Patient-Reported Outcomes with Durvalumab With or Without Tremelimumab Versus Standard Chemotherapy as First-Line Treatment of Metastatic Non–Small-Cell Lung Cancer (MYSTIC)

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Abstract

We investigated the impact of durvalumab ± tremelimumab versus chemotherapy on patient-reported symptoms, functioning, and global health status/quality of life in the phase 3 MYSTIC trial of metastatic non–small-cell lung cancer in patients with tumor cell programmed cell death ligand 1 expression ≥ 25%. Durvalumab ± tremelimumab reduced symptom burden and improved times to deterioration, suggesting there were no detrimental effects with treatment.

Background: The phase 3 MYSTIC study of durvalumab ± tremelimumab versus chemotherapy in metastatic non–small-cell lung cancer (NSCLC) patients with tumor cell (TC) programmed cell death ligand 1 (PD-L1) expression ≥ 25% did not meet its primary endpoints. We report patient-reported outcomes (PROs). **Patients and Methods:** Treatment-naïve patients were randomized (1:1:1) to durvalumab, durvalumab + tremelimumab, or chemotherapy. PROs were assessed in patients with PD-L1 TC ≥ 25% using EORTC Quality of Life Questionnaire (QLQ)-C30/LC13. Changes from baseline (12 months) for prespecified PRO endpoints of interest were analyzed by mixed model for repeated measures (MMRM) and time to deterioration (TTD) by stratified log-rank tests. **Results:** There were no between-arm differences in

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baseline PROs ($N = 488$). Between-arm differences in MMRM-adjusted mean changes from baseline favored at least one of the durvalumab-containing arms versus chemotherapy (nominal $P < .01$) for C30 fatigue: durvalumab (−9.5; 99% confidence interval [CI], −17.0 to −2.0), durvalumab + tremelimumab (−11.7; 99% CI, −19.4 to −4.1); and for C30 appetite loss: durvalumab (−11.9; 99% CI, −21.1 to −2.7). TTD was longer with at least one of the durvalumab-containing arms versus chemotherapy (nominal $P < .01$) for global health status/quality of life: durvalumab (hazard ratio [HR] = 0.7; 95% CI, 0.5-1.0), durvalumab + tremelimumab (HR = 0.7; 95% CI, 0.5-1.0); and for physical functioning: durvalumab (HR = 0.6; 95% CI, 0.4-0.8), durvalumab + tremelimumab (HR = 0.6; 95% CI, 0.5-0.9) (both C30); as well as for the key symptoms of dyspnea: durvalumab (HR = 0.6; 95% CI, 0.5-0.9), durvalumab + tremelimumab (HR = 0.7; 95% CI, 0.5-1.0) (both LC13); fatigue: durvalumab + tremelimumab (HR = 0.6; 95% CI, 0.4-0.8); and appetite loss: durvalumab (HR = 0.5; 95% CI, 0.4-0.7), durvalumab + tremelimumab (HR = 0.7; 95% CI, 0.5-0.9) (both C30). **Conclusion:** Durvalumab ± tremelimumab versus chemotherapy reduced symptom burden and improved TTD of PROs, suggesting it had no detrimental effects on quality of life in metastatic NSCLC patients.

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Introduction

Historically, the prognosis for patients with metastatic non–small-cell lung cancer (NSCLC) has been poor, with 5-year survival of approximately 6%.[1] However, the introduction of immune checkpoint inhibitors that target the programmed cell death protein 1 (PD-1) receptor or its ligand (PD-L1) has significantly improved outcomes, prolonging both overall survival (OS) and progression-free survival (PFS). Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80.[2] It is approved globally for the treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following platinum-based chemoradiotherapy.[3-5] Clinical activity of durvalumab has also been demonstrated in patients with advanced NSCLC, either alone or in combination with the anti-cytotoxic T-lymphocyte-associated antigen-4 agent tremelimumab.[6-8]

The phase 3 MYSTIC study (NCT02453282) was a global, randomized, open-label trial comparing first-line durvalumab with or without tremelimumab versus platinum-based chemotherapy in patients with metastatic NSCLC.[9] MYSTIC did not meet its primary endpoints of improved OS or PFS with durvalumab + tremelimumab versus chemotherapy in patients with tumor cell (TC) PD-L1 expression ≥ 25%. However, durvalumab alone versus chemotherapy was associated with a numerically reduced risk of death (hazard ratio [HR] = 0.76; 97.54% confidence interval [CI], 0.56-1.02; $P = .04$).[9]

The results from MYSTIC are consistent with those reported previously for other treatment-naïve, PD-L1 biomarker-selected trials, including KEYNOTE-042.[10] Based on emerging interest in tumor mutational burden (TMB) as a biomarker of response,[11] exploratory analyses were conducted for MYSTIC to assess the effect of TMB, as measured in peripheral blood (bTMB), on outcomes.[9]

In patients with bTMB ≥ 20 mutations per megabase (mut/Mb), durvalumab + tremelimumab versus chemotherapy was associated with improved OS (unadjusted HR = 0.49; 95% CI, 0.32-0.74); whereas, in patients with bTMB < 20 mut/Mb, there was no observed improvement in OS with durvalumab + tremelimumab versus chemotherapy (unadjusted HR = 1.16; 95% CI, 0.93-1.45). Among patients with bTMB ≥ 20 mut/Mb who received durvalumab alone versus chemotherapy, the OS benefit was numerically greater than the control arm but less marked than with durvalumab + tremelimumab (unadjusted HR = 0.72; 95% CI, 0.50-1.05).

Although improvements in PFS and OS provide robust evidence for clinical benefit, they are not the only measures of benefit. Symptom burden in advanced NSCLC is high, with at least 90% of patients experiencing appetite loss, chest pain, cough, dyspnea, or fatigue,[12,13] which can significantly impact quality of life (QoL).[13] As such, it is increasingly recognized that assessment of new cancer treatments should extend beyond evaluation of PFS and OS, as reflected in the value frameworks of several institutions which take into account other factors besides efficacy and safety, such as symptom impact and QoL.[14-17] Consequently, it is important that survival data are supplemented with patient-reported outcomes (PROs), in order to fully understand the impact of treatment from the patient's perspective on symptoms, functioning, and QoL.[18-20]

Here, we report PRO data from MYSTIC in order to assess the impact of first-line durvalumab with or without tremelimumab versus chemotherapy on the symptoms, functioning, and global health status/QoL of patients with metastatic NSCLC. For purposes of reporting PROs, the population of interest includes patients from the primary analysis (ie, biomarker-selected patients with PD-L1 TC ≥ 25%). However, PROs for the previously assessed bTMB populations are also reported.

Methods

Patients

Full inclusion and exclusion criteria have been reported previously.[9] Briefly, eligible patients were adults with stage IV NSCLC who had not previously received systemic therapy for advanced or metastatic NSCLC, had an Eastern Cooperative Oncology Group performance status score of 0 or 1, had ≥1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1),[21] and had known TC PD-L1 expression status

prior to randomization. Patients with sensitizing epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements or who had symptomatic, unstable brain metastases were excluded.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and tenets of the Declaration of Helsinki. The protocol and all modifications were approved by relevant ethics committees at participating centers and regulatory authorities. All patients provided written informed consent.

Study Design and Treatment

MYSTIC (NCT02453282) was a phase 3, multicenter, global, randomized, open-label study. Patients were randomized 1:1:1 to receive durvalumab 20 mg/kg every 4 weeks, durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg every 4 weeks (for up to four doses), or the investigator's choice of platinum-based doublet chemotherapy (four to six cycles). Randomization was stratified according to PD-L1 TC expression (≥25% vs. <25%) and tumor histology (squamous vs. non-squamous). Maintenance therapy with pemetrexed was allowed in patients with non-squamous histology who had not progressed after four cycles of pemetrexed/platinum therapy. Crossover from the chemotherapy arm to either of the durvalumab-containing arms was not allowed. Patients continued to receive treatment until objective disease progression (per RECIST v1.1), unacceptable toxicity, or consent withdrawal.

Endpoints and Assessments

The primary endpoints were OS (for durvalumab ± tremelimumab vs. chemotherapy) and PFS (for durvalumab + tremelimumab vs. chemotherapy), both of which were assessed in the primary analysis population of patients with PD-L1 TC ≥ 25%. Secondary endpoints included PFS for the durvalumab monotherapy arm and objective response rate for both durvalumab-containing arms, all versus chemotherapy, and safety, with adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 4.03. Patient-reported symptoms, functioning, and global health status/QoL were assessed as a secondary endpoint using the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life 30-item questionnaire (QLQ-C30), version 3, and its 13-item lung cancer module (QLQ-LC13).[22,23] Patients completed the questionnaires in their native language using validated translated versions.

The QLQ-C30 v3 questionnaire includes five multiple-item functioning scales (cognitive, emotional, physical, role, and social); three multiple-item symptom scales (fatigue, pain, and nausea/vomiting); six single-item symptom measures (appetite loss, constipation, diarrhea, dyspnea, insomnia, and perceived financial difficulties); and one multiple-item global health status/QoL scale.[22] The QLQ-LC13 is comprised of one multiple-item dyspnea scale, single-item measures of other symptoms associated with lung cancer (cough, hemoptysis, and pain in the arm/shoulder, chest, or other parts of the body), pain medicine use, side effects of conventional chemotherapy, and, less relevant to this study, radiotherapy (sore mouth, dysphagia, neuropathy, and hair loss).[23] The analyses reported here focus on symptoms associated with lung cancer and/or its treatment, as well as health-related QoL (perceived financial difficulties and pain medicine use are not reported).

Patients completed both questionnaires using a handheld electronic device. For the QLQ-C30, patients completed the questionnaire at baseline and at weeks 4 and 8, then every 8 weeks thereafter until disease progression. For the QLQ-LC13, patients completed the questionnaire at baseline and at weeks 2, 4, 6, and 8, then every 4 weeks thereafter until disease progression. Patients who discontinued treatment due to progression had their last PRO assessment at day 30, post final dose. Patients who discontinued treatment for reasons other than progression continued to complete questionnaires until disease progression. Patients who continued to receive treatment after progression (at the investigator's discretion in consultation with the study sponsor) carried on completing the questionnaires for as long as they remained on treatment.

Statistical Analysis

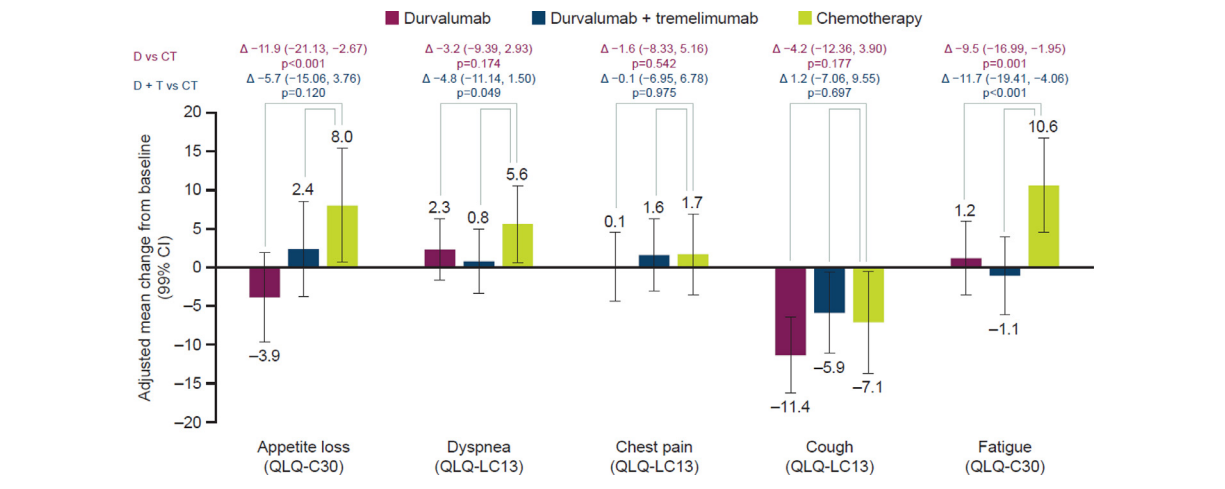
The study was powered for the primary endpoints, as described previously.[9] The secondary PROs were not part of the main multiple-testing procedure; therefore, no alpha was allocated for their analysis, and all reported *P* values are nominal. However, the following PRO endpoints were prespecified as primary symptoms of lung cancer: cough, dyspnea, and chest pain (all QLQ-LC13) and fatigue and appetite loss (both QLQ-C30). For the mixed model for repeated measures (MMRM) analyses of these five symptoms, as described below, the overall type I error (5% 2-sided) was controlled using a Bonferroni adjusted 1% significance level, and 99% CIs were reported. In addition, physical functioning and global health status/QoL (both QLQ-C30) were prespecified as PRO endpoints of interest.

Using the same data cutoff as that used for the final OS analysis (October 4, 2018), PROs were assessed and analyzed, as prespecified, in patients with PD-L1 TC ≥ 25% and, for purposes of exploratory analyses, in populations defined by a bTMB cutoff of 20 mut/Mb.

Summary statistics were compiled for overall compliance and compliance over time for both the QLQ-C30 and QLQ-LC13 questionnaires. In addition, summary statistics were compiled for all items included in the questionnaires at all assessed time points. Scores for the QLQ-30 and QLQ-LC13 questionnaires were calculated according to the published scoring guidelines or developer's guidelines. The raw scores from the scales in both questionnaires were standardized by linear transformation in order to range from 0 to 100 total. Higher scores for symptom items indicate greater symptom severity; higher scores for function and global health status/QoL items indicate better function and health status.[19,20] For both questionnaires, a ≥10-point change in score from baseline (either deterioration or improvement) was predefined as clinically meaningful.[24]

Mean change from baseline over 12 months was evaluated for the five prespecified key symptoms (cough, dyspnea, and chest pain [all QLQ-LC13] and fatigue and appetite loss [both QLQ-C30]) using MMRM analysis. The MMRM model compared the average treatment effect of PROs from randomization until disease progression or 12 months (whichever was earlier) accounting for multiple

Figure 1 MMRM-Adjusted Mean Changes from Baseline Over 12 Months in Prespecified Key Symptoms (PD-L1 TC ≥ 25% Population). Presented Are Adjusted Mean Changes From Baseline (Bars), and Between-Group Differences (Δ) with 99% CIs and Nominal *P* Values. A Negative Difference (Δ) Favors the Respective Durvalumab Arm Over Chemotherapy. A Difference (Δ) of ≥10 Was Predefined As Clinically Meaningful.
Abbreviations: CI = confidence interval; MMRM = mixed model for repeat measures; PD-L1 = programmed cell death protein ligand 1; QLQ-C30 = EORTC Core Quality of Life 30-item questionnaire; QLQ-LC13 = EORTC Core Quality of Life 13-item lung cancer questionnaire; TC = tumor cell.



visits for each patient. The MMRM analysis included treatment, age at randomization (<65 vs. ≥65 years), sex (male vs. female), smoking history (smoker vs. non-smoker), visit, and treatment-by-visit interaction as fixed effects and the baseline score as a covariate; in addition, the model adjusted for the baseline score-by-visit interaction.

Time to deterioration (TTD) of PROs was assessed in patients with baseline scores of ≥10 for functioning and global health status/QoL and ≤90 for symptoms. TTD was defined as the time from randomization until the date of the first clinically meaningful deterioration (≥10-point increase for symptoms; ≥10-point decrease for functioning items and global health status/QoL), as confirmed at a subsequent assessment, or death from any cause in the absence of clinically meaningful deterioration. TTD was analyzed using a stratified log-rank test, adjusting for histology (squamous vs. non-squamous), with ties handled using the Breslow approach; HRs and 95% CIs were estimated by a Cox proportional hazards model. Median TTD was estimated using the Kaplan–Meier method. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy (described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

Results

Patients

Overall, 1891 patients from 203 sites in 17 countries were enrolled between July 2015 and June 2016.[9] In total, 1118 patients were randomized to durvalumab monotherapy ($n = 374$), durvalumab + tremelimumab ($n = 372$), or chemotherapy ($n = 372$), comprising the intention-to-treat (ITT) population, of whom 1092 (97.7%) received at least one dose of study treatment ($n = 369$, 371, and 352, respectively).

The primary analysis population (patients with PD-L1 TC ≥ 25%) included 488 patients (43.6% of all randomized patients). Among 809 bTMB-evaluable patients, 211 patients (26.1%) had bTMB ≥ 20 mut/Mb and 598 patients (73.9%) had bTMB < 20 mut/Mb.

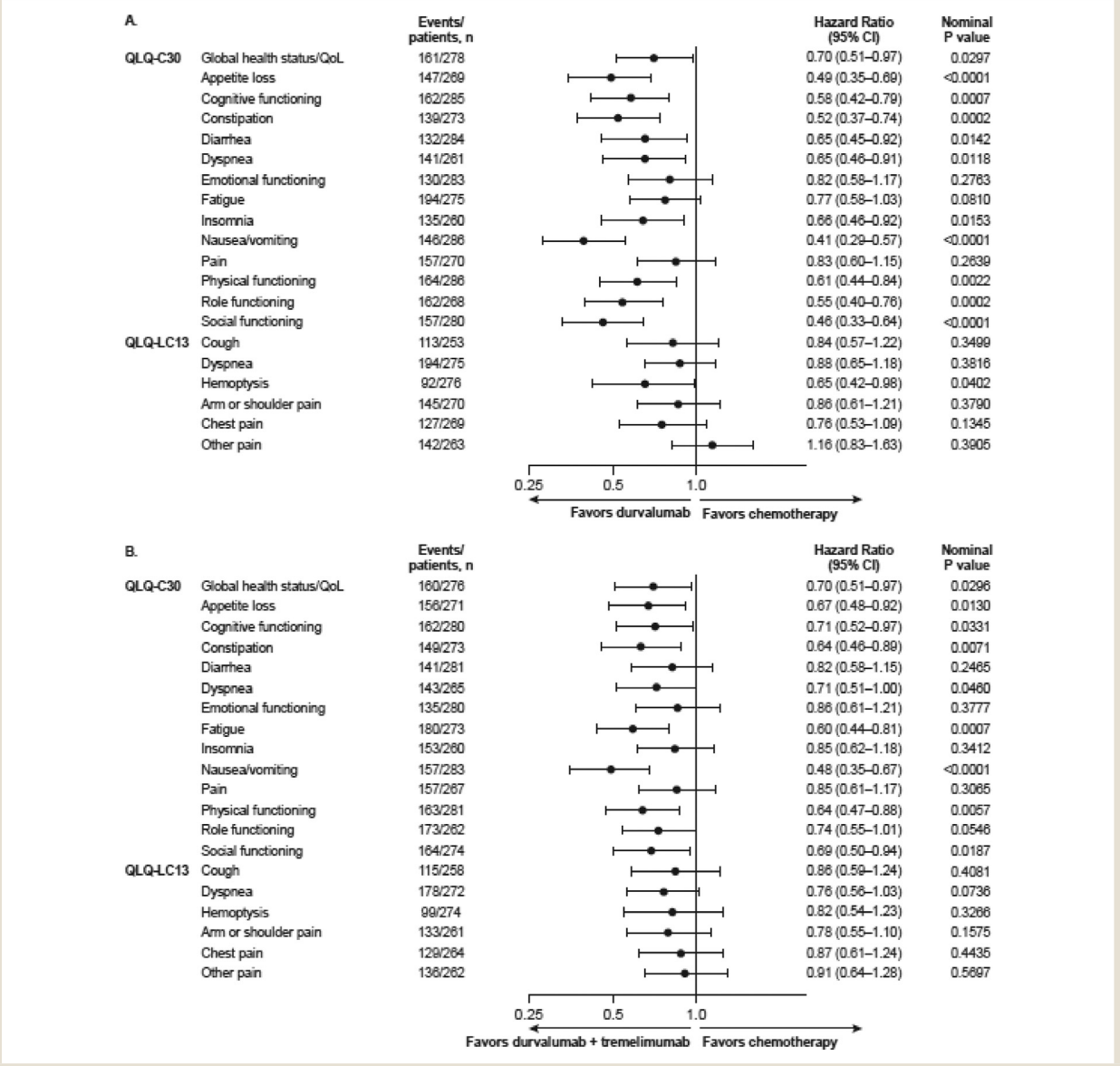
As reported previously, baseline demographics and disease characteristics of the primary analysis population (PD-L1 TC ≥ 25%), the ITT population, and the bTMB populations defined by the 20-mut/MB cutoff were generally consistent and balanced among the treatment groups.[9]

As of the data cutoff (October 4, 2018), median follow-up for OS was 30.2 (range, 0.3-37.1) months. Among patients with PD-L1 TC ≥ 25%, 44.8% in the durvalumab arm, 37.4% in the durvalumab + tremelimumab arm, and 58.6% in the chemotherapy arm had received any subsequent (post-discontinuation) anticancer therapy; among these patients in the chemotherapy arm, 67% had received subsequent immunotherapy.[9]

Baseline Scores and Compliance

Among patients with PD-L1 TC ≥ 25%, there were no clinically relevant between-treatment differences in baseline symptoms, functioning, or global health status/QoL (Supplemental Table 1). However, low baseline scores (<10 points) were reported for diarrhea and nausea/vomiting (both QLQ-C30) and alopecia, dysphagia, hemoptysis, peripheral neuropathy, and sore mouth (all QLQ-LC13), precluding the possibility of reporting clinically meaningful improvements for these endpoints. (A clinically meaningful improvement required a reduction from baseline of 10 points or more.) Similar baseline scores were observed in the bTMB

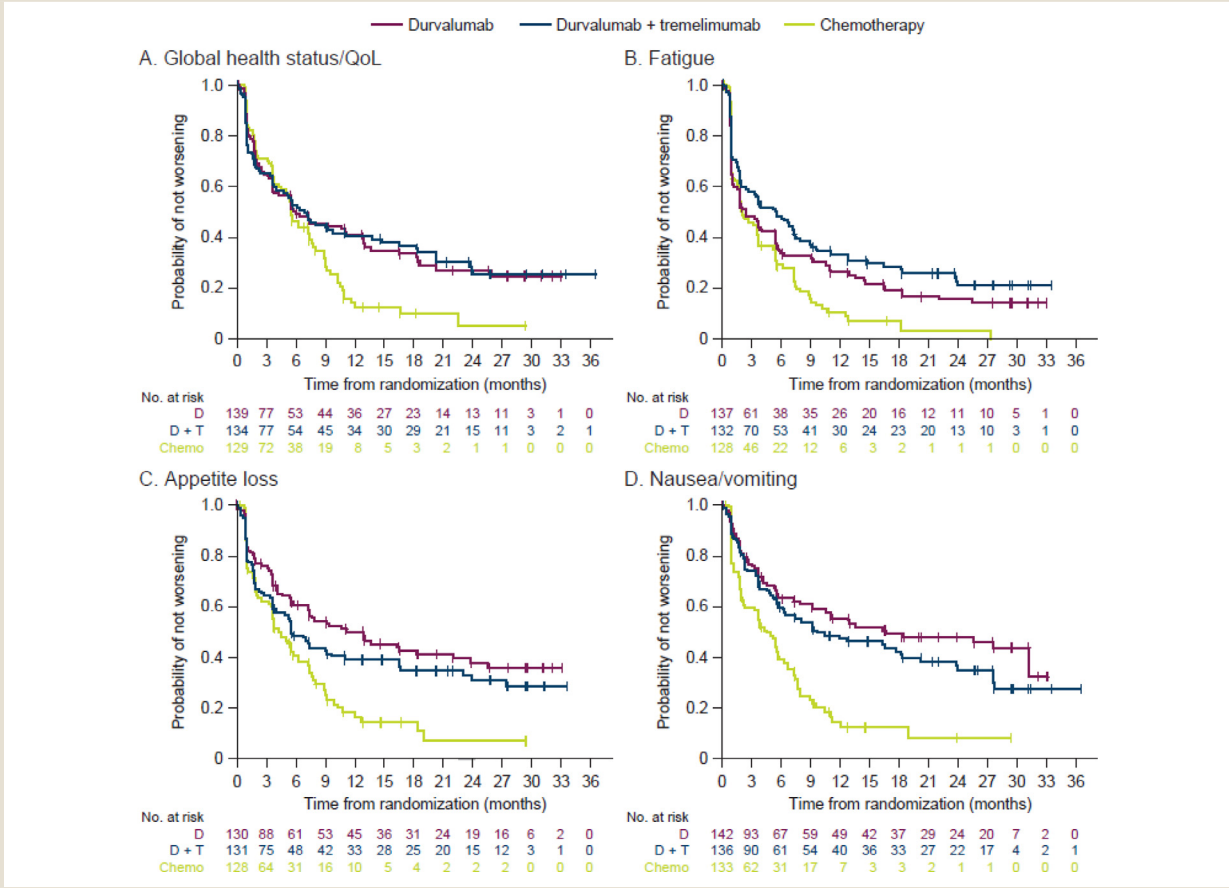
Figure 2 Time to Deterioration in Symptoms, Functioning, and Global Health Status/QoL for (A) Durvalumab Versus Chemotherapy and (B) Durvalumab + Tremelimumab Versus Chemotherapy (PD-L1 TC ≥ 25% Population). QLQ-C30 and QLQ-LC13 Symptom Scales/Items Are Based on Patients With Baseline Score ≤ 90. QLQ-C30 Functional Scales and Global Health Status/QoL Are Based on Patients With Baseline Scores ≥ 10. A Hazard Ratio < 1.0 Indicates Longer TTD With Immunotherapy Versus Chemotherapy. Stratified Log-Rank Test Adjusting for Histology (Squamous vs. Non-squamous), With Ties Handled Using the Breslow Approach.
Abbreviations: CI = confidence interval; PD-L1 = programmed cell death protein ligand 1; QLQ-C30 = EORTC Core Quality of Life 30-item questionnaire; QLQ-LC13 = EORTC Core Quality of Life 13-item lung cancer questionnaire; QoL = quality of life; TC = tumor cell.



≥ 20 mut/Mb and bTMB < 20 mut/Mb populations and the ITT population (Supplemental Table 2).

In the PD-L1 TC ≥ 25% population, compliance in completing the QLQ-C30 questionnaire was ≥60% up to week 120 in both durvalumab-containing arms and up to week 40 in the chemotherapy arm (Supplemental Figure 1A). Among these patients, compliance for the QLQ-LC13 questionnaire was ≥60% up to week 120 in both durvalumab arms and up to week 44 in the chemotherapy arm (Supplemental Figure 1B). In the bTMB-evaluable populations, compliance for both the QLQ-C30 and QLQ-LC13 questionnaires was ≥60% up to week 96 in both durvalumab arms and up to week 24 in the chemotherapy arm (data not shown).

Figure 3 Kaplan–Meier Analysis of Time to Deterioration for (A) Global Health Status/QoL and the Clinically Relevant Symptoms of (B) Fatigue, (C) Appetite Loss, (D) Nausea/Vomiting, (E) Diarrhea, (F) Dyspnea, and (G) Cough (PD-L1 TC ≥ 25% Population). QLQ-C30/QLQ-LC13 Symptom Scales/Items Are Based on Patients With Baseline Score ≤ 90. QLQ-C30 Global Health Status/QoL Is Based on Patients With Baseline Score ≥ 10.
Abbreviations: PD-L1 = programmed cell death protein ligand 1; QLQ-C30 = EORTC Core Quality of Life 30-item questionnaire; QLQ-LC13 = EORTC Core Quality of Life 13-item lung cancer questionnaire; QoL = quality of life; TC = tumor cell.

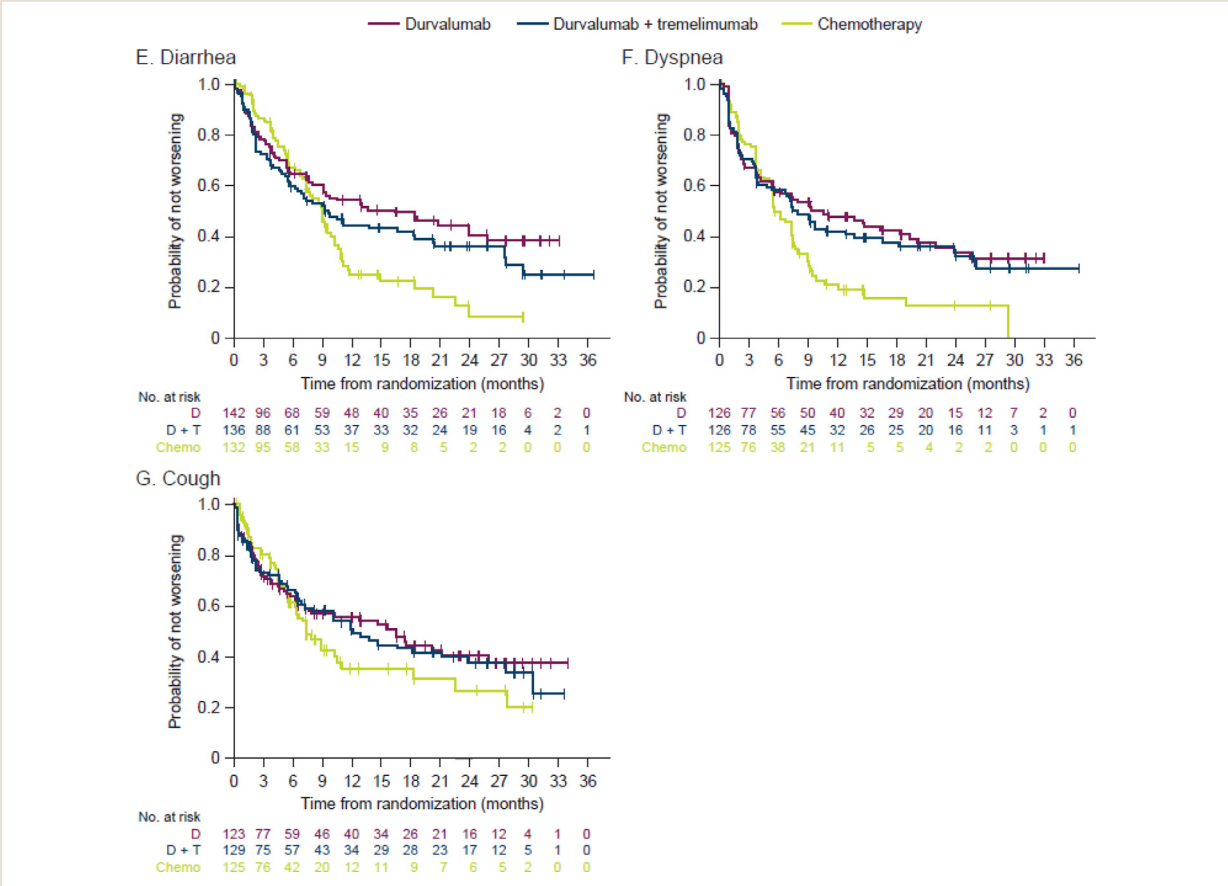


Changes from Baseline

In the PD-L1 TC ≥ 25% population, the differences in the MMRM-adjusted mean changes from baseline over 12 months (Figure 1) favored the durvalumab arm versus the chemotherapy arm for appetite loss (nominal $P < .001$) and fatigue (nominal $P = .001$) (both QLQ-C30). In addition, the between-group difference for appetite loss was clinically meaningful (−11.9 points). There was also a difference in the MMRM-adjusted mean change from baseline that favored durvalumab + tremelimumab versus chemotherapy for QLQ-C30 fatigue (nominal $P < .001$), with the between-group difference being clinically meaningful (−11.7 points). These differences were largely attributable to changes in the chemotherapy arm; whereas, in the durvalumab arms, these symptoms remained stable or decreased in frequency. For cough, dyspnea, and chest pain (all QLQ-LC13), there were no differences in the MMRM-adjusted mean changes from baseline between the durvalumab arms and the chemotherapy arm (Figure 1).

In both of the bTMB populations (≥20 and <20 mut/Mb), the MMRM-adjusted mean changes from baseline over 24 weeks did not favor durvalumab versus chemotherapy for any of the prespecified key symptoms (Supplemental Figure 2). (The MMRM analyses for the bTMB populations were based on 24 weeks, not 12 months, due to limited records after 24 weeks in the chemotherapy arm.) However, among patients with bTMB ≥ 20 mut/Mb, there were differences in the MMRM-adjusted mean changes from baseline favoring durvalumab + tremelimumab versus chemotherapy for appetite loss and fatigue (both QLQ-C30 with nominal $P < .001$); the between-arm differences were clinically meaningful for both (–17.0 and –17.5, respectively; Supplemental Figure 2). However, there were no equivalent differences among patients with bTMB < 20 mut/Mb. The reported

Figure 3 Continued



differences largely reflect a clinically meaningful deterioration in these symptoms in the chemotherapy arm. There were no differences between the durvalumab arms and chemotherapy arm in adjusted mean changes from baseline for cough, dyspnea, or chest pain (all QLQ-LC13) in either bTMB population (Supplemental Figure 2).

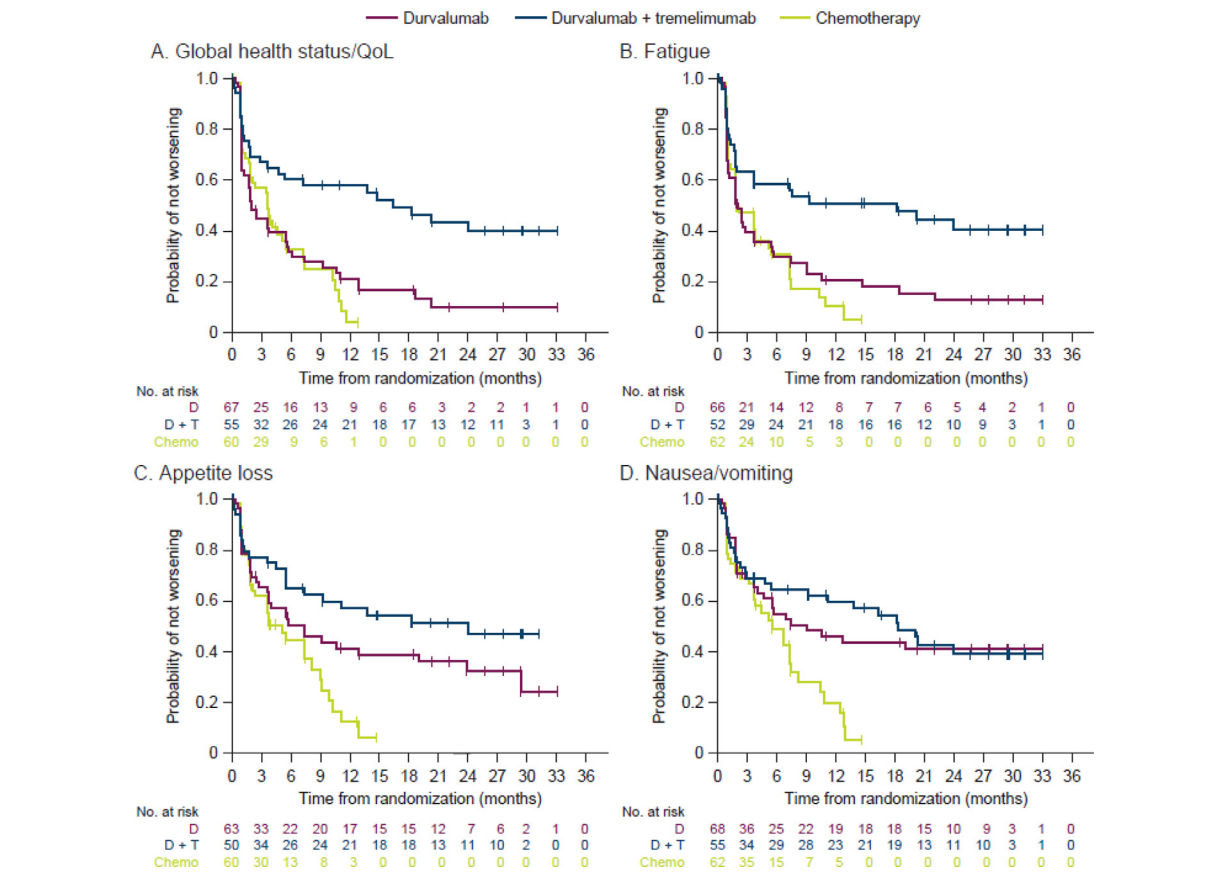
Based on absolute scores, most PROs remained stable over time among patients with PD-L1 TC ≥ 25% in the durvalumab arms, with no clinically meaningful changes from baseline to week 48 (data not shown), except for the following endpoints that showed improvement: QLQ-LC13 cough (mean change, –16.3; SD = 29.9) with durvalumab and QLQ-C30 dyspnea (mean change, –18.9; SD = 32.0) with durvalumab + tremelimumab. In contrast, within the chemotherapy arm, there were clinically meaningful changes from baseline to week 48 for several endpoints, reflecting either improvement or worsening: emotional functioning (mean change, 13.9; SD = 17.2), role functioning (mean change, –11.1; SD = 13.6), appetite loss (mean change, –11.1; SD = 40.4), constipation (mean change, –11.1; SD = 27.2), dyspnea (mean change, 11.1; SD = 17.2), and nausea/vomiting (mean change, 11.1; SD = 17.2) (all QLQ-C30); as well as cough (mean change, –16.7; SD = 35.0), arm/shoulder pain (mean change, –22.2; SD = 34.4), chest pain (mean change, –11.1; SD = 27.2), other pain (mean change, –11.1; SD = 27.2), alopecia (mean change, 11.1; SD = 17.2), and peripheral neuropathy (mean change, 22.2; SD = 34.4) (all QLQ-LC13). There were no clinically meaningful absolute changes from baseline in global health status/QoL items across all treatment groups.

Time to Deterioration

Among patients with PD-L1 TC ≥ 25%, TTD was longer with durvalumab versus chemotherapy (nominal $P < .01$) for hemoptysis (QLQ-LC13) and appetite loss, constipation, diarrhea, dyspnea, insomnia, and nausea/vomiting, as well as four functioning domains (cognitive, physical, role, and social) and global health status/QoL (all QLQ-C30) (Figure 2A). In addition, TTD was longer with durvalumab + tremelimumab versus chemotherapy (nominal $P < .01$) for appetite loss, constipation, dyspnea, fatigue, and nausea/vomiting, as well as three functioning domains (cognitive, physical, and social), and global health status/QoL (all QLQ-C30) (Figure 2B). There were no other differences between the durvalumab arms and chemotherapy for any other parameters (based on nominal *P* values).

Among patients with bTMB ≥ 20 mut/Mb, TTD was longer with durvalumab versus chemotherapy for social functioning, appetite loss, constipation, and nausea/vomiting (all QLQ-

Figure 4 Kaplan–Meier Analysis of Time to Deterioration for (A) Global Health Status/QoL and the Clinically Relevant Symptoms of (B) Fatigue, (C) Appetite Loss, (D) Nausea/Vomiting, (E) Diarrhea, (F) Dyspnea, and (G) Cough (bTMB ≥ 20 Population). QLQ-C30 Global Health Status/QoL Is Based on Patients With Baseline Scores ≥ 10. QLQ-C30/QLQ-LC13 Item/Symptom Scales Are Based on Patients With Baseline Score ≤ 90.
Abbreviations: bTMB = blood tumor mutational burden; Mb = megabase; mut = mutation; QLQ-C30 = EORTC Core Quality of Life 30-item questionnaire; QLQ-LC13 = EORTC Core Quality of Life 13-item lung cancer questionnaire; QoL = quality of life.



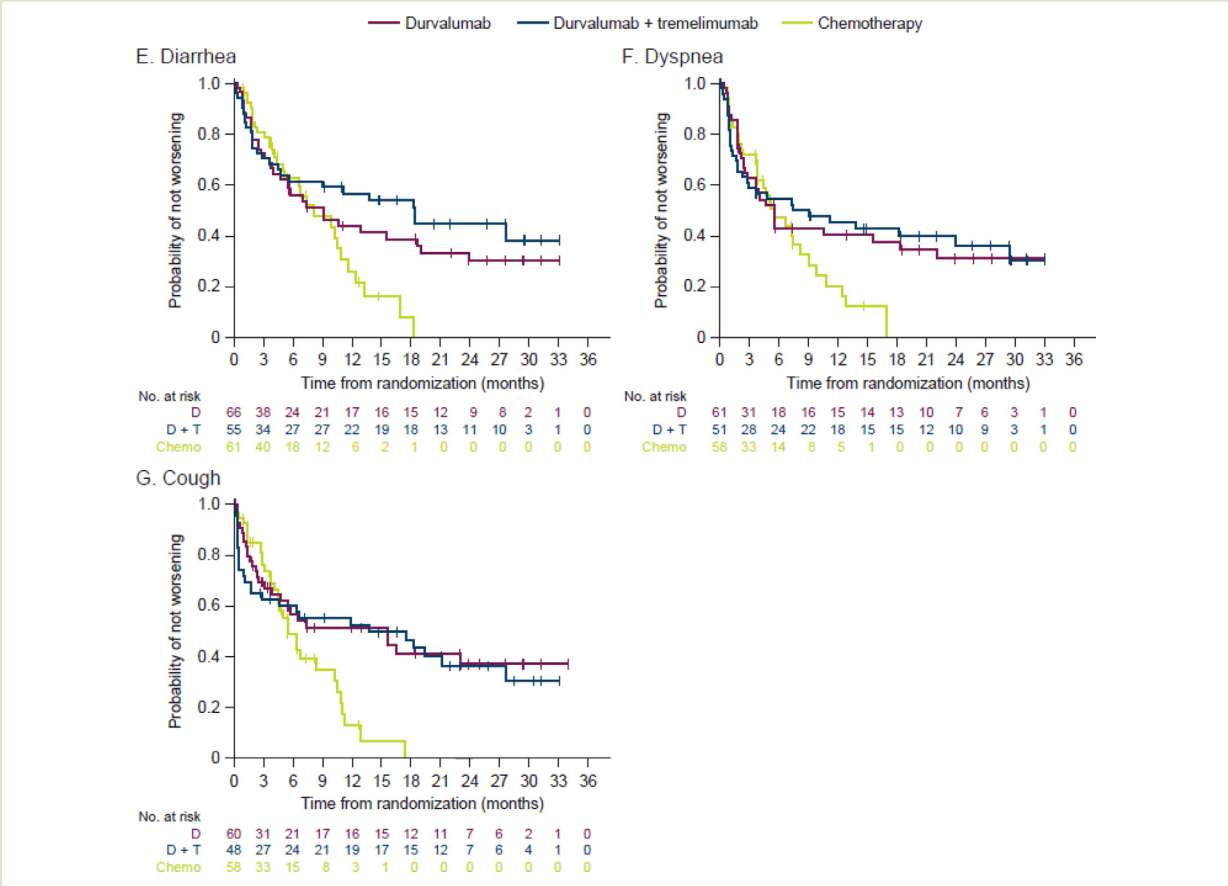
C30) and cough (QLQ-LC13) (Supplemental Figure 3A). In addition, TTD was longer with durvalumab + tremelimumab versus chemotherapy for global health status/QoL and all functioning domains (all QLQ-C30), as well as appetite loss, constipation, fatigue, nausea/vomiting, pain, and insomnia (all QLQ-C30) and cough, arm or shoulder pain, chest pain, and other pain (all QLQ-LC13) (Supplemental Figure 3B). In contrast, among patients with bTMB < 20 mut/Mb, there were no clinically important differences in TTD between the durvalumab-containing arms and the chemotherapy arm (Supplemental Figures 4A and 4B), apart from TTD for nausea/vomiting (QLQ-C30), which was longer with durvalumab versus chemotherapy, and other pain (QLQ-LC13), which was longer with chemotherapy than with durvalumab + tremelimumab.

Kaplan–Meier analyses of TTD for items considered most clinically relevant to patients—global health status/QoL, fatigue, appetite loss, nausea/vomiting, diarrhea, and dyspnea (all QLQ-C30) and cough (QLQ-LC13)—are presented in Figure 3 (PD-L1 TC ≥ 25% population), Figure 4 (bTMB ≥ 20 mut/Mb), and Supplemental Figure 5 (bTMB < 20 mut/Mb).

Discussion

Among patients with metastatic NSCLC and PD-L1 TC ≥ 25% in MYSTIC, first-line durvalumab monotherapy versus chemotherapy was associated with a numerically reduced risk of death (HR = 0.76; 97.54% CI, 0.56-1.02; $P = .04$).[9] In addition, in an exploratory analysis of patients with bTMB ≥ 20 mut/Mb, durvalumab + tremelimumab versus chemotherapy was associated with improved OS (unadjusted HR = 0.49; 95% CI, 0.32-0.74). The safety profiles of both durvalumab arms were consistent with data from prior trials, and both arms versus chemotherapy were associated with fewer grade ≥3 treatment-related AEs.[9] To fully understand the impact of treatment, here we report, for the first time, to our knowledge, the impact of first-line durvalumab,

Figure 4 Continued



with or without tremelimumab, on symptoms, functioning, and global health status/QoL in patients with metastatic NSCLC from MYSTIC.

Based on the MMRM analyses, patients with PD-L1 TC ≥ 25% who received durvalumab, with or without tremelimumab, reported clinically meaningful improvements in prespecified key symptoms of NSCLC and experienced reduced symptom burden over time, compared with patients who received chemotherapy. In both of the bTMB populations, the adjusted mean changes from baseline did not favor durvalumab versus chemotherapy for any of the key symptoms. In contrast, among patients with bTMB ≥ 20 mut/Mb, there were differences in MMRM-adjusted mean changes from baseline favoring durvalumab + tremelimumab versus chemotherapy for appetite loss and fatigue, with no equivalent differences among patients with bTMB < 20 mut/Mb. For both the PD-L1 TC ≥ 25% population and patients with bTMB ≥ 20 mut/Mb, any differences were largely attributable to changes in the chemotherapy arm (ie, deterioration in symptoms); whereas, in the durvalumab-containing arms, these symptoms remained stable or decreased in frequency (evidence of better tolerability from the patient's perspective).

Patients with PD-L1 TC ≥ 25% who received durvalumab, with or without tremelimumab, also experienced longer TTD across a broad range of symptoms, several functioning domains, and global health status/QoL, compared with patients who received chemotherapy. These results illustrate that health-related QoL appears to be maintained in patients within the durvalumab-containing arms. Among patients with bTMB ≥ 20 mut/Mb, TTD was longer with durvalumab versus chemotherapy for appetite loss, constipation, nausea/vomiting, cough, and social functioning. In addition, TTD was longer with durvalumab + tremelimumab versus chemotherapy for global health status/QoL and all functioning domains, as well as several symptoms. In contrast, among patients with bTMB < 20 mut/Mb, TTD did not generally differ between the durvalumab-containing and chemotherapy arms. Longer TTD for typical tumor symptoms, such as cough, dyspnea, and pain, suggests a better efficacy of immunotherapy in the pertaining subsets and treatment groups.

Overall, these data are consistent with PRO results from other immunotherapy studies, examining the impact of first-line monotherapy or combination therapy on symptoms and health-related QoL in patients with advanced NSCLC. In KEYNOTE-024, among treatment-naïve patients with stage IV PD-L1-positive (a tumor proportion score of ≥50%) NSCLC, pembrolizumab improved or maintained health-related QoL compared with chemotherapy.[25] In CheckMate-227, treatment-naïve patients with

stage IV NSCLC and high TMB (≥10 mut/Mb) who received nivolumab + ipilimumab experienced more rapid, durable, and clinically meaningful improvements in PROs compared with those assigned to chemotherapy.[26] Our findings also align with those from studies carried out in previously treated patients with advanced NSCLC, in which QoL and symptoms were maintained or improved to a greater degree with pembrolizumab[27] or nivolumab[28,29] than with chemotherapy. Similarly, in the OAK trial, atezolizumab prolonged TTD in physical function and role function and numerically improved patients' health-related QoL from baseline compared with chemotherapy in patients with previously treated advanced or metastatic NSCLC.[30] Finally, results of the present analyses also agreed with those from the PACIFIC study, in which clinical benefit with durvalumab monotherapy versus placebo was achieved with no detrimental effect on PROs in patients with stage III, unresectable NSCLC who had received prior chemoradiotherapy.[31]

Certain limitations of the current analysis should be acknowledged. For example, the MYSTIC study was an open-label trial, meaning that patients assigned to immunotherapy may have overestimated improvements; whereas, patients assigned to chemotherapy may have under-reported improvements, potentially biasing the results.[32,33] On the other hand, at baseline, patients assigned to receive durvalumab (with or without tremelimumab) may have overestimated their wellbeing (because they were pleased to be receiving the investigational product); whereas, those in the chemotherapy arm may have underestimated their wellbeing (owing to disappointment). This could have led to an underestimation of the effects of immunotherapy[32]; however, a small analysis of PROs collected in blinded and open-label trials of identical oncology drugs has found no between-trial differences in compliance rates or evidence to suggest overestimation of improvements in open-label trials.[34] In addition, the QLQ-C30 and QLQ-LC13 questionnaires were developed in the early 1990s in the era of chemotherapy,[22,23] which may limit their relevance in immunotherapy settings. For example, potential symptoms related to immunotherapies (eg, feeling cold, rash, weight gain or weight loss)[5] are not captured. Another limitation includes the fact that the sample size in the chemotherapy arm was markedly lower than in the immunotherapy arms from week 24 onward, potentially biasing results in favor of chemotherapy. Importantly, the study was not powered for secondary endpoints (ie, PROs); thus, these results should be considered exploratory only, as any observed benefits (which may appear overstated with results reported for two investigational arms) are based on nominal *P* values. Finally, there is no gold-standard definition for TTD, which may be influenced by the mechanism of action of a drug, disease stage, treatment line, and cancer type.

Conclusions

In summary, these data show that first-line durvalumab, with or without tremelimumab, versus chemotherapy had a positive impact on a broad range of PROs, reducing symptom burden and prolonging TTD in metastatic NSCLC patients with PD-L1 TC ≥ 25% or bTMB ≥ 20 mut/Mb. These findings complement and support the numerically reduced risk of death observed with first-line durvalumab versus chemotherapy as previously reported in patients with metastatic NSCLC. In addition, the PRO results suggest that there are no detrimental effects on QoL with immune checkpoint inhibitors compared to chemotherapy, which may prove beneficial in future studies of immunotherapy in patients with advanced NSCLC and high PD-L1 TC expression.

Clinical Practice Points

- In the phase 3 MYSTIC trial of metastatic NSCLC, the primary endpoints of improved overall survival or progression-free survival with first-line durvalumab + tremelimumab versus chemotherapy were not met in patients with PD-L1 TC expression ≥ 25%. However, durvalumab alone versus chemotherapy was associated with a numerically reduced risk of death.
- Symptom burden in advanced NSCLC is high, which can significantly impact quality of life. It is, therefore, important to supplement survival data with patient-reported outcomes, in order to fully understand the impact of treatment on symptoms, functioning, and quality of life from the patient's perspective.
- The present analyses showed that durvalumab ± tremelimumab reduced symptom burden and improved times to deterioration of patient-reported outcomes in patients with PD-L1 TC ≥ 25%, suggesting it had no detrimental effects on quality of life.
- These findings suggest that there are no detrimental effects on quality of life with immune checkpoint inhibitors, compared to chemotherapy, which may prove beneficial in future studies of immunotherapy in patients with advanced NSCLC and high PD-L1 TC expression.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2021.02.010.

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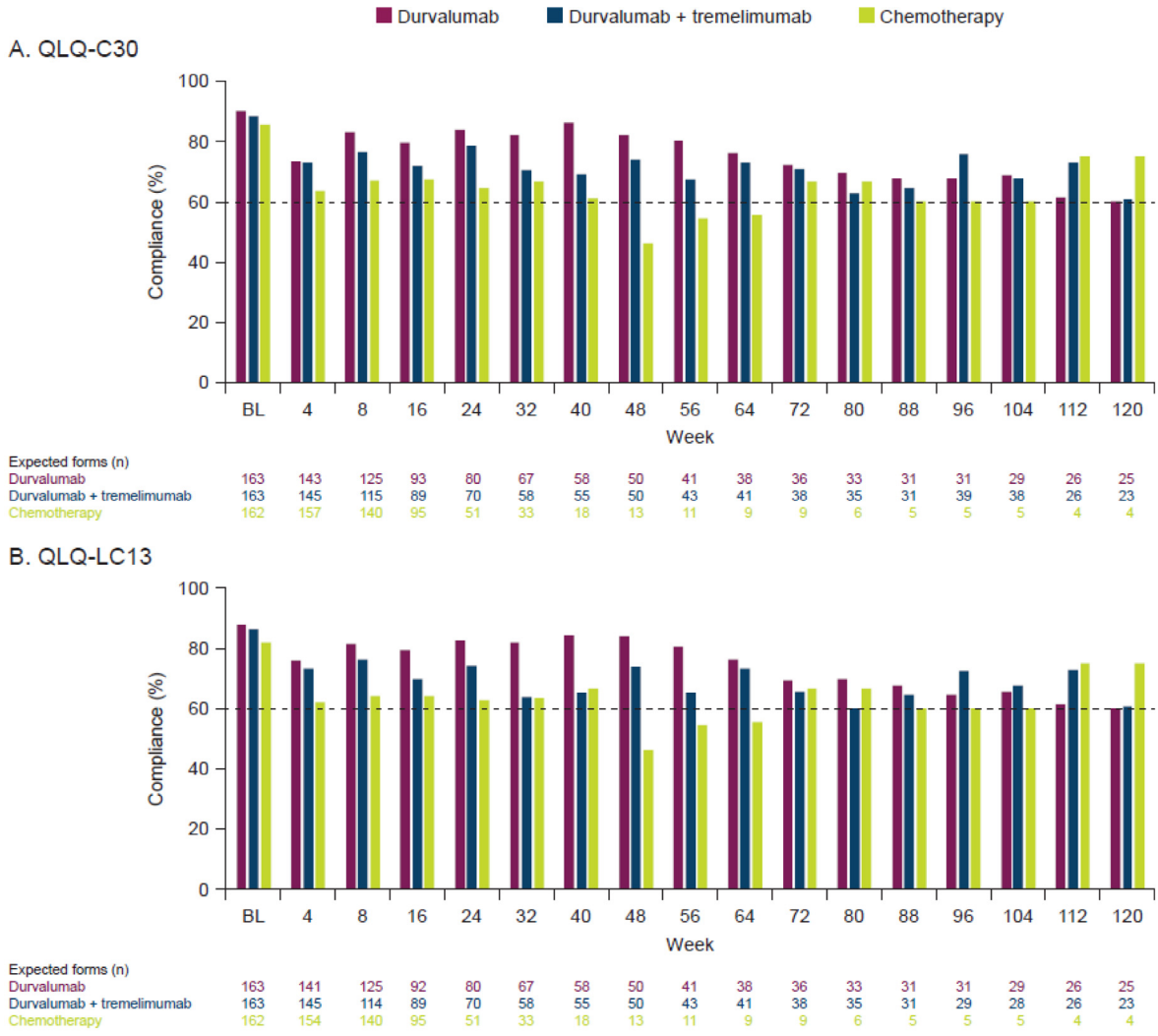
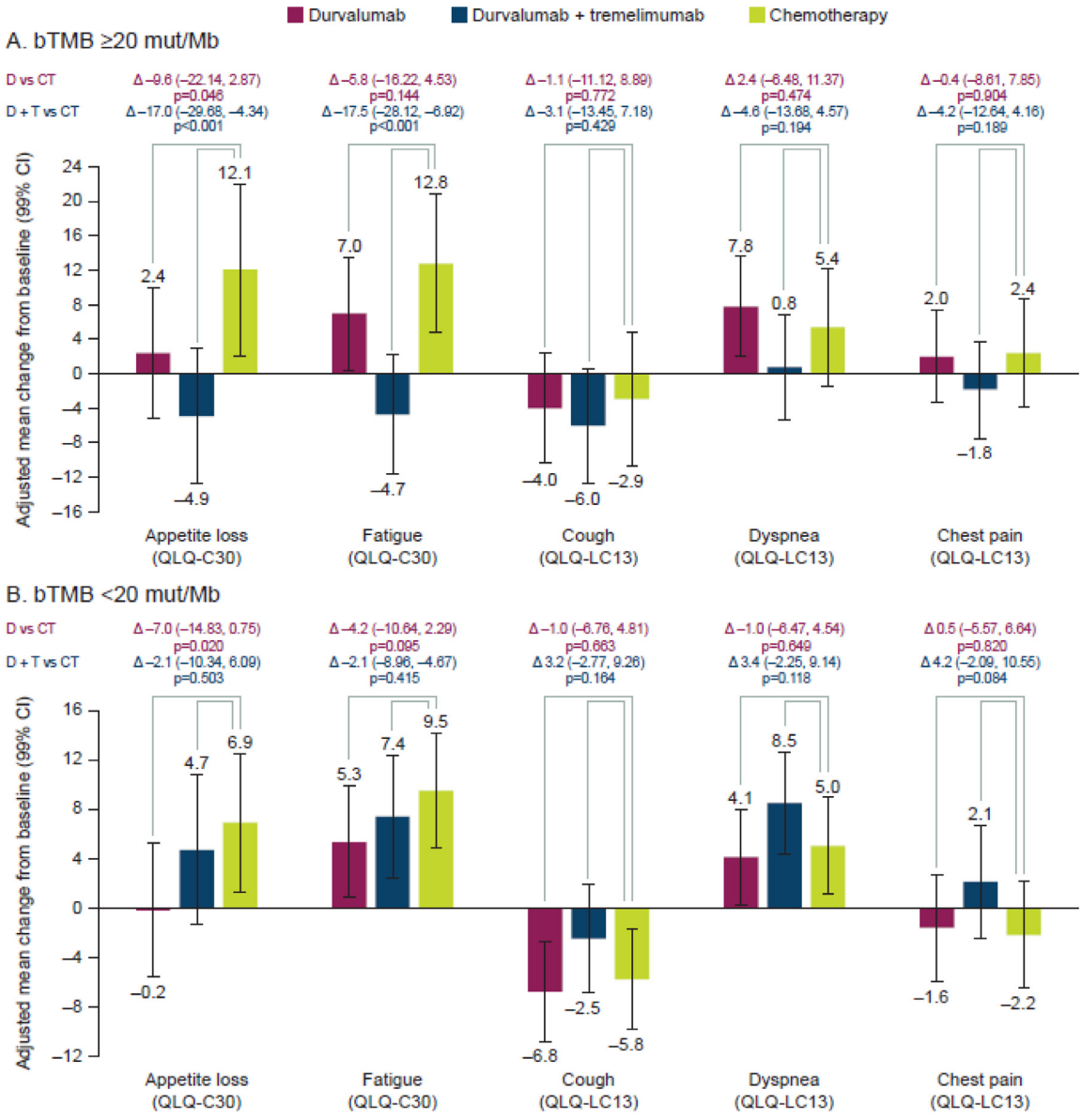
Supplemental Data

Supplemental Figure 1 Compliance Rates for the EORTC QLQ-C30 (A) and QLQ-LC13 (B) Questionnaires (PD-L1 TC ≥25% Population)
Dashed line indicates threshold for acceptable to good compliance (≥60%). Abbreviations: EORTC=European Organisation for Research and Treatment of Cancer; PD-L1=programmed cell death-ligand 1; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer



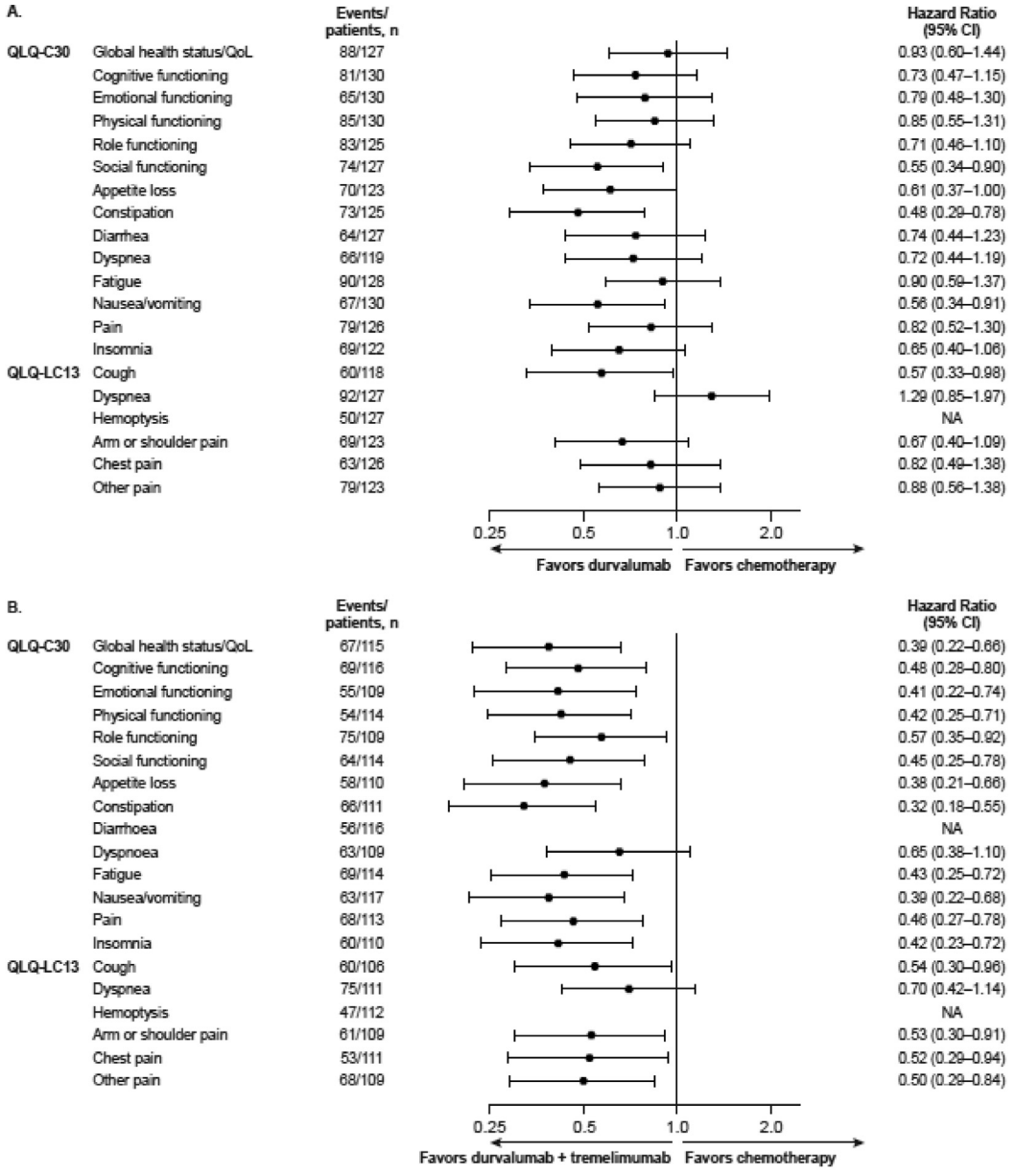
Dashed line indicates threshold for acceptable to good compliance (≥60%). Abbreviations: EORTC=European Organisation for Research and Treatment of Cancer; PD-L1=programmed cell death-ligand 1; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; TC=tumor cell.

Supplemental Figure 2 MMRM-adjusted Mean Changes from Baseline Over 24 Weeks in Pre-specified Key Symptoms in the bTMB ≥20 mut/Mb (A) and bTMB <20 mut/Mb (B) Populations.
Presented are adjusted mean changes from baseline (bars), and between-group differences (Δ) with 99% CIs and nominal *P*-values. A negative difference (Δ) favors the respective durvalumab arm over chemotherapy. A difference (Δ) of ≥10 was predefined as clinically meaningful. Abbreviations: bTMB=blood tumor mutational burden; CI=confidence interval; Mb=megabase; MMRM=mixed model for repeat measures; mut=mutation; QLQ–C30=30-item core quality of life questionnaire; QLQ–LC13=13-item lung cancer quality of life questionnaire.



Presented are adjusted mean changes from baseline (bars), and between-group differences (Δ) with 99% CIs and nominal *P*-values. A negative difference (Δ) favors the respective durvalumab arm over chemotherapy. A difference (Δ) of ≥10 was predefined as clinically meaningful. Abbreviations: bTMB=blood tumor mutational burden; CI=confidence interval; Mb=megabase; MMRM=mixed model for repeat measures; mut=mutation; QLQ–C30=30-item core quality of life questionnaire; QLQ–LC13=13-item lung cancer quality of life questionnaire.

Supplemental Figure 3 **Time to Deterioration in Symptoms, Functioning, and Global Health Status/QoL for Durvalumab Versus Chemotherapy (A) and Durvalumab Plus Tremelimumab Versus Chemotherapy (B) (bTMB ≥20 mut/Mb Population)**
QLQ-C30 and QLQ-LC13 symptom scales/items are based on patients with baseline score ≤90. QLQ-C30 functional scales and global health status/QoL are based on patients with baseline scores ≥10. A hazard ratio <1.0 indicates longer TTD with the durvalumab arms versus the chemotherapy arm. The logistic regression analyses are only presented when at least 20 patients combined for both arms deteriorated. Abbreviations: bTMB=tumor mutational burden; CI=confidence interval; Mb=megabase; mut=mutation; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; QoL=quality of life; TTD=time to deterioration.



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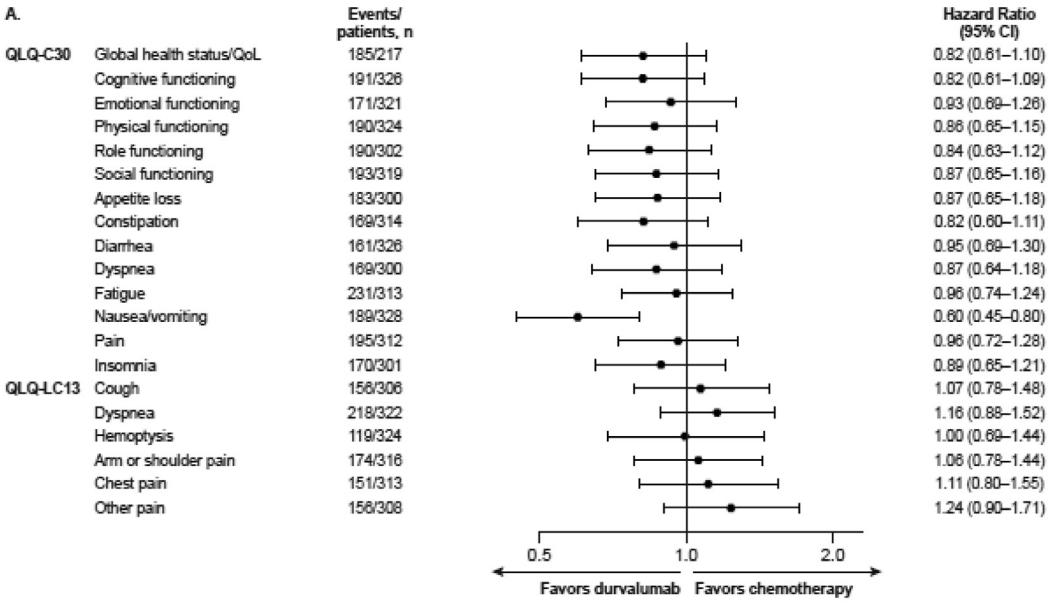
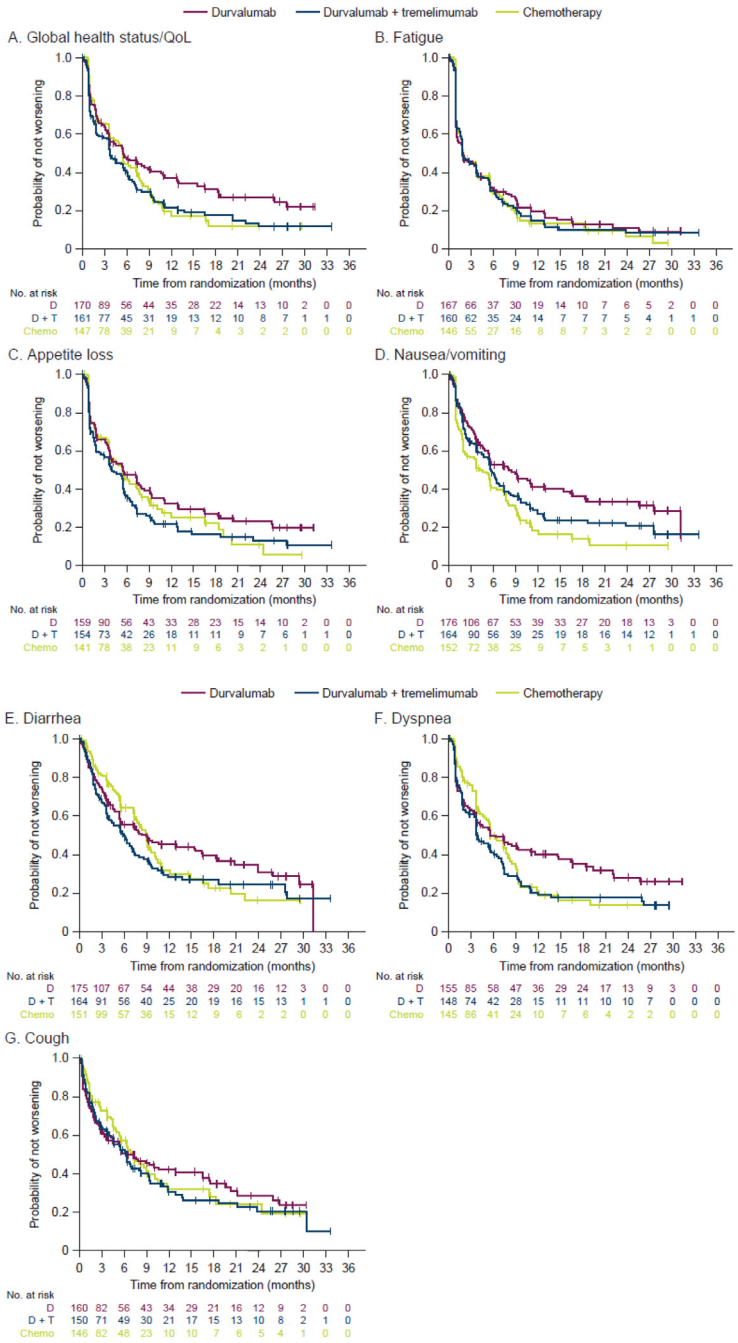
QLQ-C30 functional scales and global health status/QoL are based on patients with baseline scores ≥10. A hazard ratio <1.0 indicates longer TTD with the durvalumab arms versus the chemotherapy arm. The logistic regression analyses are only presented when at least 20 patients combined for both arms deteriorated. Abbreviations: bTMB=tumor mutational burden; CI=confidence interval; Mb=megabase; mut=mutation; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; QoL=quality of life; TTD=time to deterioration.

Supplemental Figure 4 **Time to Deterioration in Symptoms, Functioning, and Global Health Status/QoL for Durvalumab Versus Chemotherapy (A) and Durvalumab Plus Tremelimumab Versus Chemotherapy (B) (bTMB <20 mut/Mb Population)**
QLQ-C30 and QLQ-LC13 symptom scales/items are based on patients with baseline score ≤90. QLQ-C30 functional scales and global health status/QoL are based on patients with baseline scores ≥10. A hazard ratio <1.0 indicates longer TTD with the durvalumab arms versus the chemotherapy arm. The logistic regression analyses are only presented when at least 20 patients combined for both arms deteriorated. Abbreviations: bTMB=tumor mutational burden; CI=confidence interval; Mb=megabase; mut=mutation; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer



QLQ-C30 and QLQ-LC13 symptom scales/items are based on patients with baseline score ≤90. QLQ-C30 functional scales and global health status/QoL are based on patients with baseline scores ≥10. A hazard ratio <1.0 indicates longer TTD with the durvalumab arms versus the chemotherapy arm. The logistic regression analyses are only presented when at least 20 patients combined for both arms deteriorated. Abbreviations: bTMB=tumor mutational burden; CI=confidence interval; Mb=megabase; mut=mutation; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; QoL=quality of life; TTD=time to deterioration.

Supplemental Figure 5 Kaplan-Meier Analysis of Time to Deterioration for Global Health Status/QoL (A) and the Clinically Relevant Symptoms of Fatigue (B), Appetite Loss (C), Nausea/Vomiting (D), Diarrhea (E), Dyspnea (F), and Cough (G) (bTMB <20 mut/Mb Population)
QLQ-C30 global health status/QoL is based on patients with baseline scores ≥10. QLQ-C30/QLQ-LC13 item/symptom scales are based on patients with baseline score ≤90.
Abbreviations: bTMB=blood tumor mutational burden; Mb=megabase; mut=mutation; QLQ–C30=30-item core quality of life questionnaire; QLQ-LC13=13-item lung cancer module quality of life questionnaire; QoL=quality of life.



QLQ-C30 global health status/QoL is based on patients with baseline scores ≥10. QLQ-C30/QLQ-LC13 item/symptom scales are based on patients with baseline score ≤90.
Abbreviations: bTMB=blood tumor mutational burden; Mb=megabase; mut=mutation; QLQ–C30=30-item core quality of life questionnaire; QLQ-LC13=13-item lung cancer module quality of life questionnaire; QoL=quality of life.

Supplemental Table 1 Baseline Symptoms, Functioning, and Global Health Status/QoL (PD-L1 TC ≥25% Population).

		Durvalumab Monotherapy (n=163)	Durvalumab + Tremelimumab (n=163)	Chemotherapy (n=162)
QLQ−C30 score, mean (SD)	Appetite loss	27.2 (32.4)	21.3 (28.6)	23.3 (28.3)
	Constipation	19.5 (28.9)	16.9 (28.2)	18.0 (26.7)
	Diarrhea	5.7 (14.3)	3.9 (12.8)	6.0 (17.6)
	Dyspnea	34.2 (31.7)	37.0 (29.0)	34.3 (28.1)
	Fatigue	36.4 (25.5)	37.3 (24.8)	37.7 (27.9)
	Insomnia	31.1 (30.1)	29.6 (28.7)	32.9 (34.1)
	Nausea/vomiting	7.7 (14.2)	5.2 (10.3)	5.2 (11.3)
	Pain	29.5 (28.8)	31.9 (29.1)	33.5 (30.3)
	Cognitive functioning	87.1 (18.1)	86.1 (19.9)	86.5 (19.2)
	Emotional functioning	71.9 (21.2)	75.2 (22.7)	70.1 (23.4)
	Physical functioning	74.4 (21.4)	74.0 (22.1)	72.4 (22.5)
	Role functioning	71.4 (29.8)	70.0 (30.1)	68.8 (32.0)
	Social functioning	80.8 (23.0)	79.9 (25.7)	75.1 (28.5)
	Global health status/QoL	58.1 (23.4)	59.3 (19.2)	57.4 (23.0)
QLQ−LC13 score, mean (SD)	Alopecia	4.9 (15.8)	3.5 (13.0)	3.8 (11.4)
	Cough	43.4 (28.8)	43.0 (26.9)	37.6 (26.7)
	Dysphagia	7.5 (17.4)	5.4 (14.2)	7.3 (18.0)
	Dyspnea	26.9 (22.5)	28.0 (22.8)	27.2 (22.2)
	Hemoptysis	5.1 (13.9)	6.6 (14.5)	7.0 (16.4)
	Pain in arm or shoulder	15.2 (22.3)	22.2 (31.0)	21.6 (29.6)
	Pain in chest	18.6 (23.9)	21.5 (26.8)	17.8 (25.1)
	Pain in other parts	24.2 (26.6)	23.6 (27.5)	27.3 (29.3)
	Peripheral neuropathy	7.5 (17.0)	7.3 (17.0)	11.3 (20.9)
	Sore mouth	6.5 (16.9)	3.1 (9.7)	4.3 (13.2)

Shaded cells indicate symptoms for which low (<10) baseline values were reported; clinically meaningful improvements in these symptoms were therefore not possible to determine. Abbreviations: PD-L1=programmed cell death ligand-1; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; SD=standard deviation; TC=tumor cell.

Supplemental Table 2 Baseline Symptoms, Functioning, and Global Health Status/QoL in the bTMB ≥20 mut/Mb (A) and bTMB <20 mut/Mb (B) Populations.

		Durvalumab Monotherapy (n=77)	Durvalumab + Tremelimumab (n=64)	Chemotherapy (n=70)
(A) bTMB ≥20 mut/Mb				
QLQ–C30 score, mean (SD)	**Appetite loss**	26.0 (31.1)	27.4 (32.5)	22.4 (27.3)
	Constipation	17.8 (29.4)	16.7 (23.8)	14.6 (25.1)
	Diarrhea	5.5 (19.3)	4.2 (14.3)	7.3 (18.3)
	Dyspnea	36.1 (29.8)	38.1 (31.4)	33.3 (30.3)
	Fatigue	36.5 (26.9)	39.7 (26.9)	33.0 (24.1)
	Insomnia	29.2 (28.8)	29.2 (26.3)	27.1 (31.9)
	Nausea/vomiting	7.5 (14.7)	6.3 (13.3)	5.5 (9.9)
	Pain	31.5 (29.5)	28.3 (28.6)	30.0 (25.2)
	Cognitive functioning	88.8 (16.0)	87.5 (19.1)	89.3 (15.8)
	Emotional functioning	69.5 (21.3)	72.6 (23.1)	78.5 (19.2)
	Physical functioning	75.6 (20.2)	74.8 (23.4)	75.0 (18.9)
	Role functioning	75.1 (27.8)	73.5 (31.6)	71.9 (28.5)
	Social functioning	79.9 (26.5)	80.1 (26.9)	80.5 (24.0)
	Global health status/QoL	58.7 (24.2)	61.6 (20.3)	60.9 (21.3)
QLQ–LC13 score, mean (SD)	**Alopecia**	3.3 (10.0)	4.3 (17.2)	6.7 (16.0)
	Cough	43.7 (27.9)	43.8 (27.3)	34.4 (26.0)
	Dysphagia	7.5 (18.9)	4.3 (13.0)	9.4 (21.3)
	Dyspnea	26.9 (22.7)	28.8 (24.4)	25.4 (21.0)
	Hemoptysis	7.5 (16.1)	8.0 (17.1)	5.0 (12.0)
	Pain in arm or shoulder	18.8 (26.3)	19.1 (25.6)	21.7 (28.1)
	Pain in chest	16.0 (23.8)	18.5 (25.6)	20.0 (25.5)
	Pain in other parts	21.1 (28.9)	22.8 (26.6)	18.3 (24.9)
	Peripheral neuropathy	8.9 (20.3)	6.8 (13.6)	7.8 (18.8)
	Sore mouth	6.1 (18.9)	3.1 (9.8)	3.3 (10.1)

(*continued on next page*)

Supplemental Table 2 (*continued*)

		Durvalumab Monotherapy (n=77)	Durvalumab + Tremelimumab (n=64)	Chemotherapy (n=70)
(B) bTMB <20 mut/Mb				
QLQ−C30 score, mean (SD)	**Appetite loss**	30.2 (33.3)	27.3 (31.1)	27.7 (31.2)
	Constipation	21.2 (28.1)	19.1 (30.3)	15.3 (25.8)
	Diarrhea	6.8 (16.0)	4.6 (14.4)	6.4 (18.1)
	Dyspnea	36.8 (32.9)	35.8 (31.1)	32.3 (28.7)
	Fatigue	38.3 (27.5)	40.2 (25.5)	36.1 (27.4)
	Insomnia	34.1 (31.4)	35.4 (30.5)	31.1 (31.9)
	Nausea/vomiting	7.7 (14.5)	8.1 (15.4)	6.7 (13.5)
	Pain	35.2 (29.8)	37.3 (30.4)	32.2 (30.5)
	Cognitive functioning	84.6 (20.5)	82.8 (21.2)	85.4 (19.4)
	Emotional functioning	71.1 (23.0)	69.8 (24.2)	68.9 (24.5)
	Physical functioning	72.0 (22.8)	71.3 (22.0)	73.5 (22.9)
	Role functioning	66.3 (32.6)	68.2 (29.6)	68.3 (32.0)
	Social functioning	78.6 (24.7)	73.6 (28.1)	75.1 (29.1)
	Global health status/QoL	56.6 (22.9)	56.3 (21.6)	59.9 (23.1)
QLQ−LC13 score, mean (SD)	**Alopecia**	5.3 (18.1)	5.3 (16.4)	2.2 (9.1)
	Cough	37.9 (28.7)	41.8 (28.8)	39.4 (25.7)
	Dysphagia	7.2 (16.3)	6.9 (15.3)	6.9 (16.5)
	Dyspnea	27.9 (23.5)	29.8 (24.0)	28.3 (22.5)
	Hemoptysis	5.0 (14.8)	5.3 (13.3)	6.9 (17.7)
	Pain in arm or shoulder	19.8 (26.5)	25.9 (31.1)	18.4 (28.5)
	Pain in chest	25.3 (26.3)	23.9 (26.0)	20.6 (25.9)
	Pain in other parts	27.2 (29.3)	28.6 (31.7)	28.6 (29.1)
	Peripheral neuropathy	7.8 (17.0)	7.7 (16.6)	9.1 (18.4)
	Sore mouth	5.5 (14.8)	4.1 (14.1)	4.3 (15.1)

Shaded cells indicate symptoms for which low (<10) baseline values were reported; clinically meaningful improvements in these symptoms were therefore not possible to determine. Abbreviations: bTMB=blood tumor mutational burden; Mb=megabase; mut=mutation; QLQ−C30=30-item core quality of life questionnaire; QLQ−LC13=13-item lung cancer quality of life questionnaire; SD=standard deviation.