous results from the primary analysis of the ADAURA trial showed a statistically significant improvement in DFS with adjuvant osimertinib versus placebo in patients with completely resected stage IB–IIIA *EGFR*m NSCLC (13). At the time of this analysis, the OS data were immature and the follow-up for OS continues. The ADAURA analysis reported here assessed the effect of adjuvant osimertinib versus placebo on HRQoL in patients who were disease-free following surgery, with or without prior adjuvant chemotherapy. Overall, the data demonstrated that HRQoL was maintained with adjuvant osimertinib treatment, with no clinically meaningful differences versus placebo in the SF-36 component summaries and individual health domain scores.

HRQoL was measured in ADAURA using the SF-36 health survey, which is a widely used and validated international non–cancer-specific questionnaire that comprehensively measures patients' general functional status and well-being, regardless of age, disease, or treatment received (31). At the time of designing the ADAURA trial, the SF-36 had been translated into 10 languages, making it an accessible tool, and has been used in other adjuvant cancer settings, such as breast and gastric cancers (21, 22, 35–37). A generic survey, rather than a cancer-specific one, was chosen as patients were considered cancer-free before receiving osimertinib/placebo, as per the trial inclusion criteria. Furthermore, SF-36 assessments were performed only until disease recurrence, a period during which patients were considered not to have physical symptoms of cancer, although were recovering from surgery and could potentially suffer from emotional and psychological effects of, for example, chemotherapy or their recent lung cancer diagnosis, which could affect their general HRQoL. SF-36 provides a comprehensive measure of global HRQoL and comprises 36 items assessing patients' general health on 8 multi-item dimensions (38). As such, it is a sensitive tool for measuring general HRQoL: It can capture the impact of any general health event on HRQoL, and provide useful insights into the effects of adjuvant osimertinib treatment on overall HRQoL, including social and emotional functioning, in patients who are disease-free.

HRQoL was a pre-specified endpoint in ADAURA. Pre-specified, per-protocol analyses included a TTD analysis of PCS and MCS in patients with stage II–IIIA disease (primary analysis population; ref. 13) using values for clinically meaningful differences defined in the 2nd edition of the SF-36 scoring manual (32). The main HRQoL results presented here were exploratory, *post hoc* analyses, as they were based on the most recent (3rd) edition of the SF-36 scoring manual (31) and used data from the overall population (stage IB–IIIA disease), which includes more patients than the primary analysis population (stage II–IIIA disease) used in the prespecified analysis. The use of the overall population in these exploratory HRQoL analyses was deemed reasonable as the results from the primary endpoint, DFS, in patients

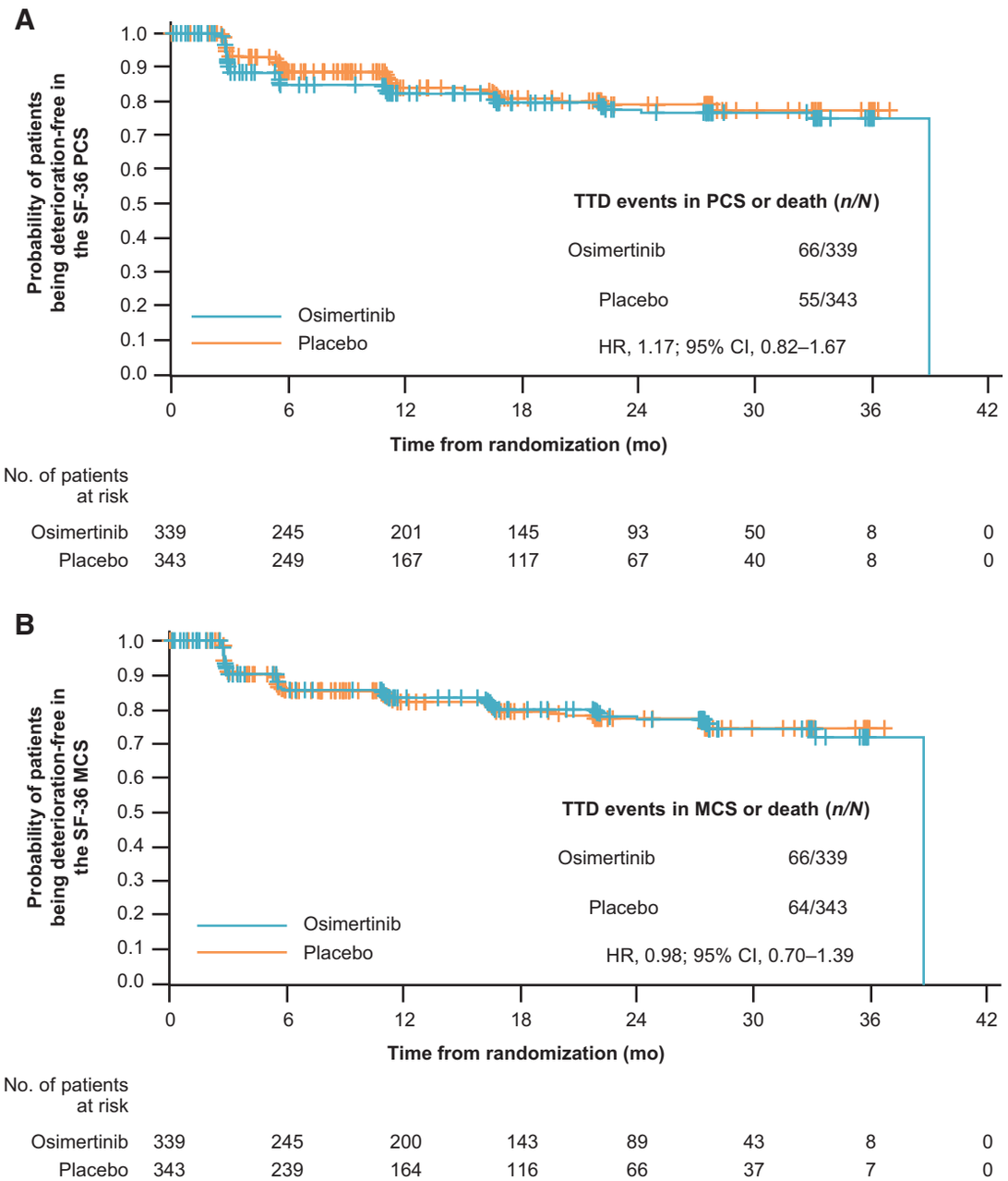

Figure 4.

TTD of the SF-36 (**A**) PCS and (**B**) MCS in the overall population. Kaplan–Meier plots are shown for the TTD analysis using clinically meaningful differences defined in the 3rd edition of the SF-36 scoring manual (31). The number of TTD events in MCS/PCS or death (*n*) in the overall population (*N*) are shown along with the HRs and 95% CIs comparing the treatment arms. The analysis was performed using an unstratified log-rank test due to low event counts. Crosses indicate censored patients, and the number of patients at risk is shown below each timepoint. CI, confidence interval; MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey; TTD, time to deterioration.

with stage II–IIIA disease (HR, 0.17; 99.06% CI, 0.11–0.26; $P < 0.001$), were similar to those reported for the overall population (HR, 0.20; 99.12% CI, 0.14–0.30; $P < 0.001$; ref. 13). Indeed the results from the TTD analyses of SF-36 PCS and MCS were similar when using the definition of clinically meaningful difference from either the 2nd or 3rd edition of the SF-36 scoring manual (31, 32) and the overall conclusions from these HRQoL analyses remained the same irrespective of the SF-36 manual edition used.

It should be noted that no HRQoL data were collected after treatment discontinuation, due to disease recurrence or other discontinuation criteria, as the objective of these analyses was to assess patients' HRQoL while they were receiving randomized treatment.

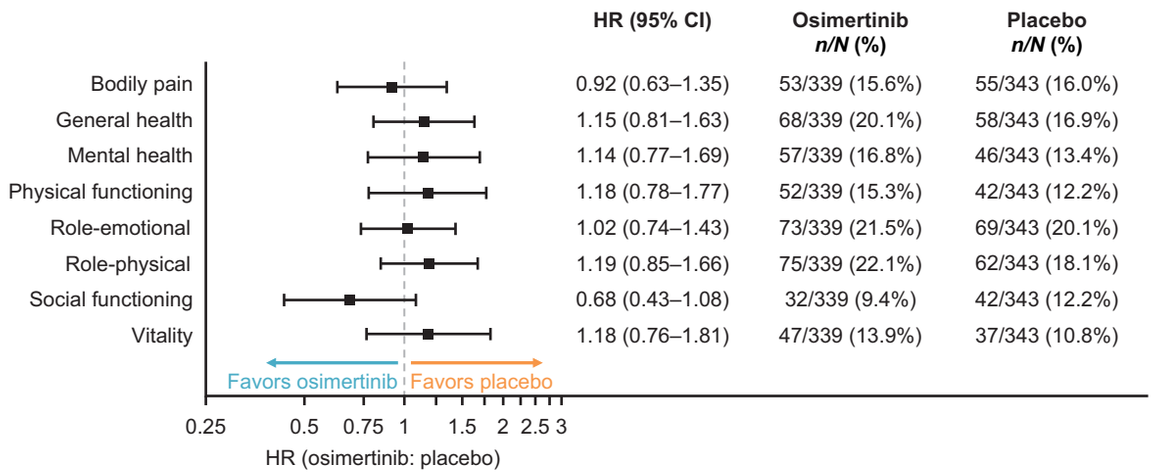

Figure 5.

Forest plot of the TTD of the SF-36 health domains in the overall population. The TTD analysis used clinically meaningful differences defined in the 3rd edition of the SF-36 scoring manual (31) and was performed using an unstratified log-rank test due to low event counts. HRs and corresponding 95% CIs are shown for each health domain along with the number of events (*n*) in the overall population (*N*). An HR <1 favors osimertinib treatment. CI, confidence interval; SF-36, Short Form-36 health survey; TTD, time to deterioration.

In addition, interpretation of post-recurrence HRQoL data may have been confounded by subsequent treatments, so it would have been difficult to isolate the effect of adjuvant osimertinib on HRQoL after disease recurrence. However, as recurrence rates were higher in the placebo arm versus the osimertinib arm in ADAURA, and with HRQoL outcomes predicted to decrease upon disease recurrence (36), the overall between-arm difference in HRQoL would likely be favoring osimertinib. This will not be explored further in the ongoing ADAURA trial, but analysis of long-term HRQoL data following disease recurrence will be important in future studies.

In patients who were disease-free following surgery, with or without prior adjuvant chemotherapy, baseline SF-36 PCS and MCS T-scores were comparable in the osimertinib and placebo arms, and only slightly lower than the mean T-scores in the general population. The majority of health domain scores were comparable with the general population; exceptions to this were for role-physical, social functioning, and role-emotional, which were lower than the general population. This may have been due to the impact of surgery, chemotherapy, or the patients' recent lung cancer diagnosis on these aspects of QoL, although patients were randomized once they had sufficiently recovered from surgery and completed adjuvant chemotherapy. Overall, the data indicated that patients enrolled in ADAURA were highly functioning in terms of HRQoL.

Both the MMRM and TTD analyses presented here were chosen to provide a comprehensive assessment of HRQoL with adjuvant osimertinib. Although the TTD analysis as presented here is an accepted method for assessing HRQoL in cancer studies (39–41), including NSCLC studies, it does not capture what happens to the patient after they experience deterioration in HRQoL. The MMRM analysis is, therefore, complementary to the TTD as it evaluates HRQoL scores in a continuous manner across visits and assesses change from baseline (39, 40). In the MMRM analysis, the SF-36 PCS, MCS, and individual health domains were maintained from baseline up to Week 96 during osimertinib treatment in patients who were disease-free following complete resection, with no clinically meaningful differences observed compared with placebo. More than 80% of patients across both arms did not experience a clinically meaningful deterioration in the SF-36 PCS and MCS and, for those patients who had deterioration, there were no differences in TTD for these summaries and the individual health domains between osimertinib and placebo.

Only a few other studies have reported the effect of adjuvant chemotherapy or EGFR-TKIs on HRQoL in patients with resected stage IB–IIIA NSCLC and have used cancer-specific questionnaires to assess HRQoL (23–25). In the JBR.10 study, adjuvant cisplatin and vinorelbine was associated with a modest and temporary worsening of the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in patients with resected stage IB–II NSCLC, with return to baseline function by 9 months in most patients (23). Other chemotherapy regimens, such as gemcitabine plus cisplatin and docetaxel plus cisplatin, do not appear to have any significant negative impact on EORTC QLQ-C30 in patients with stage IB–III NSCLC (24). In the ADJUVANT/CTONG 1104 study, the EGFR-TKI gefitinib compared with cisplatin plus vinorelbine showed significantly improved scores across three HRQoL instruments (functional assessment of cancer therapy-lung cancer, lung cancer symptom scale, and trial outcome index) and was associated with longer TTD in these HRQoL scores in Chinese patients with resected stage II–IIIA *EGFR*m NSCLC (25). Several phase III trials of adjuvant immunotherapy, with or without adjuvant chemotherapy, versus placebo/observation/best supportive care are currently ongoing in the resected stage IB–IIIA NSCLC setting (42–45); however, HRQoL data are only anticipated from one randomized phase III trial of adjuvant durvalumab (NCT02273375; ref. 45).

Several limitations should be considered when analyzing these results. First, the data presented are from exploratory analyses (stage IB–IIIA disease, 3rd edition of the SF-36 scoring manual); however, the results of these analyses are in line with the pre-specified analyses (stage II–IIIA disease, 2nd edition of the SF-36 scoring manual). Because of the earlier than planned DCO, the proportion of patients who completed the 3-year study treatment period at DCO was low (12% vs. 10% of patients receiving osimertinib vs. placebo), although the compliance rates were high (≥85% across both arms). As the analysis was designed to assess the impact on QoL of adjuvant treatment, data were not collected beyond recurrence, so provided

limited understanding on how a delay in recurrence with adjuvant osimertinib versus placebo impacts HRQoL in the longer term. Collection of long-term HRQoL data after disease recurrence could have provided useful information for payers, cost-effectiveness assessments, and regulatory bodies. On the other hand, interpretation of post-recurrence HRQoL data could be confounded by subsequent treatments and crossover to open-label osimertinib. Finally, the number of patients included in the analysis decreased over the course of the study with 40%–53% of patients included in the analysis at Week 96 compared with baseline.

Conclusions

In summary, HRQoL via the SF-36 survey was maintained during adjuvant osimertinib treatment in patients with stage IB–IIIA *EGFR*m NSCLC, who were disease-free following complete resection and prior adjuvant chemotherapy, if indicated. These results are in line with the overarching goal of adjuvant treatment, which is to treat with curative intent, while maintaining patients' HRQoL (19). Coupled with the significant DFS benefit and long-term safety profile observed with adjuvant osimertinib versus placebo in this patient population (13), these HRQoL data further support adjuvant osimertinib as an effective new treatment strategy in this setting.

Authors' Disclosures

M. Majem reports speakers bureau and advisory board fees from Sanofi, Pfizer, Janssen, Bristol-Myers Squibb, MSD, Boehringer-Ingelheim, AstraZeneca, Roche, Kyowa Kyrin, Pierre Fabre, Takeda Pharmaceutical, and Bayer AG and has received a research grant from Bristol-Myers Squibb outside the submitted work. J.W. Goldman reports research grants from AbbVie Inc., Merck & Co., Bristol-Myers Squibb, and AstraZeneca; speakers bureau fees from Merck & Co.; and honoraria from AstraZeneca outside the submitted work. T. John reports advisory board and consultancy fees from Roche AG, Bristol-Myers Squibb, Merck & Co., Ignyta, AstraZeneca, Takeda Pharmaceutical, MSD, Specialised Therapeutics, and Pfizer Inc. outside the submitted work. C. Grohe reports speakers bureau fees, advisory board fees, and honoraria from AstraZeneca, Boehringer-Ingelheim, and MSD and travel and accommodation fees from Boehringer-Ingelheim outside the submitted work. K. Laktionov reports speakers bureau fees, advisory board fees, and honoraria from AstraZeneca, Bristol-Myers Squibb, MSD, Roche, and Biocad; advisory board fees from Pfizer; and research grants from AstraZeneca outside the submitted work. S.-W. Kim reports speakers bureau and advisory board fees from Boehringer-Ingelheim; advisory board fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., and Novartis; and financial support from AstraZeneca outside the submitted work. T. Kato reports speakers bureau fees, advisory board fees, and research grants from AstraZeneca, Amgen Inc., Chugai Pharmaceutical Co., Ltd, Eli Lilly & Co., Merck Biopharma, MSD, and Pfizer Inc.; speakers bureau fees from Bristol-Myers Squibb, Novartis, Taiho Pharmaceutical, Boehringer-Ingelheim, and Roche AG; advisory board fees from Daiichi-Sankyo; speakers bureau and research grants from Novartis; and research grants from AbbVie Inc. outside the submitted work, as well as employment with Regeneron (spouse) and Eli Lilly & Co. S. Lu reports speakers bureau fees, advisory board fees, and research grants from AstraZeneca and Roche; speakers bureau fees from Hansoh; advisory board fees and research grants from Hutchison MediPharma; advisory board fees from Boehringer-Ingelheim, Simcere, ZaiLab, and GenomiCare; and research grants from Bristol-Myers Squibb, Heng, and Rui outside the submitted work. F. de Marinis reports advisory board and consultancy fees from Roche AG, Bristol-Myers Squibb, AstraZeneca, and MSD outside the submitted work. L. Bonanno reports speakers bureau fees from Roche, Bristol-Myers Squibb, and MSD and advisory board fees and a research grant from AstraZeneca. M. Domine reports speakers bureau, advisory board, and consultancy fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Pfizer Inc., and Roche AG outside the submitted work. F.A. Shepherd reports ownership of stock interest in AstraZeneca. S. Atagi reports honoraria from AstraZeneca, Eli Lilly, Ono, Taiho Pharmaceutical Co Ltd, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Hisamitsu, MSD, Chugai, Kyowa Hakko Kirin, Merck, Novartis Pharma, and Thermo Fisher Scientific and research grants from AstraZeneca, Eli Lilly, Ono, Taiho Pharmaceutical Co Ltd, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, MSD, Chugai, Merck, and F. Hoffmann-La Roche. L. Zeng reports ownership of stock interest and is an employee of AstraZeneca. N. Medic is an employee of AstraZeneca. D. Kulkarni reports ownership of stock interest and is an employee of AstraZeneca. M. Tsuboi reports advisory board fees from AstraZeneca, MSD, and Novartis and honoraria from Johnson & Johnson Japan, AstraZeneca KK, Eli Lilly Japan, Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical, Medtronic Japan, Ono Pharmaceutical Co., Ltd, MSD, Bristol-Myers Squibb KK, and Teijin Pharma outside the submitted work. R.S. Herbst reports personal fees from AbbVie Inc., ARMO Biosciences, Biodesix, Bolt Biotherapeutics, Bristol-Myers Squibb, EMD Serono, Genmab, Halozyme, Heat Biologics, IMAB Biopharma, Immunocore, Infinity Pharmaceuticals, Loxo Oncology, Mirati Therapeutics, Nektar, Neon Therapeutics, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Takeda Pharmaceutical, Tesaro, Tocagen, Cybrexa, and Oncternal Therapeutics; personal fees and research grants from AstraZeneca, Eli Lilly & Co., Genentech/Roche, and Merck & Co.; and advisory board fees from Junshi Pharmaceuticals outside the submitted work. Y.-L. Wu reports personal fees and research grants from AstraZeneca, Bristol-Myers Squibb, Pfizer Inc., and Roche AG and personal fees from Boehringer-Ingelheim, Eli Lilly & Co., MSD, and Sanofi outside the submitted work. No disclosures were reported by the other authors.

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