VOLUME 36 · NUMBER 18 · JUNE 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Patient-Reported Symptoms and Impact of Treatment With Osimertinib Versus Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The AURA3 Trial

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Published at jco.org on May 7, 2018.

Clinical trial information: NCT02151981.

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0732-183X/18/3618w-1853w/$20.00

A B S T R A C T

Purpose

Capturing patient-reported outcome data is important for evaluating the overall clinical benefits of new cancer therapeutics. We assessed self-reported symptoms of advanced non–small-cell lung cancer in patients treated with osimertinib or chemotherapy in the AURA3 phase III trial.

Patients and Methods

Patients completed the European Organisation for Research and Treatment of Cancer 13-item Quality of Life Questionnaire-Lung Cancer Module (EORTC QLQ-LC13) questionnaire on disease-specific symptoms and the EORTC 30-item Core Quality of Life Questionnaire (EORTC QLC-C30) on general cancer symptoms, functioning, global health status/quality of life. We assessed differences between treatments in time to deterioration of individual symptoms and odds of improvement (a deterioration or improvement was defined as a change in score from baseline of ≥ 10). Hazard ratios (HRs) were calculated using a log-rank test stratified by ethnicity; odds ratios (ORs) were assessed using logistic regression adjusted for ethnicity.

Results

At baseline, the questionnaires were completed by 82% to 88% of patients, and 30% to 70% had individual key symptoms. Time to deterioration was longer with osimertinib than with chemotherapy for cough (HR, 0.74; 95% CI, 0.53 to 1.05), chest pain (HR, 0.52; 95% CI, 0.37 to 0.73), and dyspnea (HR, 0.42; 95% CI, 0.31 to 0.58). The proportion of symptomatic patients with improvement in global health status/quality of life was higher with osimertinib (80 [37%] of 215) than with chemotherapy (23 [22%] of 105; OR, 2.11; 95% CI, 1.24 to 3.67; $P = .007$). Proportions were also higher for appetite loss (OR, 2.50; 95% CI, 1.31 to 4.84) and fatigue (OR, 1.96; 95% CI, 1.20 to 3.22).

Conclusion

Time to deterioration of key symptoms was longer with osimertinib than with chemotherapy, and a higher proportion of patients had improvement in global health status/quality of life, demonstrating improved patient outcomes with osimertinib.

J Clin Oncol 36:1853-1860. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Epidermal growth factor receptor (EGFR)–mutated non–small-cell lung cancer (NSCLC) is a distinct subtype of lung cancer characterized by a high response rate when treated with EGFR tyrosine kinase inhibitors (TKIs).[1] A meta-analysis has shown that in treatment-naïve patients, erlotinib and gefitinib (first-generation TKIs) are associated with a median progression-free survival (PFS) of 11.0 months compared with 5.6 months for those who received chemotherapy.[2] In addition, afatinib and dacomitinib (second-generation TKIs) have been associated with improved PFS compared with chemotherapy[3,4] and gefitinib.[5,6] Despite an initial response, most patients will ultimately develop resistance to TKIs, with approximately 60% developing an additional EGFR T790M mutation.[7-9]

Osimertinib is a third-generation, irreversible EGFR-TKI that is selective for both EGFR-sensitizing and T790M-resistance mutations.[10-13] AURA3 (NCT02151981; AZD9291 Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non–Small Cell Lung Cancer) was a randomized, phase III trial that investigated the superiority of osimertinib over platinum-pemetrexed chemotherapy in patients with confirmed T790M-positive NSCLC that had relapsed after first-line EGFR-TKI therapy.[14,15] In this trial,

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.77.2293

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.77.2293

DOI: https://doi.org/10.1200/JCO.2017.77.2293

osimertinib significantly improved PFS over chemotherapy (hazard ratio [HR], 0.30; 95% CI, 0.23 to 0.41).[14] In another recently reported study, osimertinib was shown to significantly improve PFS over gefitinib or erlotinib in treatment-naïve patients with advanced EGFR-mutant disease.[16]

Despite this recent therapeutic advancement, metastatic EGFR-mutated NSCLC remains incurable in the majority of patients, and thus treatment is aimed at palliation.[17] Furthermore, lung cancer is characterized by high symptom burden,[18] and key symptoms according to patient reports are cough, dyspnea, chest pain, fatigue, and appetite loss.[19-22] Fatigue, appetite loss, dyspnea, and pain are experienced by at least 90% of patients and have a significant negative effect on disease-specific health-related quality of life (HRQoL).[21,23] Knowledge of the effect of new therapeutics on patient experience is useful and, in combination with survival data, could provide vital information to help physicians and patients in making treatment decisions.[24,25] Indeed, it is recommended that patient-reported symptoms and HRQoL are assessed in all prospective clinical comparative effectiveness research.[26]

PFS is a commonly used primary efficacy end point in oncology trials and is widely accepted by regulators as a surrogate for treatment efficacy.[27,28] Improvement in PFS is important in incurable cancer but is not the only measure of clinical benefit and thus may be supplemented with improvement in patient-relevant symptoms.[25] PFS alone does not directly measure how a patient feels, functions, or survives,[25] but it is increasingly being used as a primary end point in recent clinical trials of advanced NSCLC.[29] Conversely, data from patient-reported outcomes (PROs) provide patients' perspectives of their symptoms, functional activities, and HRQoL.[30] These self-reported symptoms and measures of functioning reflect both tumor response and control and treatment-related toxicities. Given that past clinical trials of first-line EGFR TKIs compared with chemotherapy could not demonstrate overall survival benefit,[2,31] documenting PRO improvement can further complement PFS prolongation, substantiate the clinical meaningfulness of PFS, and help assess the net overall clinical benefit of a new therapeutic.

In this article, we report PROs from AURA3, which were a secondary outcome of this trial. The patient-reported symptoms, functioning, health status, and quality of life (QoL) were assessed by using two self-administered cancer-specific questionnaires developed by the European Organisation for Research and Treatment of Cancer (EORTC): the 30-item Core Quality of Life Questionnaire (QLQ-C30)[32] and the 13-item Quality of Life Questionnaire-Lung Cancer Module (QLQ-LC13).[33] These instruments have demonstrated reliability and validity, are commonly used in clinical trials, and provide complementary and corroborative information about HRQoL in advanced lung cancer. The QLQ-LC13 questionnaire specifically captures the key lung cancer–associated symptoms that are predominant and burdensome, particularly in this patient population. We aimed to assess prespecified self-reported symptoms and functioning of patients treated with osimertinib or platinum-based doublet chemotherapy. We investigated whether NSCLC–specific symptoms deteriorate more slowly and whether a greater proportion of symptomatic patients will have an improvement in symptoms, functioning, and global health status/quality of life when treated with osimertinib compared with chemotherapy.

PATIENTS AND METHODS

Study Design

The details of the AURA3 trial design and the PFS efficacy results are published elsewhere.[14,15]

PRO Assessments

The EORTC QLQ-C30 is a robust HRQoL instrument that gives similar results when used in different countries and in different translated versions and is considered to be suitable for use in multinational clinical trials.[34-36] The QLQ-C30 comprises questions on general cancer symptoms, functioning, global health status/quality of life and financial difficulties. It incorporates both multi-item scales and single-item measures, including one global health status/quality of life scale, five functional scales, three symptoms scales, and six single items. The 13-item QLQ-LC13 comprises questions on disease-specific symptoms. It incorporates one multi-item scale to assess dyspnea, and a series of single items to assess pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The QLQ-C30 was tested in interviews with patients with lung cancer during development of the disease-specific QLQ-LC13 module.[37]

All scales and single-item measures range in score from 0 to 100. The principle for scoring these scales is the same in all cases and involves calculating the average of the items that contribute to the scale (the raw score) and then using a linear transformation to standardize the raw score; scores therefore range from 0 to 100, with higher scores representing a better level of functioning or QoL or a worse level of symptoms. We defined symptomatic patients as those having a baseline symptom score $\geq$ 10.

The QLQ-LC13 questionnaire was administered at baseline, then once per week for 6 weeks, then once every 3 weeks up to the end of the study and at progression. The QLQ-C30 was administered at baseline, then once every 6 weeks up to the end of the study and at progression.

Assessments and Statistical Analysis

Multifaceted assessments were performed to capture various aspects of PROs. First, we examined the odds of improvement in key symptoms and functioning domains for symptomatic patients at baseline between treatment arms. The prespecified key symptoms of importance in advanced NSCLC were cough, chest pain, dyspnea, fatigue, and appetite loss.[19-21] The odds of improvement in symptoms and functioning domains were computed by using a mixed-effect logistic regression model for longitudinal binary outcome of improvement from baseline (decrease in symptom score from baseline of $\geq$ 10 or increase in functional score from baseline of $\geq$ 10) versus no improvement. Each longitudinal analysis included treatment arm, time (visit number) variable, baseline score, treatment-by-time interaction, and ethnicity (Asian or non-Asian) as covariates. The analyses for each item used all data up to disease progression and beyond. The symptom improvement rate was defined as the number (%) of patients with two consecutive assessments at least 18 days apart, which showed a clinically meaningful improvement (a decrease from baseline score $\geq$ 10 for EORTC QLQ-LC13 or QLQ-C30 scales or items) in that symptom from baseline.

Second, treatment arms were also compared for differences in time to deterioration of symptoms and functioning domains over the course of the study for all patients with baseline readings. A deterioration or improvement in a particular symptom was defined as a change (increase or decrease) in score from baseline of $\geq$ 10, which corresponded to the minimal threshold for a moderate change.[38] HRs and 95% CIs were calculated using a log-rank test stratified by ethnicity (Asian or non-Asian).

Finally, the mean continuous differences in symptoms and functioning domains were calculated using the mixed-effect model repeat measurement (average over 6 months). Each longitudinal analysis included treatment arm, time variable, baseline symptom/functioning domains score, and treatment-by-time interaction as covariates. Patient was defined as a random variable, and the covariance structure was assumed to be

unstructured. Estimates of the least-squares means for treatment effects within and between treatment groups were reported with corresponding 95% CIs. The analyses for each item included postbaseline data up to week 24 and excluded assessments completed outside this prespecified time range.

Sensitivity Analysis

Our main analysis examined all PRO data collected from baseline to after progression. In the sensitivity analysis, we limited our assessment from baseline to disease progression to evaluate whether these subset data were consistent with our overall analyses.

The trial sponsor collected and analyzed the data, and the lead investigators had full access to the data. For all analyses, *P* values are provided to aid interpretation but must be interpreted conservatively, given the multiple scales, time points, and hypotheses. The data cutoff date was April 15, 2016.

RESULTS

Completion of PRO Instrument

A total of 279 patients were allocated to osimertinib and 140 to chemotherapy (Fig 1). At baseline, 82.4% of patients who received osimertinib and 82.9% who received chemotherapy completed the QLQ-LC13; 88.2% and 82.8%, respectively, completed the QLQ-C30 (Fig 2). At 3 months, 80.7% of patients who received osimertinib and 73.4% who received chemotherapy completed the QLQ-LC13; 84.4% and 72.8% of patients receiving osimertinib and chemotherapy, respectively, completed the QLQ-C30. At 1 year, questionnaire completion rates were at least 60% for both treatment arms.

Baseline PRO Data

The baseline scores were relatively well balanced between treatment arms (Table 1). Apart from chest pain and appetite loss, approximately 50% to 70% of patients experienced one or more of the key lung cancer symptoms.

Odds of Improvements in PRO Symptoms and Functioning

The symptom improvement rate was enhanced with osimertinib compared with chemotherapy for the five prespecified key symptoms; the greatest improvements with osimertinib were seen in dyspnea, fatigue, and appetite loss (Fig 3). A higher proportion of patients had improvement in functioning domains with osimertinib than with chemotherapy, particularly for the physical, role, and social functioning and global health status/quality of life domains (Appendix Fig A1, online only). The corresponding data for improvement in the remaining QLQ-LC13 and QLQ-C30 symptoms are shown in Appendix Figure A2 (online only). Improvements in other symptoms were also generally in favor of osimertinib, with particularly large differences seen for nausea or vomiting and insomnia. The only exception was for diarrhea, which improved in more patients treated with chemotherapy than in patients treated with osimertinib.

Time to Deterioration of Symptoms and Functioning

The time to deterioration of key symptoms was prolonged with osimertinib compared with chemotherapy, particularly for chest pain and appetite loss (Fig 4). For the other symptoms and functioning domains (Appendix Fig A3, online only), HRs for deterioration were in favor of osimertinib, except for diarrhea (HR, 1.63; 95% CI, 1.19 to 2.23).

Mean Changes in Symptoms and Functioning From Baseline

Figure 5 shows the mean difference between treatment arms in the key symptoms calculated by the mixed-effect model repeat

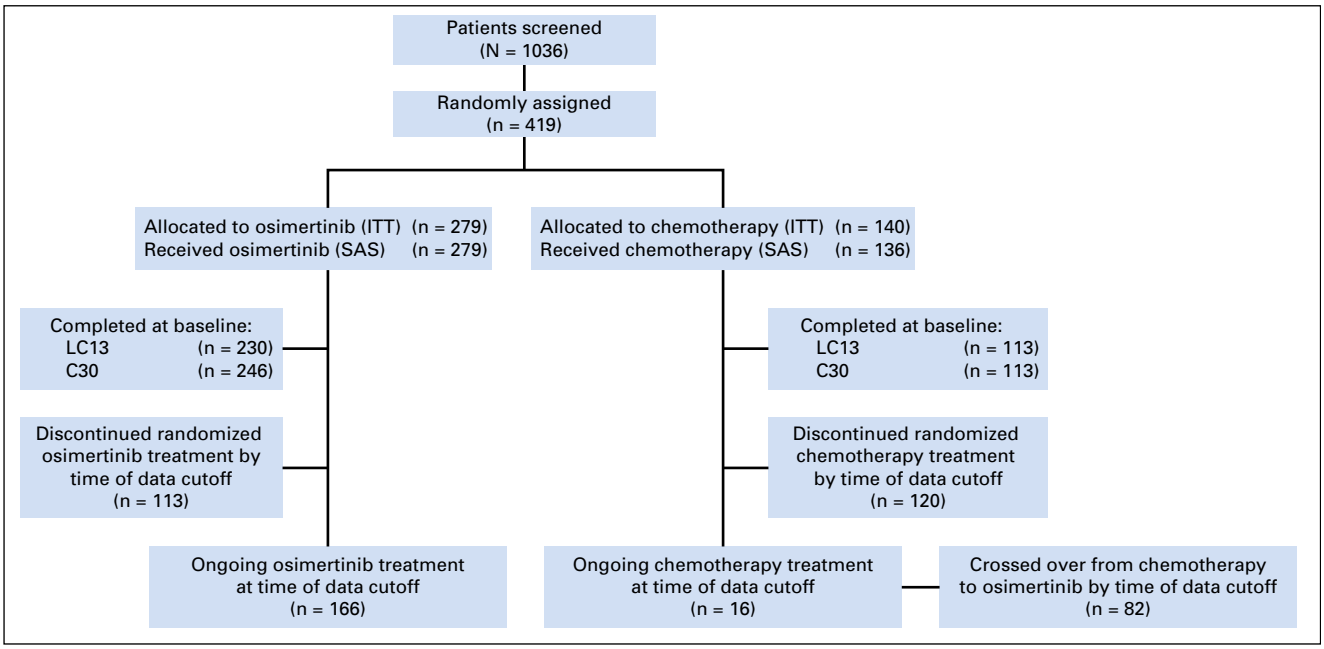

Fig 1. CONSORT diagram. C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; ITT, intention-to-treat; LC13, EORTC 13-item Quality of Life Questionnaire-Lung Cancer Module; SAS, safety analysis set.

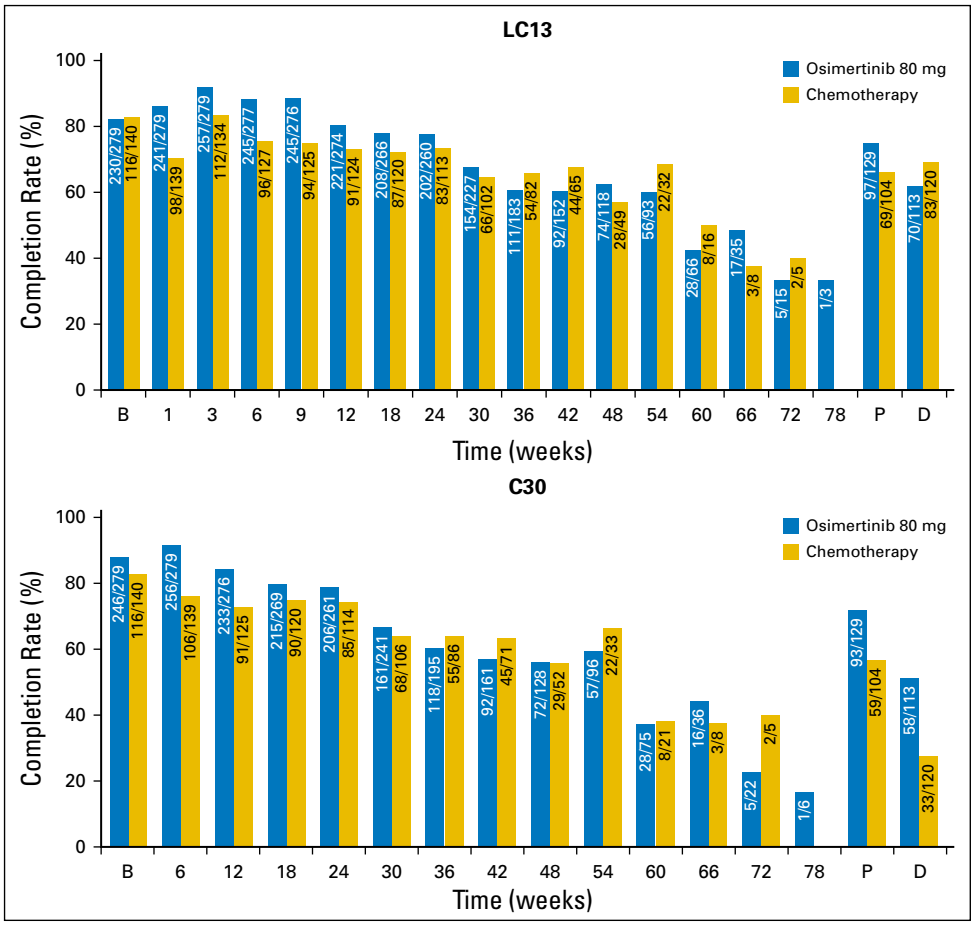

Fig 2. PRO questionnaire completion rates calculated as the number of evaluable forms divided by the number of expected forms. B, baseline; C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; D, at discontinuation; LC13, EORTC 13-item Quality of Life Questionnaire Lung Cancer Module; P, at progression.

measurement. In addition, to aid clinical interpretation of the difference between treatments at various cutoffs (eg, 10%, 15%), Appendix Figures A4 and A5 (online only) show the cumulative distribution changes in key symptom scores from baseline at 6 and 12 weeks, respectively. Using a cutoff of 10% or higher, significant differences between treatment arms were observed for dyspnea, fatigue, and appetite loss. Appendix Figure A6 (online only) shows the mean difference between treatment arms for all functional scales calculated by the mixed-effect model repeat measurement.

Sensitivity Analysis: Data Evaluation up to Progression

When evaluating data only up to progression, the time to deterioration of key symptoms was longer with osimertinib than with chemotherapy, and a greater proportion of patients reported an improvement in global health status/quality of life, as was found in our main analyses (Appendix Tables A1 and A2, online only).

DISCUSSION

In this study, we demonstrated that osimertinib delayed time to deterioration of several key patient-reported symptoms in advanced NSCLC compared with chemotherapy. We also showed a higher rate of symptom improvement with osimertinib over chemotherapy among symptomatic patients at baseline. With an increasing understanding of the multifaceted nature of HRQoL in advanced cancers, time to deterioration and improvement in symptoms and function are different but important aspects of PROs for patients who participated in the AURA 3 trial. The PRO data further substantiate the clinical meaningfulness of the statistically significant prolongation in PFS with osimertinib over chemotherapy. The data support regulatory approval and drug labeling and aid physicians and patients in treatment decision making.

To the best of our knowledge, this is the first detailed study to report on the symptom control and PRO benefits of treatment with osimertinib. As anticipated, the sensitivity analysis that limited PRO data up to progression was consistent with our main analyses, which included postprogression data. However, greater effect sizes were observed because patients randomly assigned to the chemotherapy arm that crossed over to osimertinib at disease progression diluted the effect on the relative difference in PROs in our main analysis.

The data from our study are comparable to that in other trials that compared a TKI with chemotherapy. For example, in the LUX-Lung 3 (BIBW 2992 [Afatinib] Versus Chemotherapy as First Line Treatment in NSCLC With EGFR Mutation) trial,[39] a contemporary study that used the same PRO instruments, afatinib was associated with a longer time to deterioration of cough and dyspnea but not pain when compared with chemotherapy. Physical and role functioning, global health status/quality of life were also improved over time with afatinib compared with chemotherapy. It

Table 1. Patients With Symptoms and Mean Score at Baseline

Symptom	Questionnaire	Treatment	Patients With Symptoms at Baseline*		Patients With a Baseline Score		Score at Baseline	
			No.	%	No.	%	Mean	95% CI
Cough	LC13	Osimertinib	150	53.8	230	82.4	31.2	27.4 to 35.0
		Chemotherapy	84	60.0	116	82.9	35.9	30.5 to 41.3
Chest pain	LC13	Osimertinib	84	30.1	230	82.4	15.4	12.4 to 18.4
		Chemotherapy	56	40.0	116	82.9	20.4	15.9 to 24.9
Dyspnea	LC13	Osimertinib	169	60.6	230	82.4	22.8	20.0 to 25.6
		Chemotherapy	89	63.6	116	82.9	26.6	22.4 to 30.8
Fatigue	C30	Osimertinib	192	68.8	246	88.2	30.4	27.3 to 33.5
		Chemotherapy	100	71.4	116	82.9	36.7	31.7 to 41.7
Appetite loss	C30	Osimertinib	108	38.7	246	88.2	21.4	17.9 to 24.9
		Chemotherapy	60	42.9	116	82.9	27.0	21.2 to 32.8

Abbreviations: C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; LC13, EORTC 13-item Quality of Life Questionnaire-Lung Cancer Module.
*Number of patients with individual symptom scores ≥ 10 at baseline indicative of symptomatic status.

should be noted, however, that the LUX-Lung 3 trial enrolled treatment-naive patients whereas AURA3 enrolled previously treated patients (second-line therapy), which further emphasizes the effectiveness of osimertinib in controlling these key NSCLC symptoms.

The PRO instruments are widely used in studies of advanced NSCLC[40] and have previously been well validated.[32,37,41] Our primary analysis was based on an improvement cutoff score of ≥ 10% from baseline to determine clinical relevance, which is based on observations in other cancers,[38] as well as a recent meta-analysis of multiple cancers and a variety of clinical situations.[42,43] Other studies have also examined other thresholds for improvement based on clinical (performance status and weight)[44] and HRQoL[45] anchors in defining minimal important differences. There were considerable variations in thresholds for the same symptom across different studies and also for different symptoms within the same studies. The thresholds also varied depending on the types of anchors used. The results of differences in means of symptoms (Fig 5) and change in function scores (Appendix Fig A6) between treatment arms have generally reached the thresholds considered to be minimal important differences for improvement in the AURA 3 trial.

This analysis has several limitations. First, 82% to 88% of patients at baseline completed the PRO questionnaires, a completion rate that is in line with that of other NSCLC clinical trials.[46,47] Second, mean absolute symptom scores were lower at baseline in the osimertinib than in the chemotherapy arm, but these differences were not statistically significant. Despite these differences, the baseline scores of the osimertinib and chemotherapy arms of the AURA3 population were within the range of the EORTC reference population.[48] Most importantly, our analysis focused on relative differences (rather than absolute differences), and thus any potential imbalance in baseline scores would have minimal effect on the results. In all of our analyses, we also adjusted for relative differences according to the baseline PRO ratings. Third, we did not adjust for multiple testing in our analyses. Because PROs were a secondary end point in AURA3 and because the trial was not powered for each of the individual PRO hypotheses, the results of this analysis should be considered exploratory and hypothesis-generating. Fourth, the time interval of once every 6 weeks assessment of QLQ-C30 questionnaires might potentially be too long to capture time to deterioration compared with QLQ-LC13 questionnaires being assessed once per week for the first 6 weeks. However, there is a low potential for bias because the procedure for collecting data was similar for both treatment arms, and consistent treatment effects were demonstrated (Fig 4) despite differences in the assessment time points. Finally, cultural and language factors could affect the data captured by PROs and therefore such factors need to be considered in multinational trials,[30] although prior studies have shown that those factors made

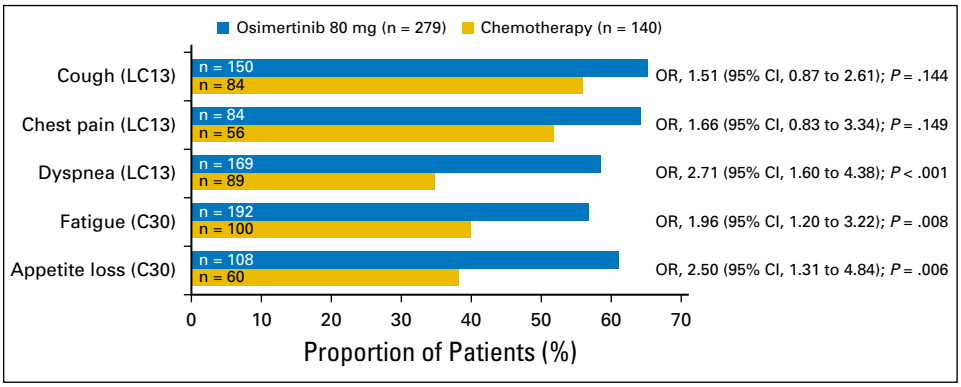

Fig 3. Proportions of patients with improvement in key lung cancer symptoms. C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; LC13, EORTC 13-item Quality of Life Questionnaire Lung Cancer Module; OR, odds ratio.

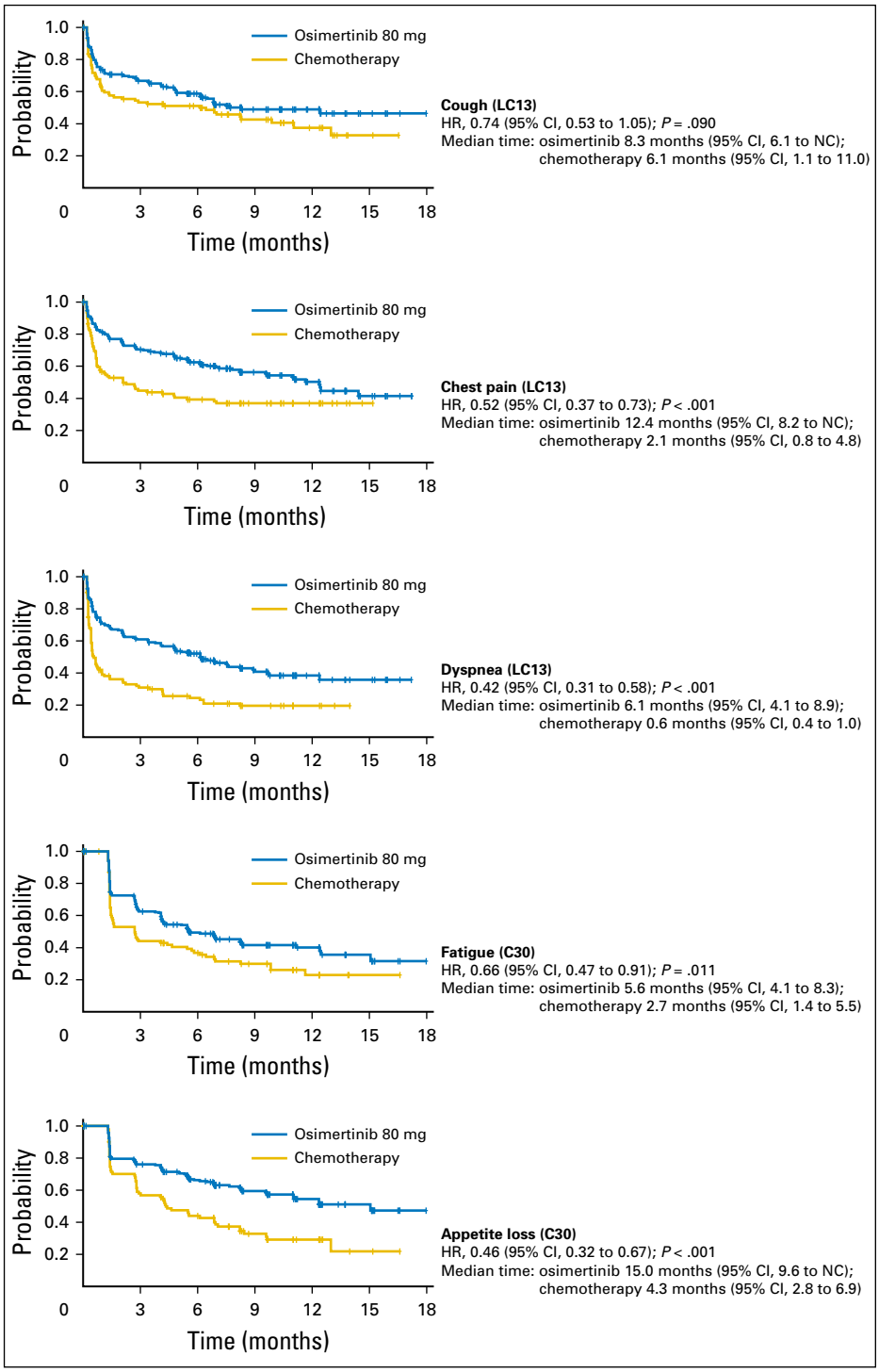

Fig 4. Time to symptom deterioration of key lung cancer symptoms. C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; HR, hazard ratio; LC13, EORTC 13-item Quality of Life Questionnaire Lung Cancer Module. NC, not calculable.

only a modest contribution to the variation in PROs.[49] A study of 13 different translations from 22 countries reported good linguistic equivalence for most of the QLQ-C30 items, but several scales showed strongly discrepant results for some translations.[34] Another study reported that most response patterns to QLQ-C30 items were similar, but some international differences in how the questionnaire was answered were noted, particularly for Eastern Europeans and East Asians.[34] Different cultural groups also emphasized certain aspects of their HRQoL assessment differently.[35] The potential effect of these factors is limited because our analysis focused on the relative differences between two treatment arms, and we also adjusted for baseline PRO ratings. Furthermore, AURA3 was a large study in which the randomization process resulted in a distribution between the two arms of patients who were similar in terms of their cultural and language backgrounds. This trial was further stratified according to Asian or non-Asian

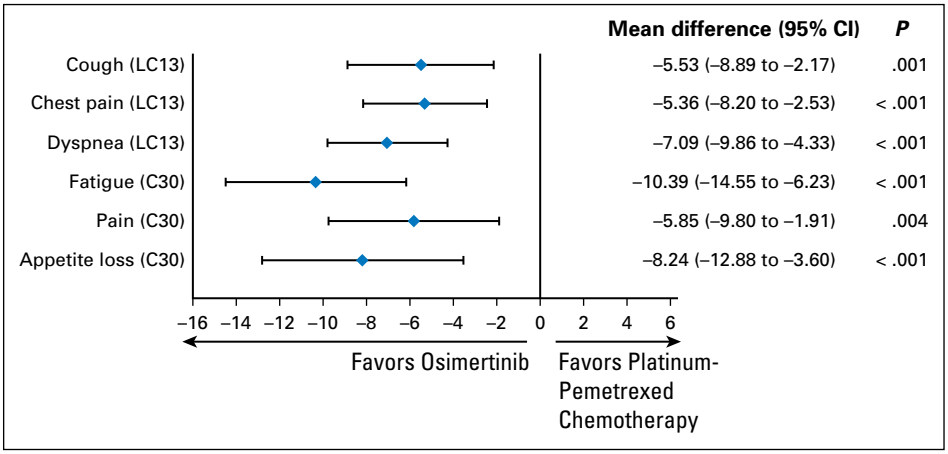

Fig 5. Longitudinal analyses for the prespecified key lung cancer symptoms. The mean differences for each symptom are represented by diamonds, and the horizontal line crossing the diamond represents the 95% CIs. A positive mean difference favors platinum-pemetrexed chemotherapy, and a negative difference favors osimertinib. C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; LC13, EORTC 13-item Quality of Life Questionnaire Lung Cancer Module.

race. Therefore, differences in these factors should not substantially affect the conclusion of our analysis.

Prospective evaluation of PROs with the appropriate hypothesis and instruments is vital, particularly in clinical trials that evaluate new therapeutics in incurable cancers. Benefit in terms of PROs may be expected if a drug is efficacious and has a good tolerability profile. By contrast, if a new treatment is found to be efficacious but highly toxic, it is impossible to evaluate the trade-off of efficacy versus toxicity without collecting prospective PRO data.

With the increasing costs of health care, the value of new cancer treatments is being scrutinized more closely.[50] The European Society for Medical Oncology (ESMO) has developed and validated the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)[51] for grading the magnitude of clinically meaningful benefit. Osimertinib has been shown to improve surrogate end points of antitumor activity, such as response rate and PFS[12-14]; such a benefit would be scored as 3 of the maximum rating of 5 using the ESMO-MCBS. Because the ESMO-MCBS also emphasizes the effect of new treatments on global HRQoL in incurable cancers, improvement in PROs increases the score to 4. PRO data, as reported in our study, provide a clear contribution to evaluation of the overall clinical benefit.

In conclusion, AURA3 demonstrated substantially improved PROs with osimertinib when compared with chemotherapy together with substantial improvement in PFS. These PRO data further support the role of osimertinib as the new standard of care in the second-line setting for patients with advanced EGFR T790M-positive NSCLC who progressed after first-line EGFR-TKI therapy.

AUTHOR CONTRIBUTIONS

Conception and design: Chee Khoon Lee, Silvia Novello, Anna Rydén, Helen Mann, Tony Mok
Provision of study materials or patients: Chee Khoon Lee, Silvia Novello
Collection and assembly of data: Chee Khoon Lee, Silvia Novello, Tony Mok
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

This work was funded by AstraZeneca.

Prior Presentation

Presented at the European Lung Cancer Conference, Geneva, Switzerland, May 5-8, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient-Reported Symptoms and Impact of Treatment With Osimertinib Versus Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The AURA3 Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca (Inst)
Travel, Accommodations, Expenses: AstraZeneca

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Speakers' Bureau: AstraZeneca, Eli Lilly, Bristol-Myers Squibb, MSD Oncology, Roche

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Stock or Other Ownership: AstraZeneca

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Employment: The Chinese University of Hong Kong
Leadership: Sanomics Limited
Stock or Other Ownership: Sanomics Limited, Cirina
Honoraria: AstraZeneca, Genentech, Eli Lilly, Bristol-Myers Squibb, Boehringer Ingelheim, Novartis, Merck Sharp & Dohme, Pfizer
Consulting or Advisory Role: AstraZeneca, Genentech, Eli Lilly, Merck Serono, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis, Clovis Oncology, Vertex Pharmaceuticals, SFJ Pharmaceuticals Group, ACEA Biosciences, Merck Sharp & Dohme, geneDecode, OncoGenex, Celgene, Ignyta, Cirina
Research Funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Novartis (Inst), SFJ Pharmaceuticals Group (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Clovis Oncology (Inst), Bristol-Myers Squibb (Inst), Taiho Pharmaceutical (Inst), Eisai (Inst)

Acknowledgment

We thank the patients and investigators involved in the AURA studies and the team at AstraZeneca. Nesta Hughes, PhD, of Oxford PharmaGenesis, Oxford, United Kingdom, provided medical writing support, funded by AstraZeneca.

Appendix

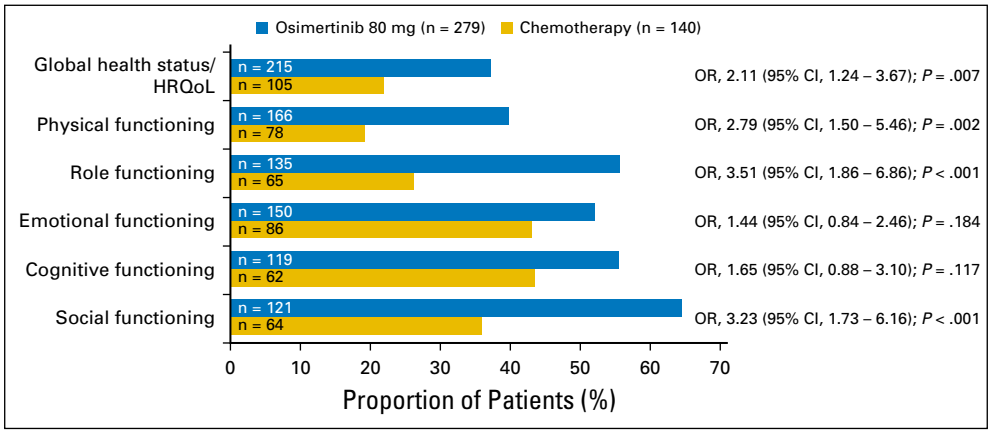

Fig A1. The proportion of patients with improvement in functioning scales. HRQoL, health-related quality of life; OR, odds ratio.

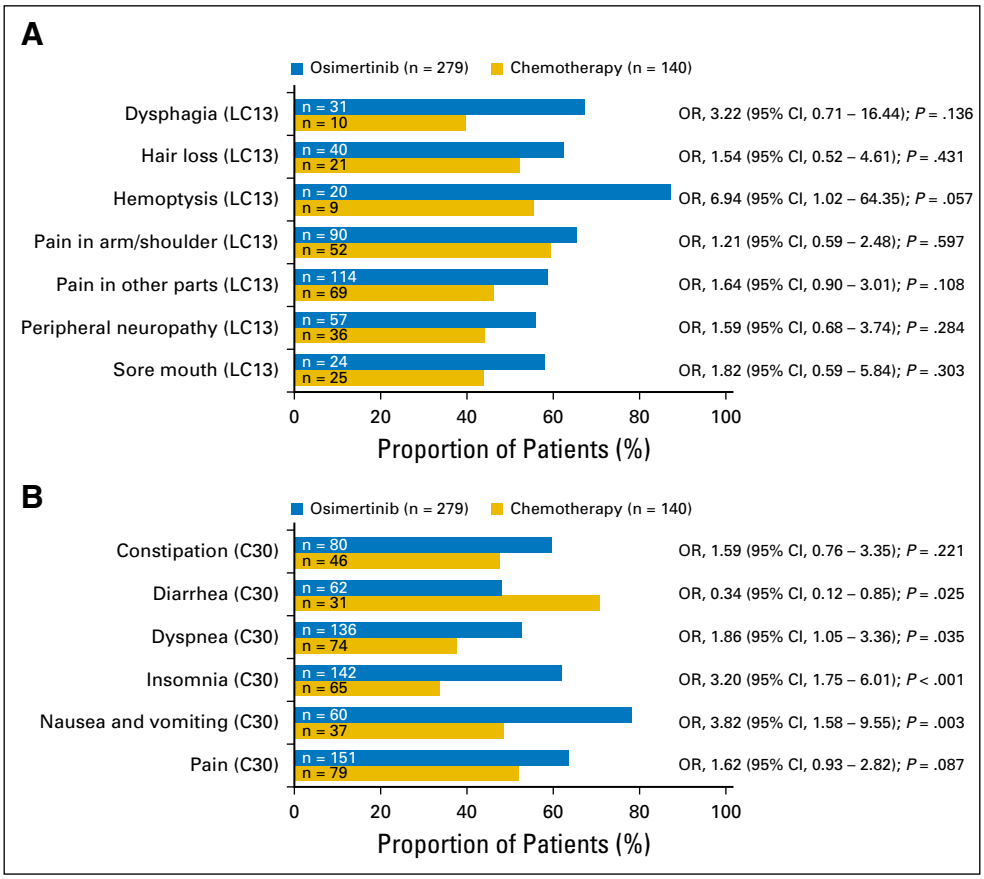

Fig A2. The proportion of patients with improvement in remaining symptoms (other than the five key symptoms). C30, European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire; LC13, EORTC 13-item Quality of Life Questionnaire Lung Cancer Module; OR, odds ratio.

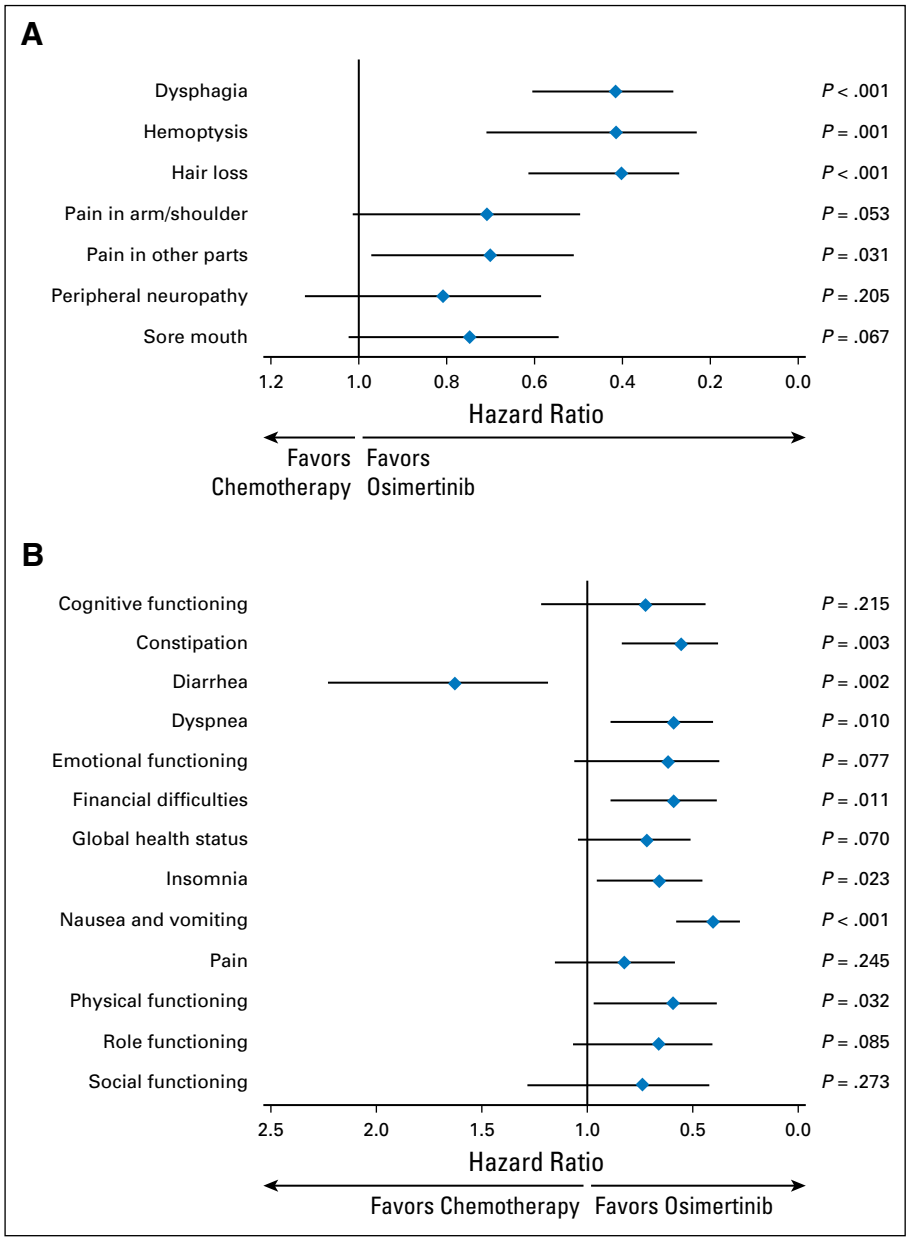

Fig A3. Forest plot of hazard ratios for symptoms (other than the five key symptoms) and functioning domains.

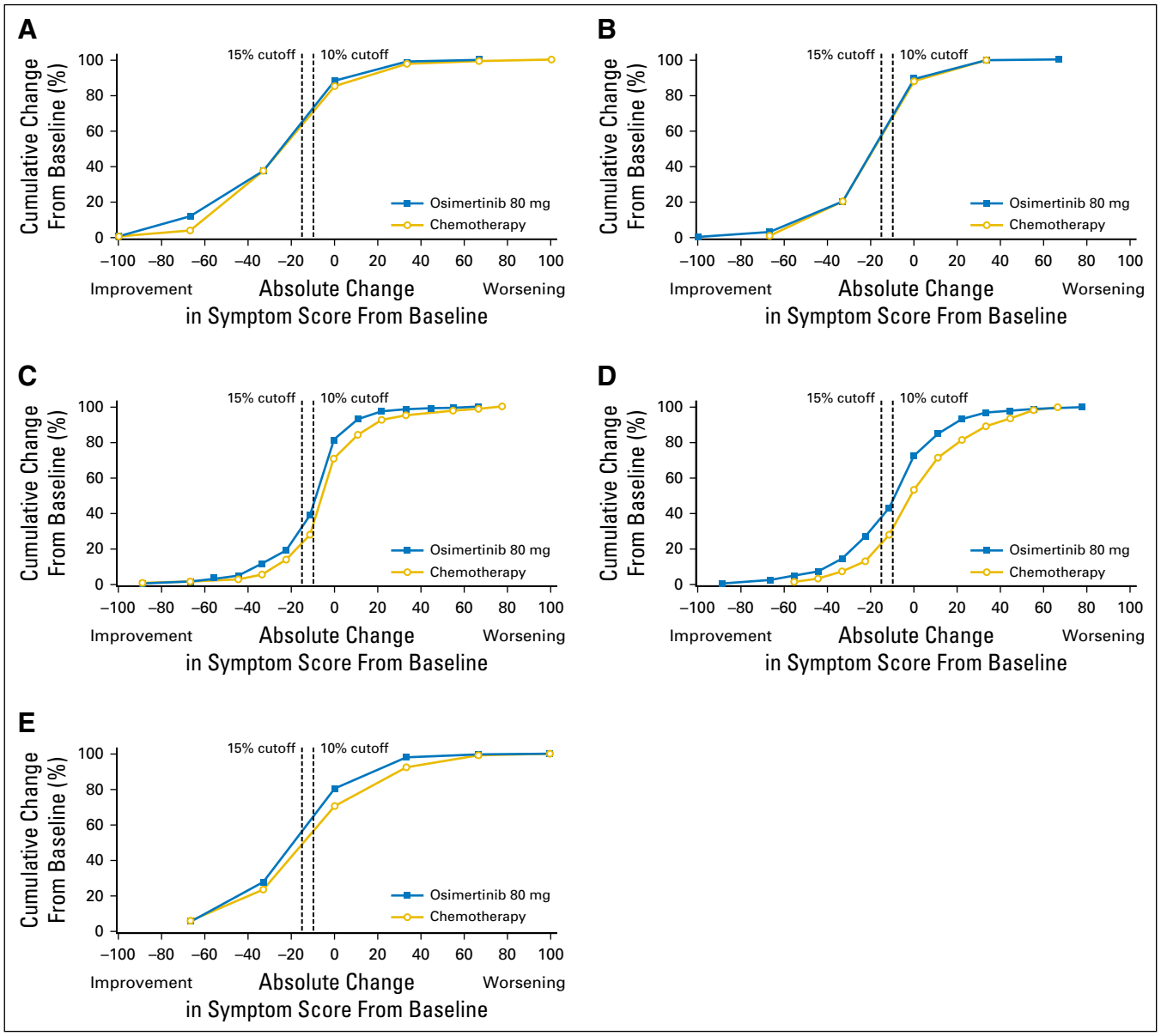

Fig A4. Cumulative distribution functions of absolute change in key symptom scores from baseline at 6 weeks for (A) cough, (B) chest pain, (C) dyspnea, (D) fatigue, and (E) appetite loss.

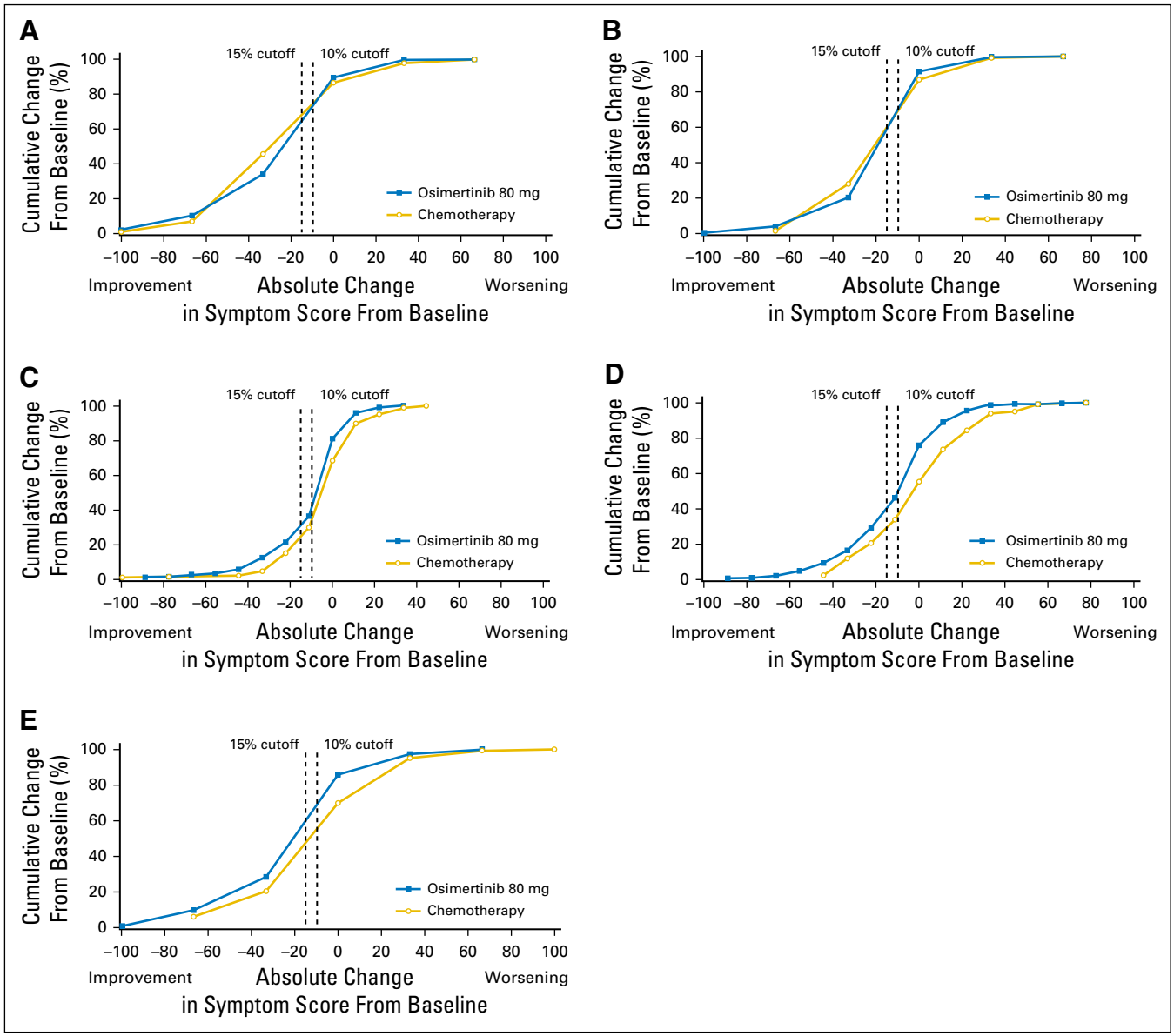

Fig A5. Cumulative distribution functions of absolute change in key symptom scores from baseline at 12 weeks for (A) cough, (B) chest pain, (C) dyspnea, (D) fatigue, and (E) appetite loss.

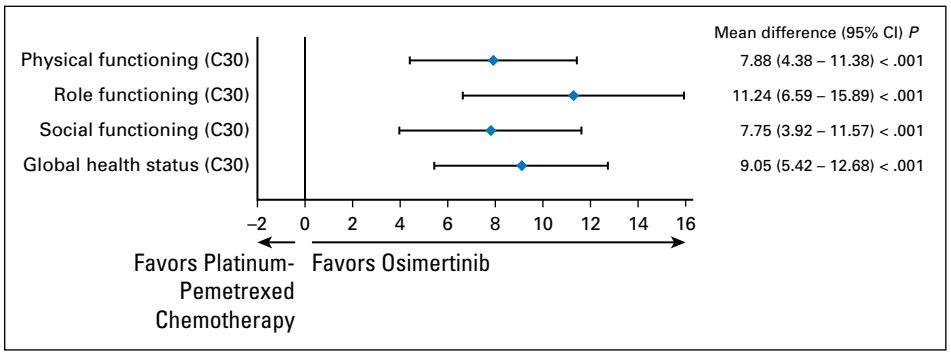

Fig A6. Longitudinal analyses for the functioning scales. The mean differences for each functioning scale are represented by diamonds, and the horizontal line crossing the diamond represents the 95% CIs. A positive mean difference favors osimertinib, and a negative difference favors platinum-pemetrexed chemotherapy.

Table A1. Sensitivity Analysis Examining Relative Symptom Improvement Rate Between Treatment Arms from Random Assignment Until Disease Progression

Symptom	No./N1 (%)	OR (95% CI)	RR (95% CI)	Risk Difference	*P*
Cough (LC13)	Osimertinib: 91/150 (60.7) Chemotherapy 36/84 (42.9)	2.06 (1.20 to 3.56)	1.42 (1.09 to 1.91)	17.8 (4.5-30.7)	.009
Chest pain (LC13)	Osimertinib: 49/84 (58.3) Chemotherapy: 23/56 (41.1)	2.01 (1.02 to 4.03)	1.42 (1.01 to 2.10)	17.3 (0.4-33.4)	.045
Dyspnoea (LC13)	Osimertinib: 95/169 (56.2) Chemotherapy: 26/89 (29.2)	3.11 (1.81 to 5.45)	1.92 (1.39 to 2.81)	27.0 (14.6-38.6)	< .001
Fatigue (C30)	Osimertinib: 103/192 (53.6) Chemotherapy: 28/100 (28.0)	2.98 (1.78 to 5.07)	1.92 (1.39 to 2.76)	25.6 (14.0-36.5)	< .001
Appetite loss (C30)	Osimertinib: 63/108 (58.3) Chemotherapy: 18/60 (30.0)	3.27 (1.69 to 6.51)	1.94 (1.32 to 3.08)	28.3 (13.0-42.5)	< .001

NOTE. An OR or RR > 1 or a risk difference > 0 favors osimertinib.
Abbreviations: C30; European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire; LC13; European Organisation for Research and Treatment of Cancer 13-Item Quality of Life Questionnaire-Lung Cancer Module; No., number of patients with improvement; N1, number of patients with symptom scales baseline individual scores ≥ 10; RR, relative risk. OR, odd ratio; RR, relative risk.

Table A2. Sensitivity Analysis Examining Relative Time to Symptom Deterioration Between Treatment Arms From Random Assignment Until Disease Progression

Symptom	No./N1 (%)	HR (95% CI)	*P*	Median Time to Deterioration (months)
Cough (LC13)	Osimertinib: 89/215 (41.4) Chemotherapy: 52/106 (49.1)	0.68 (0.48 to 0.96)	.028	12.42 (6.28-NC) 3.38 (0.99-NC)
Chest pain (LC13)	Osimertinib: 83/226 (36.7) Chemotherapy: 61/113 (54.0)	0.48 (0.34 to 0.67)	< .001	12.42 (9.66-NC) 2.27 (0.89-5.45)
Dyspnoea (LC13)	Osimertinib: 112/228 (49.1) Chemotherapy: 77/114 (67.5)	0.44 (0.32 to 0.59)	< .001	6.21 (4.76-9.69) 0.56 (0.43-0.99)
Fatigue (C30)	Osimertinib: 115/242 (47.5) Chemotherapy: 54/110 (49.1)	0.63 (0.46 to 0.88)	.008	6.83 (4.21-11.17) 2.69 (1.45-5.68)
Appetite loss (C30)	Osimertinib: 79/237 (33.3) Chemotherapy: 50/107 (46.7)	0.45 (0.32 to 0.65)	< .001	NC (9.63-NC) 4.27 (2.79-6.87)

NOTE. A hazard ratio < 1 favors osimertinib.
Abbreviations: HR, hazard ratio; LC13; European Organisation for Research and Treatment of Cancer 13-Item Quality of Life Questionnaire-Lung Cancer Module; No., number of patients with deterioration; N1, number of patients who have baseline individual score ≤ 90; NC, Noncalculable.