Original Research

Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer

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KEYWORDS
EORTC QLQ-C30; EORTC QLQ-LC13; Non-small-cell lung cancer; Osimertinib; Patient-reported outcomes

Abstract  Background: In the FLAURA trial, osimertinib demonstrated superior progression-free survival and a favorable toxicity profile to erlotinib or gefitinib as initial therapy in patients with EGFR-mutated advanced non-small-cell lung cancer. Patient-reported outcomes from FLAURA are discussed here.

Methods: Patients (N = 556) completed the EORTC QLQ-LC13 weekly for 6 weeks, then every 3 weeks, and the QLQ-C30 every 6 weeks. Prespecified key symptoms were cough, dyspnea, chest pain, appetite loss, and fatigue. Score changes from baseline to randomized treatment discontinuation were assessed using a mixed-effects model. A ≥10-point change was considered clinically relevant. Odds of improvement and time to deterioration were investigated. QLQ-C30 functioning scores were assessed post hoc.

Results: Questionnaire completion rates were >70% at most time points. Baseline mean scores were similar in the osimertinib and erlotinib/gefitinib arms. Scores improved in both arms, but none reached clinical relevance at 5% significance level. A statistically significant difference

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favoring osimertinib for chest pain was not clinically relevant (−6.84 vs −3.88; p = 0.021). Odds of improvement and time to deterioration were similar between treatments. In post hoc analyses, improvements favored osimertinib for emotional functioning (8.79 vs 4.91; p = 0.004) and social functioning (7.66 vs 1.74; p < 0.001). Cognitive functioning remained stable with osimertinib but deteriorated with erlotinib/gefitinib (0.03 vs −3.91; p = 0.005).

Conclusions: Key symptoms improved from baseline in both treatment arms in FLAURA. Key symptom improvements that were both statistically significant and clinically relevant were not observed in favor of either treatment arm.

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1. Introduction

For patients with advanced non-small-cell lung cancer (NSCLC) and sensitizing epidermal growth factor receptor mutations (EGFRm), the introduction of targeted therapy with EGFR–tyrosine kinase inhibitors (TKIs) has markedly improved clinical outcomes [1–7].

Symptom management is crucial in the treatment of patients with advanced NSCLC. Cough, dyspnea, chest pain, fatigue, and appetite loss are key patient-reported symptoms and have a marked negative impact on health-related quality of life (HRQoL) [8,9]. Patients with advanced NSCLC who received first-line treatment with erlotinib, gefitinib, or afatinib experienced improvements in symptoms and HRQoL compared with patients who received chemotherapy [10–12]. In the LUX-Lung 7 trial that compared first-line afatinib and gefitinib, similar improvements in patient-reported outcomes (PROs) were observed in both treatment arms [13]. In the ARCHER 1050 trial, progression-free survival (PFS) and overall survival (OS) were longer with dacomitinib than with gefitinib [14]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18]. The greater selectivity for mutated EGFR and relative sparing of wild-type EGFR also mean that osimertinib is associated with less toxicity than earlier EGFR-TKIs [15–18].

Osimertinib is an oral, irreversible, central nervous system (CNS)-active, third-generation EGFR-TKI with preclinical and clinical evidence of potent activity against EGFRm NSCLC and the T790M resistance mutation, the most common cause of resistance to early-generation EGFR-TKIs [19–21]. The FLAURA trial, in patients in the osimertinib arm compared with those in the erlotinib/gefitinib arm.

2. Methods

2.1. Study design and patients

FLAURA (NCT02296125) was a multinational, phase 3, double-blind, double-dummy, randomized trial [16]. The methods and primary efficacy results have been reported in detail [16]. In brief, eligible patients had locally advanced or metastatic EGFRm (exon 19 deletion or L858R) NSCLC and were eligible for first-line treatment with an EGFR-TKI. Patients were randomized 1:1 to receive oral osimertinib 80 mg once daily (n = 279) or either oral gefitinib 250 mg once daily or oral erlotinib 150 mg once daily (n = 277). The cut-off date for the current analysis was 12 June 2017.

FLAURA was conducted in accordance with the Declaration of Helsinki and is consistent with the International Conference on Harmonisation and Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca Bioethics Policy. The study was approved by the institutional review board and/or independent ethics committee associated with each study center. All patients provided written
2.2. Questionnaires

Patients completed the questionnaires using electronic devices. The EORTC QLQ-LC13 was completed at baseline, then every week for 6 weeks, followed by every 3 weeks. The EORTC QLQ-C30 was completed at baseline and then every 6 weeks. The EORTC QLQ-LC13 is a 13-item lung-cancer-specific questionnaire that measures disease-related symptoms and treatment-related side effects [20]. The EORTC QLQ-C30 is a 30-item cancer questionnaire that measures symptoms and functional aspects commonly related to cancer [21]. An outcome variable consisting of a score from 0 to 100 was derived from each of the symptom scales and items in the two questionnaires [20,21]. A higher score on the symptom scale represents more/worse symptoms [20,21]. Higher functional scores represent a higher (“better”) HRQoL or level of functioning [20,21]. For both questionnaires, a difference in score of at least 10 points was considered clinically relevant, corresponding to at least a moderate change in HRQoL [22]. The prespecified key symptoms of importance in advanced NSCLC were cough, dyspnea, chest pain, appetite loss, and fatigue [8,9]. Changes from baseline in these symptoms were prespecified as key endpoints (Supplementary Table 1).

Changes from baseline in QLQ-C30 global health status/quality of life (QoL) and functioning from baseline were assessed in a post hoc analysis.

2.3. Data analyses

Scores for EORTC QLQ-LC13 and QLQ-C30 prespecified key symptoms were summarized descriptively in the full analysis set. The analyses for each item used all data up to disease progression and beyond. Changes in scores from baseline until randomized treatment discontinuation were assessed using mixed-effects model for repeated measures (MMRM) analysis. Missing data were not imputed. The \( p \) value was determined using MMRM analysis, with patient, treatment, visit, and treatment by visit interaction as explanatory variables and baseline symptom score and baseline symptom score by visit interaction as covariates. Patient was fitted as a random effect, and compound symmetry covariance structure was used for all models. The mean differences for each symptom are reported with corresponding 95% CIs. A sensitivity analysis was conducted that used PRO data from baseline to 9 months, and results were compared for consistency with those from the main analysis.

The proportion of patients with clinically relevant improvements in key symptoms, defined as a decrease in score from baseline of at least 10 at two consecutive assessments at least 21 days apart, was compared using logistic regression, with a factor for treatment arm. Odds ratios with 95% CIs are reported.

Time-to-symptom deterioration, defined as time from randomization until the date of the first clinically relevant symptom deterioration or death from any cause, was assessed for the five key symptoms until randomization until the date of the first clinically relevant symptom deterioration or death from any cause, using Kaplan–Meier analysis. The difference in time-to-symptom deterioration was assessed by log-rank test, and \( p \) values are reported.

Owing to the exploratory nature, all analyses must be interpreted conservatively given the multiple scales, time points, and hypotheses (a two-sided 5% significance level has been used for interpretation purposes only, no adjustments have been made for multiplicity).

### Table 1

<table>
<thead>
<tr>
<th>Scale/items</th>
<th>Osimertinib, mean (SD)</th>
<th>Erlotinib/gefitinib, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom scale/items</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.2 (24.9)</td>
<td>35.8 (26.2)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7.3 (14.9)</td>
<td>7.2 (13.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>25.8 (27.5)</td>
<td>27.2 (27.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24.4 (28.4)</td>
<td>25.2 (27.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25.6 (27.9)</td>
<td>30.2 (28.4)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>22.7 (28.5)</td>
<td>25.6 (29.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13.3 (23.0)</td>
<td>16.2 (25.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.4 (14.6)</td>
<td>5.7 (15.1)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>15.4 (24.3)</td>
<td>16.5 (26.7)</td>
</tr>
<tr>
<td><strong>Global health status/QoL</strong></td>
<td>62.5 (23.2)</td>
<td>58.8 (22.8)</td>
</tr>
<tr>
<td><strong>Functional scales</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>79.6 (21.6)</td>
<td>75.7 (21.0)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>77.8 (28.2)</td>
<td>75.0 (29.1)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>74.8 (20.0)</td>
<td>72.9 (22.1)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>86.5 (18.4)</td>
<td>84.6 (19.5)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>80.6 (24.6)</td>
<td>77.3 (26.1)</td>
</tr>
</tbody>
</table>

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-LC13, Quality of Life Questionnaire Lung Cancer 13 items; QLQ-C30, Quality of Life Questionnaire Core 30 items; QoL, quality of life; SD, standard deviation.

* Prespecified key symptom.
gefitinib arm at the time of data cut-off [16]. The median duration of follow-up for PFS was 15.0 months in the osimertinib arm and 9.7 months in the erlotinib/gefitinib arm [16]. Ninety-one (66.9%) patients in the osimertinib arm and 145 (70.4%) patients in the erlotinib/gefitinib arm remained on randomized treatment after progression, for a similar length of time.

3.1. Questionnaire completion rates

Questionnaire completion rates at baseline were >90% in both arms. Completion rates declined faster in the erlotinib/gefitinib arm than in the osimertinib arm, likely reflecting differences in PFS rates between the two treatment arms (Supplementary Tables 2 and 3).

3.2. Baseline symptoms

Mean key symptom scores at baseline were low and similar in the osimertinib and erlotinib/gefitinib arms (Table 1). Many patients responded “not at all” to the key symptom severity questions, and most patients who reported baseline symptoms graded their severity as “a little” (Fig. 1). The proportion of patients reporting at least “a little” severity was lowest for “dyspnea when rested” (osimertinib: 23.0%; erlotinib/gefitinib: 30.3%) and highest for “felt tired” (66.3% vs 70.8%) (Fig. 1).

3.3. Changes from baseline

Key symptoms improved from baseline until treatment discontinuation in both groups (Table 2). None of the improvements in key symptoms reached the predefined 10-point threshold for clinical relevance at 5% significance level. For chest pain, improvements from baseline were statistically significantly better with osimertinib than with erlotinib/gefitinib (mean change in score: −6.84 vs −3.88; estimated difference: −2.96; 95% CI: −5.47, −0.45; p = 0.021). Improvements in cough were seen as early as week 1 in both treatment arms (mean change in score, osimertinib: −6.6; erlotinib/gefitinib: −4.9) and were maintained throughout the study period. Results from the sensitivity analysis using data from baseline to 9 months were consistent with those from the main analysis, except for chest pain (Supplementary Table 4).

Similar proportions of patients in the two treatment arms had clinically relevant improvements in key symptoms during randomized treatment. No significant difference in odds of improvement of prespecified key symptoms was detected (Fig. 2).

![Symptom severity at baseline](image_url)

Fig. 1. Proportion of patients in the osimertinib and erlotinib/gefitinib arms reporting key symptoms at baseline, shown by reported symptom severity. E/G, erlotinib/gefitinib; Osi, osimertinib.
The proportion of patients who had a clinically relevant symptom deterioration event from randomization until randomized treatment discontinuation was the lowest for chest pain (osimertinib: 37.3%; erlotinib/gefitinib: 33.6%) and highest for dyspnea (osimertinib: 57.0%; erlotinib/gefitinib: 56.3%) (Table 3). For patients with a clinically relevant deterioration event, the median time from randomization to the first event was similar in the two treatment arms, with overlapping 95% CIs for medians (Table 3 and Supplementary Fig. 1).

Improvements in global health status/QoL and functional scores from baseline to randomized treatment discontinuation were seen in both treatment arms (Fig. 3). Improvements in the osimertinib arm were statistically significantly greater than in the erlotinib/gefitinib arm for emotional functioning (8.79 vs 4.91; \( p = 0.004 \)) and social functioning (7.66 vs 1.74; \( p < 0.001 \)). Cognitive functioning remained stable in the osimertinib arm but deteriorated in the erlotinib/gefitinib arm (0.03 vs –3.91; \( p = 0.005 \)). None of the mean changes reached the 10-point improvement threshold for clinical relevance.

4. Discussion

In the FLAURA trial, first-line treatment with osimertinib demonstrated superior efficacy to erlotinib or gefitinib in patients with EGFRe advanced NSCLC, including in patients with CNS metastases at trial entry [16]. The PRO analyses presented here show improvements in key lung cancer symptoms in both treatment arms from baseline until randomized treatment discontinuation. Statistically significant differences in favor of osimertinib were observed for changes from baseline in chest pain, and emotional, social, and cognitive functioning, although these differences did not meet the predefined threshold for clinical relevance.

The overall burden of key lung cancer symptoms was low at baseline, with most patients in both treatment arms reporting symptom severity of “not at all” or “a little.” The low baseline symptom burden, which is common in patients receiving first-line treatment for NSCLC [23], poses technical challenges in the measurement of improvements. A 10-point change in QLQC30 score is commonly used as the minimal clinically important difference in phase 3 advanced NSCLC trials [24]. However, results from the French Cooperative Thoracic Intergroup (IFCT) indicate that a lower, 5-point cut-off could be clinically relevant [25]. Use of the IFCT definition for the data reported here reveals clinically relevant improvements during randomized treatment in both arms for cough and in the osimertinib arm for chest pain, appetite loss, global health status/QoL, and emotional and social functioning.

Only one-third to just over half of patients remaining on protocol therapy in the current analysis experienced a clinically relevant deterioration in key lung cancer symptoms at any time from randomization to randomized treatment discontinuation. Among patients who experienced a clinically relevant deterioration in symptoms, the time to the first recorded event was similar in the two treatment arms. A challenge in clinical oncology research is the lack of a standardized definition or method of analysis for deterioration. Patients may experience only asymptomatic progression such as radiological progression (e.g. a new asymptomatic lesion) or symptomatic progression involving nonkey symptoms (e.g. due to CNS metastasis). In FLAURA, sites of progression differed between treatment arms. Furthermore, patients in the erlotinib/gefitinib arm progressed significantly earlier than those in the osimertinib arm, making those remaining on treatment...
highly selected. There is thus a bias in the sensitivity of the time to deterioration analysis.

The FLAURA trial showed a significant and clinically meaningful improvement in PFS of osimertinib compared with standard of care (18.9 months vs 10.2 months), but with no clinically meaningful difference between arms in key symptoms. There may be a few reasons for this apparent disparity. PFS is measured by radiological progression (increase in tumor size; new lesion). Progression can be asymptomatic, depending on the location and nature of the tumor(s) leading to progression, and it is common practice for patients to continue treatment in such cases. In this trial, approximately 70% of patients continued randomized treatment beyond progression in both treatment arms for a similar median duration. If a progression event is symptomatic, it may lead to symptoms that are not detected in the PRO data or to a small increase in symptoms that is not considered clinically meaningful using current analytical methods.

In the FLAURA trial, 19% of patients in the osimertinib arm and 23% in the erlotinib/gefitinib arm had known or treated CNS metastases at trial entry [16]. Irrespective of status of CNS metastases at baseline, the rate of CNS progression was higher in the erlotinib/gefitinib arm (15%) than in the osimertinib arm (6%) [16]. Cognitive function deteriorated in the erlotinib/gefitinib arm in the current analysis but did not change from baseline in the osimertinib arm, which may reflect differences in CNS progression between the two treatment arms.

In real-world management of patients with advanced NSCLC, incremental gains in PFS or OS are regarded as clinically meaningful only if they are achieved without a marked negative effect on HRQoL [26]. As such, it is important to record PROs (symptoms, function, HRQoL) in trials. Results from FLAURA demonstrate that the efficacy of osimertinib was superior to that of first- and second-generation EGFR-TKIs, without increased toxicity [16]. Improvements in key lung cancer symptoms are listed in Table 3.

![Symptom Improvement Rate](image)

**Table 3**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
<th>Patients with deterioration event, n (%)</th>
<th>Median time to deterioration (95% CI)</th>
<th>Probability of no deterioration (% at 6 months)</th>
<th>Probability of no deterioration (% at 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Osimertinib</td>
<td>109 (44.0)</td>
<td>NR (9.92–NR)</td>
<td>63.08</td>
<td>55.44</td>
</tr>
<tr>
<td></td>
<td>Erlotinib/gefitinib</td>
<td>113 (44.8)</td>
<td>13.08 (8.25–NR)</td>
<td>58.88</td>
<td>52.45</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Osimertinib</td>
<td>159 (64.1)</td>
<td>2.79 (1.38–6.18)</td>
<td>44.00</td>
<td>33.41</td>
</tr>
<tr>
<td></td>
<td>Erlotinib/gefitinib</td>
<td>156 (61.9)</td>
<td>4.14 (2.00–6.90)</td>
<td>44.85</td>
<td>37.23</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Osimertinib</td>
<td>104 (41.9)</td>
<td>21.36 (15.24–NR)</td>
<td>67.65</td>
<td>59.95</td>
</tr>
<tr>
<td></td>
<td>Erlotinib/gefitinib</td>
<td>93 (36.9)</td>
<td>11.48 (7.53–15.43)</td>
<td>67.21</td>
<td>60.83</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Osimertinib</td>
<td>150 (58.1)</td>
<td>6.87 (4.17–11.01)</td>
<td>50.59</td>
<td>41.66</td>
</tr>
<tr>
<td></td>
<td>Erlotinib/gefitinib</td>
<td>138 (53.7)</td>
<td>8.25 (5.62–10.61)</td>
<td>56.76</td>
<td>39.13</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>Osimertinib</td>
<td>110 (42.6)</td>
<td>NR (13.77–NR)</td>
<td>69.46</td>
<td>59.93</td>
</tr>
<tr>
<td></td>
<td>Erlotinib/gefitinib</td>
<td>102 (39.7)</td>
<td>15.24 (11.01–NR)</td>
<td>66.12</td>
<td>56.49</td>
</tr>
</tbody>
</table>

CI, confidence interval; NR, not reached.

a Kaplan–Meier analysis. Time-to-symptom deterioration was defined as the time from randomization until the date of the first clinically relevant symptom deterioration (an increase in the score from baseline ≥10 for symptom scales) or death (from any cause).

b The denominator n is all patients with nonmissing baseline values.
symptoms, global health status/QoL, and functioning were observed up to treatment discontinuation, with the median duration of response approximately twice as long in the osimertinib arm as in the erlotinib/gefitinib arm [16].

The FLAURA PRO assessments had several strengths. The EORTC QLQ-LC13 and QLQ-C30 questionnaires are well established and widely used in advanced NSCLC treatment trials [11,27–30], and have been thoroughly validated [20,21,31]. Questionnaire completion rates were high, with more than 70% of patients in both treatment arms completing the questionnaires at most time points. Data for PRO assessments were collected at a large number of time points. The current report highlights limitations inherent to trials of targeted therapy in advanced NSCLC, including the need to identify the most appropriate analyses for time to deterioration and CNS progression when disease and therapy burden may be low. The current report does not include an analysis of whether CNS metastases were associated with differences in PROs. The MMRM analysis used all available data, which assumes that characteristics of patients with incomplete questionnaires were similar to those with complete questionnaires. PROs were secondary outcome measures in FLAURA, and, as such, the trial was not powered for each PRO hypothesis. PRO results should thus be interpreted with caution and are considered exploratory.

In conclusion, PRO results from FLAURA show improvements from baseline in key lung cancer symptoms in both treatment arms. Improvements in key symptoms that were both statistically significant and clinically relevant were not observed in favor of either treatment arm. Further work may be beneficial to explore the effects of CNS metastases on PROs and definitions of improvement and deterioration.

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Conflict of interest statement

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CRSU, Gritstone Oncology, ICON Japan, inVentiv Health, Linical, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Parexel International, Quintiles, Taiho Pharmaceutical, and Takeda Pharmaceutical and fees from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Nichi-Iko Pharmaceutical, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Pfizer, SymBio Pharmaceuticals, and Taiho Pharmaceutical. He has also acted as a consultant for Astellas Pharma and Ono Pharmaceutical. B.C.C. has no disclosures to report. J.E.G. is an advisor for and receives research funding from AstraZeneca. T.H. is a consultant statistician (PHASTAR) for AstraZeneca. A.W. and A.R. are employees of AstraZeneca and hold AstraZeneca shares. S.N. is a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Roche, and Takeda Pharmaceutical.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.11.006.

References


