Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study

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Summary

Background In the ongoing, phase 3 PACIFIC trial, durvalumab improved the primary endpoints of progression-free survival and overall survival compared with that for placebo, with similar safety, in patients with unresectable, stage III non-small-cell lung cancer. In this analysis, we aimed to evaluate one of the secondary endpoints, patient-reported outcomes (PROs).

Methods PACIFIC is an ongoing, international, multicentre, double-blind, randomised, controlled, phase 3 trial. Eligible patients were aged at least 18 years, had a WHO performance status of 0 or 1, with histologically or cytologically documented stage III, unresectable non-small-cell lung cancer, for which they had received at least two cycles of platinum-based chemoradiotherapy, with no disease progression after this treatment. We randomly assigned patients (2:1) using an interactive voice response system and a blocked design (block size=3) stratified by age, sex, and smoking history to receive 10 mg/kg intravenous durvalumab or matching placebo 1–42 days after concurrent chemoradiotherapy, then every 2 weeks up to 12 months. The primary endpoints of progression-free survival and overall survival have been reported previously. PROs were a prespecified secondary outcome. We assessed PRO symptoms, functioning, and global health status or quality of life in the intention-to-treat population with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) at the time of random allocation to groups, at weeks 4 and 8, every 8 weeks until week 48, and then every 12 weeks until progression. Changes from baseline to 12 month in key symptoms were analysed with mixed model for repeated measures (MMRM) and time-to-event analyses. A 10-point or greater change from baseline (deterioration or improvement) was deemed clinically relevant. This study is registered with ClinicalTrials.gov, NCT02125461, and EudraCT, 2014-000336-42.

Findings Between May 9, 2014, and April 22, 2016, 476 patients were assigned to receive durvalumab, and 237 patients were assigned to receive placebo. As of March 22, 2018, the median follow-up was 25·2 months (IQR 14·1–29·5). More than 79% of patients given durvalumab and more than 82% of patients given placebo completed questionnaires up to week 48. Between baseline and 12 months, the prespecified longitudinal PROs of interest, cough (MMRM-adjusted mean change 1·8 [95% CI 0·06 to 3·54] in the durvalumab group *vs* 0·7 [–1·91 to 3·30] in the placebo group), dyspnoea (3·1 [1·75 to 4·36] *vs* 1·4 [–0·51 to 3·34]), chest pain (–3·1 [–4·57 to –1·60] *vs* –3·5 [–5·68 to –1·29]), fatigue (–3·0 [–4·53 to –1·50] *vs* –5·2 [–7·45 to –2·98]), appetite loss (–5·8 [–7·28 to –4·36] *vs* –7·0 [–9·17 to –4·87]), physical functioning (0·1 [–1·10 to 1·28] *vs* 2·0 [0·22 to 3·73]), and global health status or quality of life (2·6 [1·21 to 3·94] *vs* 1·8 [–0·25 to 3·81]) remained stable with both treatments, with no clinically relevant changes from baseline. The between-group differences in changes from baseline to 12 months in cough (difference in adjusted mean changes 1·1, 95% CI –1·89 to 4·11), dyspnoea (1·6, –0·58 to 3·87), chest pain (0·4, –2·13 to 2·93), fatigue (2·2, –0·38 to 4·78), appetite loss (1·2, –1·27 to 3·67), physical functioning (–1·9, –3·91 to 0·15), or global health status or quality of life (0·8, –1·55 to 3·14) were not clinically relevant. Generally, there were no clinically important between-group differences in time to deterioration of prespecified key PRO endpoints.

Interpretation Our findings suggest that a clinical benefit with durvalumab can be attained without compromising PROs. This result is of note because the previous standard of care was observation alone, with no presumed detriment to PROs.

Funding AstraZeneca.

Introduction

Non-small-cell lung cancer accounts for more than 80% of all cases of lung cancer worldwide, which is a leading cause of cancer-related deaths.[1,2] Patients with non-small-cell lung cancer often present with advanced disease and approximately a third of patients present

Research in context

Evidence before this study

We searched PubMed for reports published in English between Jan 1, 2010, and Feb 8, 2019, with the search terms "advanced non-small-cell lung cancer" and "patient-reported outcomes" (PRO) or "health-related quality of life", and we limited our results to studies of anti-PD-1 and anti-PD-L1 therapies. Evidence regarding the effect of immunotherapy on PROs in patients with advanced or metastatic non-small-cell lung cancer is emerging. For example, pembrolizumab improved health-related quality of life, symptoms, and function, and delayed time to deterioration in chest symptoms compared with platinum-based doublet chemotherapy in treatment-naive patients with stage IV non-small-cell lung cancer whose tumours showed a high expression of PD-L1 (≥50%; KEYNOTE-024 study). Similar improvements in quality of life over chemotherapy were reported in other studies of anti-PD-1 drugs; improvements have been found with nivolumab in patients with advanced non-squamous non-small-cell lung cancer (CheckMate 057) and squamous non-small-cell lung cancer (CheckMate 017), with pembrolizumab in patients with advanced PD-L1-expressing non-small-cell lung cancer (KEYNOTE-010), and with atezolizumab in patients with advanced or metastatic non-small-cell lung cancer (OAK). To our knowledge, there have been no PRO data reported for immunotherapies in patients with unresectable, stage III non-small-cell lung cancer to date.

Added value of this study

In our trial (PACIFIC), durvalumab (an anti-PD-L1 antibody) increased progression-free survival and overall survival (the primary endpoints) compared with placebo in patients with stage III, locally advanced, unresectable non-small-cell lung cancer who had not progressed after two or more cycles of platinum-based concurrent chemoradiotherapy. The addition of up to 12 months of durvalumab treatment did not compromise patients' symptoms, functioning, or global health status or quality of life compared with placebo during the study period, complementing previous efficacy and safety findings and further establishing the PACIFIC regimen (durvalumab after concurrent chemoradiotherapy) as a standard of care.

Implications of all the available evidence

The findings of improved progression-free survival and overall survival during PACIFIC suggest that durvalumab represents a new standard of care in patients with locally advanced, unresectable non-small-cell lung cancer, as reflected by its inclusion in the National Comprehensive Cancer Network clinical practice guidelines and regulatory approvals in the USA, Europe, Japan, and other regions. PRO data from PACIFIC further suggest that clinical benefit with durvalumab can be attained without compromising patients' quality of life, which is notable because the previous standard of care was observation alone, with no presumed detriment to PROs.

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with stage III, locally advanced tumours.[3] The standard of care for patients with unresectable, stage III non-small-cell lung cancer was previously platinum-based concurrent chemoradiotherapy.[1] Patients who respond to concurrent chemoradiotherapy are then typically monitored for disease progression.[4] However, the prognosis for patients receiving concurrent chemoradiotherapy is poor, with a median progression-free survival of approximately 8 months and between 15% and 30% of patients showing 5-year survival.[3,5–7] Previous trials[5,8–11] have shown no benefit of systemic therapy with curative intent chemoradiotherapy after stable disease, highlighting the unmet clinical need for an efficacious treatment for unresectable, stage III non-small-cell lung cancer.

At the first interim analysis[12] of the PACIFIC study, durvalumab, an anti-PD-L1 antibody, significantly improved the primary endpoint of progression-free survival compared with that for placebo (median 16·8 months *vs* 5·6 months; stratified hazard ratio [HR] 0·52; 95% CI 0·42–0·65; p<0·0001). Durvalumab also had a manageable safety profile, which was consistent with that of other immunotherapies. These data formed the basis for subsequent approvals of durvalumab as a treatment for patients with unresectable, stage III non-small-cell lung cancer whose disease had not progressed following platinum-based chemoradiotherapy. We also reported the findings of the second primary endpoint, overall survival.[13] Durvalumab significantly improved overall survival compared with that for placebo (not reached *vs* 28·7 months; 0·68; 99·73% CI 0·47–0·997; p=0·0025).

Improved survival is an important endpoint, but this endpoint is not the only measure of benefit. Although safety endpoints provide evidence for treatment toxicity, they are assessed directly by clinical investigators and they do not provide insight into subjective patient experience. Therefore, patient-reported outcomes (PROs), which reflect patients' perspective of their symptoms, functioning, and health-related quality of life, can provide important complementary data to efficacy and safety endpoints. This outcome is particularly important because the previous standard of care was observation alone, with no therapeutic intervention for which there is no presumed detriment to PROs. Patient-focused drug development and the use of PROs are priorities of the US Food and Drug Administration's new Oncology Center of Excellence.

We aimed to evaluate the PROs in the phase 3 PACIFIC study, particularly detailing the effects of durvalumab versus placebo on patients' symptoms, functioning, and global health status (ie, quality of life).

Methods

Study design and participants

PACIFIC is an ongoing, international, multicentre, double-blind, randomised, controlled, phase 3 trial. The primary and secondary endpoints of this phase 3 trial have been reported previously.[12,13] This was a global trial, conducted at 235 cancer treatment centres across 26 countries in Asia, Australia, Europe, north and south America, and south Africa. A full list of the study sites is provided in the appendix (pp 12–21).

See Online for appendix

Patients were eligible if they had histologically or cytologically documented stage III, unresectable non-small-cell lung cancer, as per the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology (version 7), and had received at least two cycles of platinum-based chemoradiotherapy, with no disease progression after this treatment. Eligible patients were aged at least 18 years, had a WHO performance status of 0 or 1, an estimated life expectancy of at least 12 weeks, and had completed the last radiation dose within the past 1–14 days (which became 1–42 days after a protocol amendment on Feb 18, 2015, after the trial had begun) before randomisation.

Key exclusion criteria were previous exposure to anti-PD-1 or anti-PD-L1 antibodies; receipt of immunotherapy or an investigational drug within 4 weeks before the first dose of durvalumab (or 6 weeks for monoclonal antibodies); evidence of uncontrolled, concurrent illness or ongoing or active infections; active or previous autoimmune disease (within the past 2 years) or primary immunodeficiency history; and unresolved toxicity from previous chemoradiotherapy at a severity of more than grade 2 (as per Common Terminology Criteria for Adverse Events) or pneumonitis of at least grade 2. Full inclusion and exclusion criteria are in the appendix (pp 78–83).

All patients provided written, informed consent for participation in the study. The study protocol and amendments were approved by relevant local or central ethics committees, and the study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki. The protocol is provided in the appendix (pp 22–231).

Randomisation and masking

Patients were randomly assigned (2:1) to receive durvalumab or matching placebo 1–42 days after chemoradiotherapy. An interactive voice response system was used to assign unique enrolment numbers to each patient. Randomisation was done with a blocked design (block size=3) that resulted in one randomisation list for each of the randomisation strata, and all centres used the same list to minimise between-group imbalances. Patients were stratified by age (<65 *vs* ≥65 years), sex (male *vs* female), and smoking history (current or former smoker *vs* never smoked). The principal investigator or a suitably trained delegate (RH, MÖ, AV, DD, DV, SM, TY, AC, KHL, MdW, BCC, JEG, or SJA) enrolled the patients at each study site. The patients, investigators, and study centre staff were masked to study drug allocation via opaque sleeves fastened with tamper-evident tape over the intravenous bags and colour-matched reconstituted intravenous solutions. However, the study centre pharmacist was not masked to groups, such that they could prepare durvalumab or placebo for each patient as specified by the randomisation schedule.

Procedures

Patients provided archived tumour tissue samples for PD-L1 testing if available; however, enrolment was not restricted to any PD-L1 expression thresholds. Patients received 10 mg/kg intravenous durvalumab (AstraZeneca; Wilmington, DE, USA) or matching placebo, every 2 weeks for up to 12 months. Dose reductions were not permitted. Dose delays, interruptions, or discontinuation were allowed for management of toxicity, as defined in the protocol (appendix pp 210–31). Patients who had a dose interruption because of toxicity at any time during the first 12 months of treatment could resume treatment, but the treatment period could not exceed 12 months (including the interruption time). Study drug could be discontinued because of confirmed progression, initiation of an alternative anticancer therapy, unacceptable toxicity, or withdrawal of consent. Patients could be treated with their study drug during progression if they fulfilled predefined criteria, and treatment could resume if disease control was achieved at the end of 12 months and the disease progressed during follow-up.

PROs were assessed with paper-based questionnaires at the time of random allocation to groups, week 4, week 8, every 8 weeks until week 48, then every 12 weeks until disease progression. The last assessment for patients who discontinued treatment because of progression was day 30 after the final dose. Patients who continued treatment after progression because of clinical benefit, at the investigator's discretion, continued completing questionnaires for as long as they received treatment. Patients who discontinued treatment for reasons other than confirmed progression continued completing the questionnaires until confirmed progression.

We evaluated patient-reported symptoms, functioning, and global health status or quality of life with two questionnaires that were developed by the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on quality of life: the Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life

Questionnaire-Lung Cancer 13 (QLQ-LC13). We also used the EuroQoL 5-dimension utility index (EQ-5D), a standardised measure of health status that was developed by the EuroQoL Group, as a prespecified exploratory measure to assess the effects of treatment and disease state on health status.

EORTC QLQ-C30 version 3 is a 30-item core questionnaire that consists of five multiple-item functioning scales (physical, role, cognitive, emotional, and social); one multiple-item global health status or quality of life scale; three multiple-item symptom scales (fatigue, pain, and nausea or vomiting); and six single-item measures for dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and perceived financial difficulties.[14]

To assess additional symptoms associated with lung cancer and its treatment, we used a complementary 13-item lung cancer module: the EORTC QLQ-LC13.[15] This module consists of one multiple-item dyspnoea scale and single-item measures for other lung cancer-associated symptoms (cough, haemoptysis, and site-specific pain in the chest, arm or shoulder, or other body parts), pain medicine use, and side-effects from conventional chemoradiotherapy (sore mouth, dysphagia, neuropathy, and hair loss). This analysis focuses on lung cancer-associated symptoms.

QLQ-C30 was tested in interviews of patients with lung cancer during development of the disease-specific lung cancer module. Both QLQ-C30 and QLQ-LC13 are widely used in patients with advanced non-small-cell lung cancer, and they have been well validated in psychometric testing.[14,15]

The EQ-5D descriptive health system consists of five dimensions of health: mobility, ability to care for oneself, ability to undertake usual activities, pain and discomfort, and anxiety and depression. The five-level version of the questionnaire used in our study includes five levels of severity for each dimension (no, slight, moderate, severe, or extreme problems), which the patient is asked to indicate for each dimension. The questionnaire also includes a visual analogue scale, in which the patient is asked to rate their current health status on a scale of 0 to 100, with 0 being the worst health state and 100 the best.

Outcomes

The primary endpoints were progression-free survival (as per Response Evaluation Criteria In Solid Tumors version 1.1), which was assessed by blinded independent central review, and overall survival.[12,13] The prespecified secondary endpoints were further efficacy outcomes (the proportion of patients with an objective response, duration of response, the proportion of patients alive and progression free at 12 months and 18 months after random assignment to groups, and time to death or distant metastasis, all of which were assessed by blinded independent central review; and overall survival at 24 months and time between random assignment and second progression); safety and tolerability (in which adverse events were graded with the Common Terminology Criteria for Adverse Events version 4.03); PROs; pharmacokinetics; and immunogenicity. This analysis represents the report on the secondary endpoint PROs (ie, symptoms, functioning, and health-related quality of life). Analyses by disease progression status and data regarding financial difficulties or pain medication will not be reported.

Statistical analysis

The study was powered for the two primary endpoints (progression-free survival and overall survival) and details of the sample size have been reported previously.[12,13] Approximately 702 patients were required to be randomised in a 2:1 ratio to obtain 458 progression-free survival events and 491 overall survival events for the primary analyses. Assuming an HR of 0·67 for progression-free survival and of 0·73 for overall survival, then the study would have at least 95% power for the progression-free survival endpoint and 85% power for the overall survival endpoint, to detect a statistically significant difference, with a 2·5% two-sided significance level, adjusted for interim analyses for each endpoint.

The analysis of data on PROs in the intention-to-treat population was a prespecified secondary endpoint.[13] We aimed to assess the effect of 12 months of treatment with durvalumab versus placebo on PROs. We calculated scores on the basis of scoring manuals or guidelines, and scores ranged from 0 to 100. Higher scores on symptom scales and items represent greater symptom severity, and higher scores on the global health status or quality of life and functioning scales indicate better health status or function. Times to deterioration of QLQ-C30 functional scales and global health status or quality of life were assessed in patients with baseline scores of at least 10. Times to deterioration of QLQ-C30 and QLQ-LC13 symptom scales or items were assessed in patients with baseline scores of 90 or less. A 10-point change or more from baseline (either deterioration or improvement; classified as a moderate change) in a scale or item was deemed clinically relevant.[16]

We also made post-hoc comparisons of baseline EORTC QLQ-C30 and QLQ-C13 scores from this study with baseline data from a reference group of unselected patients with non-small-cell lung cancer (sourced from the EORTC quality of life group's Cross-Cultural Analysis Project).[17,18]

We evaluated changes at each visit in key symptoms, physical functioning, and global health status or quality of life from baseline to 12 months with a mixed model for repeated measures (MMRM) analysis. This model assumes that PROs were collected at several visits and allows for missing data. The MMRM included fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, age at randomisation, sex, and smoking history, and continuous fixed covariates of baseline score

and baseline score-by-visit interaction. Longitudinal PRO endpoints of interest comprised key symptoms (cough, dyspnoea, and chest pain [all QLQ-LC13]; fatigue and appetite loss [QLQ-C30]); and physical functioning and global health status or quality of life (QLQ-C30).

Time to deterioration was defined as the time from random allocation to groups until the date of the first clinically relevant deterioration (≥10-point increase for symptoms; ≥10-point decrease for function items and global health status or quality of life) or death, regardless of whether the patient withdrew from the study treatment or received another anticancer therapy before deterioration. Time to deterioration was analysed using a stratified log rank test, stratified by age at randomisation, sex, and smoking history. HR and 95% CIs were estimated with a Cox proportional hazards model. We identified time to deterioration of cough, dyspnoea, chest pain, haemoptysis (all QLQ-LC13), and global health status or quality of life (QLQ-C30) as primary PRO endpoints, and we calculated 99% CIs for these data.

To reduce possible bias from transient symptom change (eg, temporary symptoms due to treatment side-effects or comorbidities), which might have confounded symptom changes associated with disease progression, we did an exploratory, post-hoc analysis of time to deterioration. In this post-hoc analysis, clinically relevant deterioration had to be confirmed at a next consecutive timepoint after the first observation. In patients in whom disease progression occurred after the first timepoint at which deterioration was observed, patients were still considered to have had a worsening event. This conclusion was only reversed if there was a direct contradiction at the next consecutive timepoint (ie, an improvement or a deterioration of less than 10 points *vs* baseline). The statistical methods used were identical to those used in the prespecified analysis of time to deterioration.

As part of a prespecified analysis, we defined the proportion of patients with improvement as the percentage of patients with two consecutive assessments, separated by at least 14 days, that showed clinically relevant improvements from baseline (≥10-point decrease for symptoms; ≥10-point increase for function items and global health status or quality of life). Odds ratios (ORs) and 95% CIs were calculated with logistic regression, which was adjusted for study treatment, age at randomisation, sex, and smoking history.

Descriptive statistics are reported for the exploratory EQ-5D index and EQ-visual analogue scale scores. SAS (version 9.2) was used for all analyses. An independent data monitoring committee oversaw the study. This study is registered with ClinicalTrials.gov, NCT02125461, and EudraCT, 2014-000336-42.

Role of the funding source

The funder of the study contributed to the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between May 7, 2014, and April 22, 2016, we screened 983 patients for the trial, of whom 270 (27%) patients were excluded because they did not meet eligibility criteria (n=225), did not consent to be included (n=35), died (n=6), or for other reasons (n=4; figure 1). Between May 9, 2014, and April 22, 2016, we randomly assigned 713 (73%) patients to groups. 476 (67%) patients were assigned to receive durvalumab, of whom 473 (99%) patients received the drug, and 237 (33%) patients were assigned to receive placebo, of whom 236 (>99%) patients received placebo. Three patients in the durvalumab group (two who withdrew consent and one who developed neutropenia) and one patient in the placebo group (who reported worsening chronic obstructive pulmonary disease) did not receive their assigned treatment. As of the data cut-off date, March 22, 2018, the median follow-up was 25·2 months (IQR 14·1–29·5). Patient characteristics, including use of and response to previous chemo-radiotherapy treatment, were well balanced between treatment groups.[12]

More than 79% of patients in the durvalumab group and more than 82% of patients in the placebo group completed questionnaires up to week 48 (appendix p 1). There were no clinically relevant between-group differences at baseline for any symptoms, function scales, or global health status or quality of life (appendix pp 2,3, and 8–10). Symptom scores were low overall: the mean baseline key symptom scores with durvalumab versus placebo were 35·7 (SD 26·7) versus 35·6 (27·7) for cough, 22·3 (21·1) versus 20·6 (18·5) for dyspnoea, 15·3 (23·5) versus 16·4 (22·4) for chest pain, 32·6 (23·6) versus 30·6 (21·2) for fatigue, and 19·1 (28·1) versus 20·5 (26·2) for appetite loss (appendix pp 8–10). For physical function, the mean baseline scores with durvalumab versus placebo were 79·5 (SD 18·9) and 81·0 (16·1). Finally, for global health status or quality of life, mean baseline scores were 66·8 (SD 19·9) versus 68·0 (17·4; appendix pp 2,3, and 8–10).

In the prespecified MMRM analysis of adjusted mean change between baseline and 12 months (which we averaged by visit over 12 months separately for the durvalumab versus placebo groups), we found that patient reports of cough (MMRM-adjusted mean change 1·8 [95% CI 0·06 to 3·54] in the durvalumab group *vs* 0·7 [–1·91 to 3·30] in the placebo group), dyspnoea (3·1 [1·75 to 4·36] *vs* 1·4 [–0·51 to 3·34]), and chest pain (–3·1 [–4·57 to –1·60] *vs* –3·5 [–5·68 to –1·29]; all assessed with QLQ-LC13); and fatigue (–3·0 [–4·53 to –1·50] *vs* –5·2 [–7·45 to –2·98]) and appetite loss (–5·8 [–7·28 to –4·36] *vs* –7·0 [–9·17 to –4·87]; both assessed with QLQ-C30) remained stable throughout the study for both durvalumab

and placebo (figure 2). Physical functioning (0·1 [–1·10 to 1·28] *vs* 2·0 [0·22 to 3·73]) and global health status or quality of life (2·6 [1·21 to 3·94] *vs* 1·8 [–0·25 to 3·81]; both QLQ-C30) also remained stable with both treatments throughout the study. We found no difference between durvalumab and placebo on the reported between-group differences in changes from baseline to 12 months in cough (difference in adjusted mean changes 1·1, 95% CI –1·89 to 4·11), dyspnoea (1·6, –0·58 to 3·87), chest pain (0·4, –2·13 to 2·93), fatigue (2·2, –0·38 to 4·78), appetite loss (1·2, –1·27 to 3·67), physical functioning (–1·9, –3·91 to 0·15), or global health status or quality of life (0·8, –1·55 to 3·14). All absolute scores in PROs remained stable from baseline to week 48, with no clinically relevant between-group differences, with the exception of dysphagia and alopecia, for which there were clinically relevant changes from baseline. Similar improvements between baseline and week 48 were observed for durvalumab and placebo: the mean changes after treatment with durvalumab versus placebo were –14·2 (SD 25·9) versus –15·7 (26·3) for dysphagia and –23·2 (33·9) and –20·7 (28·9) for alopecia (appendix pp 8–10).

No clinically important between-group differences were observed in prespecified analyses of time to deterioration for most symptoms, functioning terms, or global health status or quality of life (figure 3). However, time to deterioration of other pain (ie, any pain other than in the chest, arms, or shoulders) was longer in patients receiving durvalumab than in those receiving placebo. This between-group difference was not reflected in any other pain terms (ie, QLQ-C30 pain, QLQ-LC13 chest pain, QLQ-LC13 arm or shoulder pain).

We found no clinically important between-group differences in the proportion of patients with clinically relevant improvements in most symptoms (figure 4). We also found no clinically important between-group differences in the proportion of patients whose scores improved for global health status or quality of life or most functioning terms, except in emotional functioning (which favoured durvalumab).

In the prespecified exploratory analysis of health state utility, the mean baseline EQ-5D index scores with durvalumab versus placebo were 0·798 (SD 0·177) versus 0·803 (0·183). The mean changes in EQ-5D index score between baseline and week 48 with durvalumab versus placebo were –0·014 (SD 0·177) versus 0·012 (0·122). The mean baseline EQ-VAS scores with durvalumab and placebo were 74·3 (SD 16·8) and 74·8 (15·4). The mean changes in the visual analogue score between baseline and week 48 with durvalumab versus placebo were 2·1 (SD 16·5) versus 0·6 (11·9). We found no clinically relevant changes[19] from baseline in either score for either treatment group.

In a post-hoc analysis in which clinically relevant deterioration had to be confirmed at the consecutive timepoint after its first observation, time to deterioration in nausea or vomiting, insomnia, constipation, overall pain, chest pain, arm or shoulder pain, haemoptysis, emotional functioning, and global health status or quality of life were longer with durvalumab versus placebo (appendix p 4). Time to deterioration in all other symptom and functioning scales did not differ between groups. Kaplan–Meier plots of time to deterioration for items that differed notably between the prespecified and post-hoc analyses are presented in the appendix (pp 5–7).

In a post-hoc comparison, baseline EORTC QLQ-C30 and EORTC QLQ-C13 data were mostly comparable with baseline data from a reference group of 1262 unselected patients with non-small-cell lung cancer (1046 patients

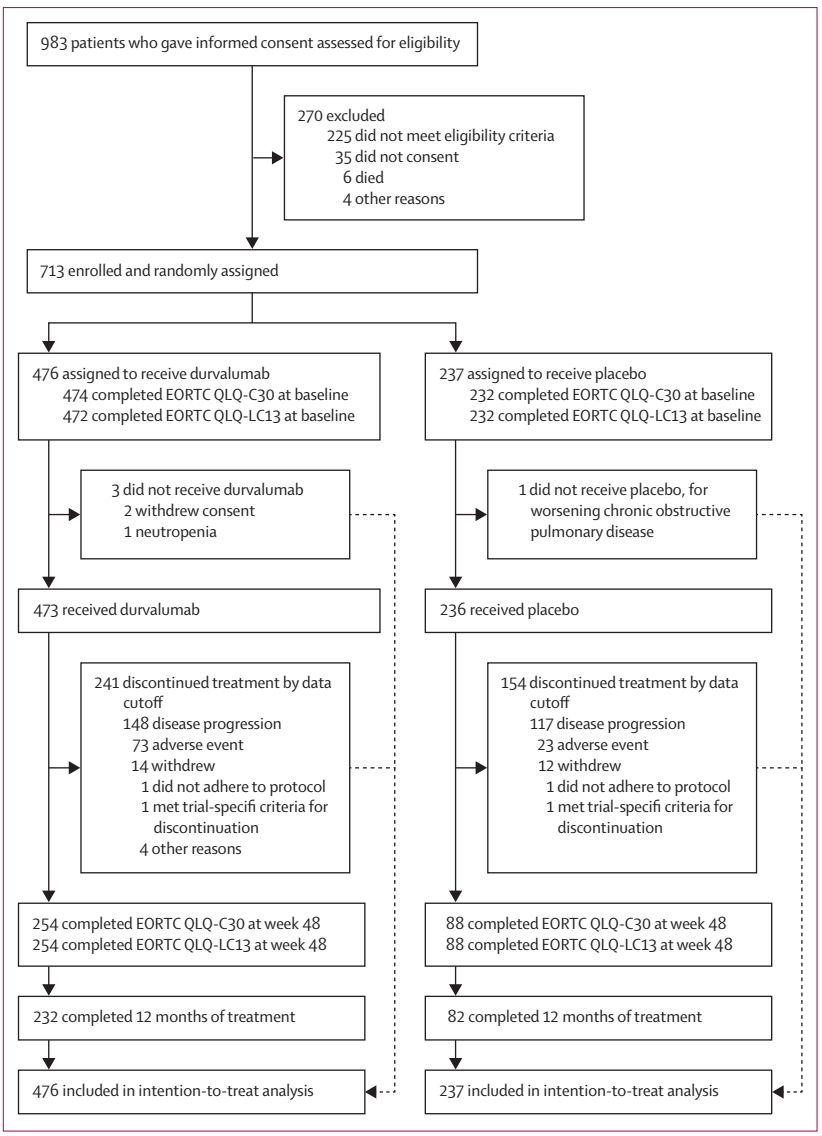

Figure 1: **Trial profile**
EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13.

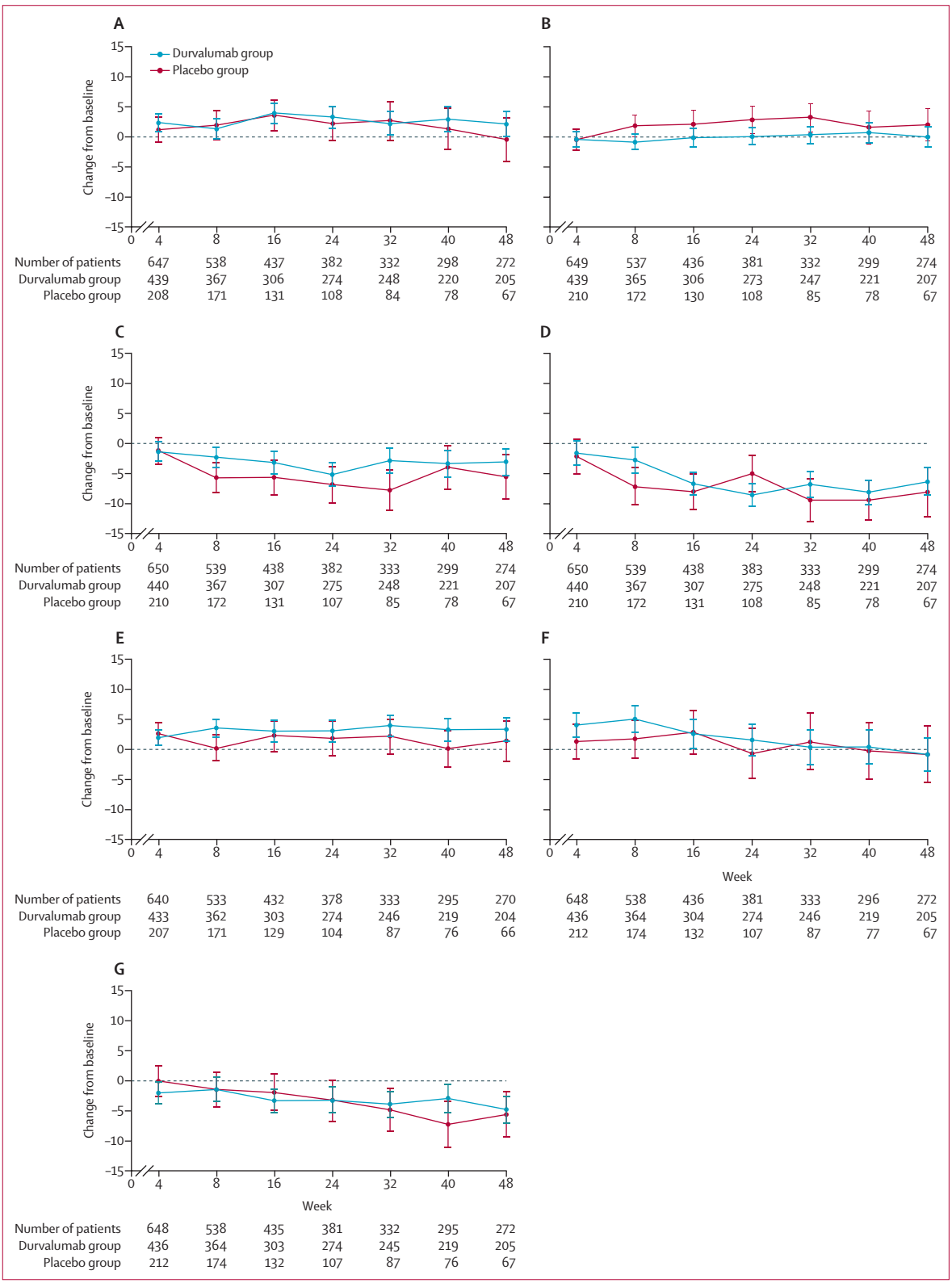

***Figure 2*: Changes in key symptoms, functioning, and global health status or quality of life between baseline and week 48**

Data are mean change in mixed model for repeated measures-adjusted scores (95% CI). Data are global health status or quality of life (A), physical functioning (B), fatigue (C), appetite loss (D); all from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30), dyspnoea (E), cough (F), and chest pain (G; all from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13).

	Durvalumab		Placebo		HR (95% CI)
	Number of events/number of patients	%	Number of events/number of patients	%	
Global health status or quality of life (C30)	274/470	58·3	129/232	55·6	0·95 (0·77–1·18)*
Physical functioning (C30)	245/472	51·9	118/232	50·9	1·01 (0·81–1·26
Role functioning (C30)	273/454	60·1	134/225	59·6	1·01 (0·83–1·25)
Emotional functioning (C30)	223/470	47·4	120/230	52·2	0·85 (0·68–1·07)
Cognitive functioning (C30)	281/473	59·4	130/232	56·0	1·03 (0·84–1·27)
Social functioning (C30)	234/464	50·4	116/231	50·2	1·00 (0·80–1·25)
Fatigue (C30)	289/463	62·4	152/229	66·4	0·90 (0·74–1·10)
Pain (C30)	302/471	64·1	148/228	64·9	0·87 (0·71–1·06)
Nausea or vomiting (C30)	192/473	40·6	104/231	45·0	0·84 (0·66–1·07)
Dyspnoea (C30)	273/453	60·3	141/223	63·2	0·92 (0·75–1·13)
Insomnia (C30)	259/457	56·7	130/226	57·5	0·91 (0·74–1·13)
Appetite loss (C30)	222/452	49·1	105/224	46·9	1·01 (0·80–1·27)
Constipation (C30)	198/466	42·5	110/226	48·7	0·85 (0·67–1·07)
Diarrhoea (C30)	213/474	44·9	112/231	48·5	0·85 (0·67–1·07)
Dyspnoea (LC13)	341/467	73·0	158/230	68·7	1·06 (0·88–1·29)*
Cough (LC13)	266/442	60·2	141/216	65·3	0·91 (0·74–1·12)*
Haemoptysis (LC13)	125/472	26·5	75/232	32·3	0·75 (0·56–1·00)*
Chest pain (LC13)	233/463	50·3	114/229	49·8	0·94 (0·75–1·19)*
Arm or shoulder pain (LC13)	254/466	54·5	133/231	57·6	0·82 (0·66–1·02)
Other pain (LC13)	241/456	52·9	147/229	64·2	0·70 (0·57–0·87)

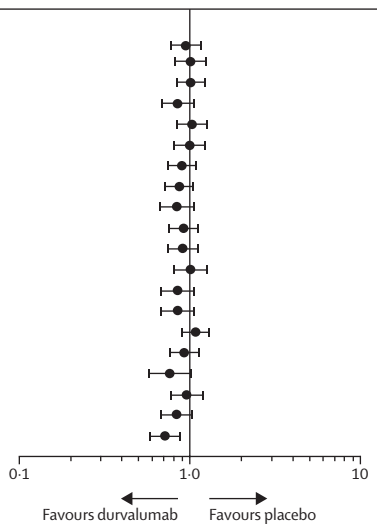

Figure 3: **Time to deterioration of symptoms, functioning, and global health status or quality of life**
Data were gathered from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and Quality of Life Questionnaire-LC13. C30 global health status or quality of life and functional scales were assessed in patients with baseline scores of at least 10. C30 and LC13 symptom scales and items were assessed in patients with baseline scores of 90 or less. Other pain is any pain other than in the chest, arm, or shoulder. C30=Core 30. LC13=Lung Cancer 13. *Time to deterioration of cough (hazard ratio 0·91, 99% CI 0·69–1·20), dyspnoea (1·06, 0·83–1·37), chest pain (0·94, 0·70–1·28), and haemoptysis (0·75, 0·52–1·10; all LC13); and time to deterioration of global health status or quality of life (0·95, 0·72–1·26; C30).

	Durvalumab		Placebo		OR (95% CI)
	Number with improvements/ number of patients	%	Number with improvements/ number of patients	%	
Global health status or quality of life (C30)	149/418	35·6	62/208	29·8	1·30 (0·90–1·87)
Physical functioning (C30)	113/319	35·4	53/159	33·3	1·07 (0·71–1·61)
Role functioning (C30)	136/261	52·1	67/131	51·1	1·03 (0·68–1·57)
Emotional functioning (C30)	116/246	47·2	38/112	33·9	1·72 (1·08–2·76)
Cognitive functioning (C30)	106/212	50·0	53/104	51·0	0·95 (0·59–1·53)
Social functioning (C30)	153/261	58·6	65/128	50·8	1·36 (0·89–2·09)
Fatigue (C30)	208/407	51·1	93/202	46·0	1·22 (0·87–1·72)
Pain (C30)	162/272	59·6	59/118	50·0	1·32 (0·85–2·07)
Nausea or vomiting (C30)	106/140	75·7	47/63	74·6	1·08 (0·53–2·13)
Dyspnoea (C30)	113/288	39·2	48/127	37·8	1·05 (0·68–1·62)
Insomnia (C30)	111/230	48·3	45/108	41·7	1·28 (0·81–2·05)
Appetite loss (C30)	127/183	69·4	59/107	55·1	1·86 (1·13–3·10)
Constipation (C30)	104/155	67·1	56/85	65·9	1·07 (0·61–1·87)
Diarrhoea (C30)	51/75	68·0	27/44	61·4	1·51 (0·67–3·43)
Dyspnoea (LC13)	133/353	37·7	57/180	31·7	1·31 (0·89–1·92)
Cough (LC13)	116/366	31·7	68/176	38·6	0·74 (0·51–1·08)
Haemoptysis (LC13)*	26/29	89·7	14/19	73·7	3·02 (0·62–17·07)
Chest pain (LC13)	103/168	61·3	48/94	51·1	1·49 (0·89–2·51)
Arm or shoulder pain (LC13)	72/133	54·1	28/52	53·8	0·95 (0·49–1·83)
Other pain (LC13)	100/182	54·9	34/69	49·3	1·09 (0·60–1·95)

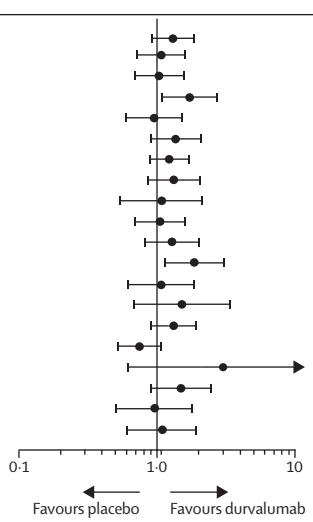

Figure 4: **Improvement in symptoms, functioning, and global health status or quality of life**
Data were gathered from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and Quality of Life Questionnaire-LC13. C30 global health status or quality of life and functional scales were assessed in patients with baseline scores of at least 10. C30 and LC13 symptom scales and items were assessed in patients with baseline scores of 90 or less. Other pain is any pain other than in the chest, arm, or shoulder. C30=Core 30. LC13=Lung Cancer 13. *The upper value of the 95% CI for the improvement for haemoptysis (17·07) is not shown because the scale has been truncated, to improve legibility.

with stage III–IV disease) from the EORTC Quality of Life group's Cross-Cultural Analysis Project (appendix pp 2,3).[17,18] However, PACIFIC patients in both treatment groups reported better global health status or quality of life, and a lower burden of symptoms related to dyspnoea, chest pain, fatigue, and appetite loss than patients in the reference group (appendix pp 2–3).

Discussion

We found that up to 12 months of durvalumab treatment had no clinically important detrimental effect on symptoms, functioning, or global health status or quality of life, which was comparable to placebo, further supporting its benefit after concurrent chemoradiotherapy in patients with stage III, unresectable non-small-cell lung cancer. Notably, we observed no overall worsening in key symptoms up to week 48. The only symptoms that showed clinically meaningful changes from baseline to week 48 were dysphagia and alopecia, which improved with both durvalumab and placebo, which probably reflects resolution of toxicities related to previous concurrent chemoradiotherapy.[20]

The benefits of any treatment must be weighed against the risks of detrimental effects through assessment of the occurrence of adverse events and the effects of treatment on PROs. However, evidence for the effect of immuno-oncological treatment on PROs in patients with unresectable, stage III non-small-cell lung cancer is poor. Although use of durvalumab after concurrent chemoradiotherapy was previously reported to be well tolerated with a manageable safety profile, it is important to evaluate the patient's perspective and to show that durvalumab does not result in worse PROs than placebo.

Time to deterioration was generally similar between treatment groups, apart from that of other pain (any pain other than chest, arm, or shoulder pain), which favoured durvalumab. However, the between-group difference in other pain was not reflected in the other QLQ-LC13 pain-related items and the QLQ-C30 overall pain item. Therefore, the favourable result for durvalumab regarding other pain should be interpreted with caution. Notably, in an exploratory post-hoc analysis in which clinically relevant deterioration was required to be confirmed in the consecutive timepoint after its first report, delays in worsening of overall pain and lung cancer-specific pain symptoms favoured durvalumab. Further, delays in worsening were observed for nausea or vomiting, constipation, insomnia, and haemoptysis with durvalumab relative to placebo. Of note, when this confirmation of worsening at the next consecutive timepoint was required, the number of deterioration events reduced in more patients with durvalumab than with placebo, suggesting the possibility that transient changes in symptoms (ie, those that might not have been associated with disease progression) might have disproportionally affected the durvalumab group.

The proportion of patients whose scores improved for symptoms, functioning, and global health status or quality of life were similar between treatment groups, except for emotional functioning, which favoured durvalumab. This finding might be associated with the improved efficacy observed with durvalumab.

These PRO data complement previously reported data on the safety profile of durvalumab use after concurrent chemoradiotherapy.[13] Grade 3 or 4 adverse events were comparable between durvalumab (30·5%) and placebo (26·1%).[13] Therefore, although the incidence of some adverse events was greater with durvalumab versus placebo (eg, cough, pneumonitis, or radiation pneumonitis), these were low-grade events with no clinically meaningful impairment to PROs (for instance, there were no between-group differences in times to deterioration or the proportion of patients whose score improved for dyspnoea in the QLQ-LC13).[9] Overall, analysis of investigator-assessed adverse events in PACIFIC suggested a manageable safety profile.[13]

Patients with advanced non-small-cell lung cancer who were treated with immune checkpoint inhibitors have shown stable or improved quality of life and a manageable safety profile in other trials.[21–24] The PRO data we report are consistent with these observations.

Improvement in quality of life is likely to be observed with first-line and second-line anti-PD-1 drugs in stage IV non-small-cell lung cancer; however, such improvement in stage III non-small-cell lung cancer after chemoradiotherapy was not expected because of a lower symptom burden and better baseline functioning. Furthermore, patients with stage III non-small-cell lung cancer who receive frequent surveillance imaging in the study protocol would usually have a low symptom burden at the time of radiological disease progression (although other determinants of deterioration of quality of life besides progression might contribute). Although durvalumab significantly improved progression-free survival compared with placebo, it was not expected that patients' quality of life would be affected. In PACIFIC, baseline scores were low for symptoms and high for functioning and global health status or quality of life when compared with a historical reference group,[17–19] possibly due to the inclusion of patients with stage IV non-small-cell lung cancer in the reference population. Nonetheless, this finding indicates that patients with stage III locally advanced disease without disease progression after concurrent chemoradiotherapy had satisfactory baseline wellbeing. Thus, large improvements from baseline were not anticipated and, notably, the addition of up to 12 months of durvalumab after concurrent chemoradiotherapy did not compromise quality of life or have a detrimental effect on quality of life in these patients with earlier stage non-small-cell lung cancer. Additionally, post-hoc exploratory analyses[25] of patients from the PACIFIC study found that tumour PD-L1 expression had no clinically meaningful effect on PROs.

The PACIFIC study protocol was randomised, double-blind, and rigorous in design. The EORTC QLQ-C30 and QLQ-LC13 questionnaires have been well validated in previous studies.[26] Developed in the chemotherapy era, some items in these questionnaires might not be relevant to immuno-oncology. However, research supports the use of these measures in clinical non-small-cell lung cancer contexts.[27–29]

Possible durvalumab-related symptoms that were not captured by EORTC questionnaires include weight gain, weight loss, poor ability to tolerate cold, feeling hot, rash, and tremor.[30] These are mainly symptoms that might result from the reported treatment-related events of hyperthyroidism or hypothyroidism, infusion-related reaction, acute kidney injury, and tumour flares.[30] However, we found no clinically important differences between treatment groups in time to deterioration in symptoms (in the QLQ-LC13 and QLQ-C30) and health-related quality of life, despite a longer treatment duration in the durvalumab group compared with the placebo group. This finding suggests that durvalumab treatment-related symptoms had no detrimental effect on patients' health-related quality of life.

Certain limitations of this analysis should be acknowledged. Since we randomly assigned patients to groups up to 42 days after concurrent chemoradiotherapy, these PRO data did not fully evaluate the patient experience from time of diagnosis. However, this delay is unlikely to have affected the results. PRO data were only collected until disease progression, and time to disease progression differed significantly between the durvalumab and placebo groups. Therefore, the quantity of data differs between treatment groups, potentially favouring placebo, given the potential for a detrimental effect on PROs with longer exposure to durvalumab. Moreover, these prespecified and post-hoc analyses are exploratory and therefore lack formal statistical testing for some outcomes. Prespecified statistical analysis did not show clinically meaningful differences in PROs between durvalumab and placebo treatment. Finally, there is no gold standard regarding the definition of time to deterioration, which can depend on the compound's mechanism of action, disease stage, treatment line, or cancer type, and certain PROs might be more susceptible to transient effects than others (such as PROs with transient worsening that resolves with intervention).

In conclusion, our analyses of PROs showed that the addition of up to 12 months of durvalumab treatment did not compromise patients' symptoms, functioning, or global health status or quality of life during the study period compared with placebo. These findings complement the previously reported improvements in progression-free survival and overall survival and investigator-reported toxicity profile with durvalumab and provide evidence to support the PACIFIC regimen (durvalumab after concurrent chemoradiotherapy) as a new standard of care in unresectable, stage III non-small-cell lung cancer.

Contributors

DV, AR, and SJA conceived of and designed the study. RH, MÖ, AV, DD, DV, SM, AC, KHL, MdW, BCC, JEG, and SJA provided study materials or recruited patients. RH, MÖ, DD, TY, KHL, MdW, BCC, LV, LP, and SJA collected and assembled data. RH, MÖ, AC, MdW, BCC, JEG, AR, LV, LP, YZ, and PAD analysed and interpreted data. All authors were involved in writing the manuscript and approved the final version. SJA provided administrative support.

Declaration of interests

RH reports serving on advisory boards for AstraZeneca, MSD, Novartis, Roche, Bristol-Myers Squibb, and Eli Lilly and reports honoraria from AstraZeneca, MSD, Novartis, Roche, Bristol-Myers Squibb, and Eli Lilly. MÖ reports serving on an advisory board for Janssen Pharmaceutica. AV reports honoraria from AstraZeneca, Gilead Sciences, and Seattle Genetics. DD reports research funding to his institution from ER Squibb and Sons, AstraZeneca, Boehringer Ingelheim, Genentech, Eli Lilly, Novartis, Pfizer, Celgene, and Roche. AC reports speaker's fees from Genentech, Merck & Co, Takeda, Novartis, Boehringer-Ingelheim, and Celgene and research funding from Novartis and Bristol-Myers Squibb. MdW reports speaker's fees from AstraZeneca. JEG reports serving on an advisory board for AstraZeneca and reports research funding from AstraZeneca, Merck & Co, Bristol-Myers Squibb, and Genentech. AR, LP, YZ, and PAD are employed by and own stock in AstraZeneca. All other authors declare no competing interests.

Data sharing

Data underlying the findings of this study can be obtained in accordance with AstraZeneca's data sharing policy described online.

For the **AstraZeneca data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

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