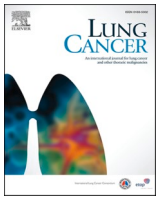
Lung Cancer 186 (2023) 107422

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Patient-reported outcomes with durvalumab, with or without tremelimumab, plus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer (POSEIDON)

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ARTICLE INFO

Keywords:
Durvalumab
Tremelimumab
Metastatic non-small-cell lung cancer
Patient-reported outcomes
Health-related quality of life
POSEIDON

ABSTRACT

Objectives: In the phase 3 POSEIDON study, first-line tremelimumab plus durvalumab and chemotherapy significantly improved overall survival and progression-free survival versus chemotherapy in metastatic non-small-cell lung cancer (NSCLC). We present patient-reported outcomes (PROs).

Patients and methods: Treatment-naïve patients were randomized 1:1:1 to tremelimumab plus durvalumab and chemotherapy, durvalumab plus chemotherapy, or chemotherapy. PROs (prespecified secondary endpoints) were assessed using the European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire version 3 (QLQ-C30) and its 13-item lung cancer module (QLQ-LC13). We analyzed time to deterioration (TTD) of symptoms, functioning, and global health status/quality of life (QoL) from randomization by log-rank test and improvement rates by logistic regression.

Results: 972/1013 (96 %) patients randomized completed baseline QLQ-C30 and QLQ-LC13 questionnaires, with scores comparable between treatment arms. Patients receiving tremelimumab plus durvalumab and chemotherapy versus chemotherapy had longer median TTD for all PRO items. Hazard ratios for TTD favored tremelimumab plus durvalumab and chemotherapy for all items except diarrhea; 95 % confidence intervals did not cross 1.0 for global health status/QoL, physical functioning, cognitive functioning, pain, nausea/vomiting, insomnia, constipation, hemoptysis, dyspnea, and pain in other parts. For durvalumab plus chemotherapy, median TTD was longer versus chemotherapy for all items except nausea/vomiting and diarrhea. Hazard ratios

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https://doi.org/10.1016/j.lungcan.2023.107422
Received 10 July 2023; Received in revised form 3 November 2023; Accepted 7 November 2023
Available online 11 November 2023

favored durvalumab plus chemotherapy for all items except appetite loss; 95 % confidence intervals did not cross 1.0 for global health status/QoL, physical functioning, role functioning, dyspnea, and pain in other parts. For both immunotherapy plus chemotherapy arms, improvement rates in all PRO items were numerically higher versus chemotherapy, with odds ratios > 1.

Conclusions: Tremelimumab plus durvalumab and chemotherapy delayed deterioration in symptoms, functioning, and global health status/QoL compared with chemotherapy. Together with significant improvements in survival, these results support tremelimumab plus durvalumab and chemotherapy as a first-line treatment option in metastatic NSCLC.

1. Introduction

In recent years, immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1), used either alone or in combination with chemotherapy, have significantly improved survival outcomes for metastatic non-small-cell lung cancer (NSCLC) lacking actionable driver mutations (e.g., in *EGFR*, *ALK*, *ROS1*, *BRAF*) [1]. Despite these improvements, a substantial proportion of patients with NSCLC do not respond to anti-PD-1/PD-L1 inhibitors or acquire resistance to treatment; although the characteristics of responders are not fully understood, evidence suggests that patients with tumors expressing higher levels of PD-L1 have better long-term treatment outcomes [1].

Combinations of immune checkpoint inhibitors targeting different pathways that regulate the immune system via non-redundant mechanisms may provide additive or synergistic effects with activity across a broader patient population, including those with PD-L1-low or -negative tumors. However, the feasibility of using such combinations in addition to chemotherapy is dependent on the safety and tolerability of these regimens, as well as ensuring that patient quality of life (QoL) is not compromised.

The phase 3 POSEIDON study (NCT03164616) compared the efficacy and safety of first-line treatment with tremelimumab plus durvalumab and chemotherapy, and of durvalumab plus chemotherapy, with chemotherapy alone in patients with metastatic NSCLC. Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, while tremelimumab is a human immunoglobulin G2 monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), enhancing binding of CD80 and CD86 to CD28 [2,3]. A limited course of tremelimumab added to durvalumab and four cycles of chemotherapy significantly improved both progression-free survival (PFS; median, 6.2 versus 4.8 months; hazard ratio [HR], 0.72; 95 % confidence interval [CI], 0.60–0.86; P = 0.0003; data cutoff [DCO] July 24, 2019) and overall survival (OS; median, 14.0 versus 11.7 months; HR, 0.77; 95 % CI, 0.65–0.92; P = 0.0030; DCO March 12, 2021) versus chemotherapy alone [4]. Although PFS was significantly longer with durvalumab plus chemotherapy versus chemotherapy alone (median, 5.5 versus 4.8 months; HR, 0.74; 95 % CI, 0.62–0.89; P = 0.0009), a trend for improved OS was not statistically significant [4]. On the basis of these results, tremelimumab plus durvalumab and chemotherapy was approved for use in this setting in the US, Japan, and the EU [5–7].

A key consideration with the addition of anti-CTLA-4 to combinations of anti-PD-(L)1 plus chemotherapy is the potential for any negative impact on tolerability, which could compromise treatment exposure and negate any potential gains in clinical benefit. Reassuringly, although in POSEIDON the addition of a limited course of tremelimumab to durvalumab and four cycles of chemotherapy did increase the frequency of immune-mediated adverse events (as expected), there was only a small increase in the incidence of grade 3 and higher immune-mediated adverse events. Of note, the incidence of treatment discontinuation due to treatment-related adverse events was similar in the tremelimumab plus durvalumab and chemotherapy arm and the durvalumab plus chemotherapy arm [4].

In addition to monitoring of treatment tolerability, patient symptom burden is an important element in the clinical management of NSCLC. Advanced NSCLC is associated with numerous symptoms, including fatigue, loss of appetite, shortness of breath, cough, and pain, all of which are present in more than 90 % of patients [8,9], but may be relieved by treatment with anticancer therapies and/or symptomatic treatments such as steroids and analgesics [10–12]. Several studies have shown that specific lung cancer symptoms are significantly linked to QoL in patients with advanced lung cancer [8,9,13–17]. Patient-reported outcomes (PROs) capturing the patient perspective on disease-related symptoms, functioning domains, and overall QoL during treatment not only complement clinician assessment of efficacy and safety but are vital to providing a comprehensive view of the benefits of treatment. These data are widely recognized as having provided important and clinically relevant information on the risk/benefit profile of several approved first-line immunotherapy-based regimens for NSCLC [18–23].

Here, we report analyses of PROs from the POSEIDON study which show the impact of adding tremelimumab and durvalumab, or only durvalumab, to chemotherapy on the symptoms, functioning, and health-related QoL (HRQoL) of patients with metastatic NSCLC.

2. Methods

2.1. Study design and patients

POSEIDON is a phase 3, global, randomized, open-label study, for which full entry criteria and primary and secondary analyses have been previously reported [4]. Briefly, eligible patients were aged ≥ 18 years and had stage IV NSCLC which was treatment-naïve for metastatic disease; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [24]; and tumors with no sensitizing *EGFR* mutations or *ALK* rearrangements and PD-L1 expression status determined centrally before randomization. Patients with brain metastases were eligible providing they were treated and stable.

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

2.2. Study treatment

Patients were randomly assigned in a 1:1:1 ratio to receive tremelimumab 75 mg plus durvalumab 1500 mg and chemotherapy every 3 weeks (q3w) for up to 4 cycles, followed by durvalumab 1500 mg every 4 weeks (q4w), with a fifth dose of tremelimumab post chemotherapy; durvalumab 1500 mg plus chemotherapy q3w for up to 4 cycles followed by durvalumab 1500 mg q4w; or chemotherapy q3w for up to 6 cycles. In all arms, chemotherapy comprised either carboplatin plus nab-paclitaxel (any histology), cisplatin or carboplatin plus gemcitabine (squamous histology), or cisplatin or carboplatin plus pemetrexed followed by optional pemetrexed maintenance therapy if eligible (non-squamous histology). Randomization was stratified by PD-L1 expression (≥ 50 % versus < 50 % of tumor cells), disease stage (IVA versus IVB) [25], and histology (squamous versus non-squamous).

Patients continued treatment until disease progression, unacceptable toxicity, or consent withdrawal. Patients continuing to receive benefit could continue durvalumab monotherapy beyond disease progression provided that they met the criteria per protocol.

2.3. Study endpoints and assessments

Primary endpoints were PFS and OS for the comparison of durvalumab plus chemotherapy with chemotherapy alone. Key alpha-controlled secondary endpoints were PFS and OS for the comparison of tremelimumab plus durvalumab and chemotherapy with chemotherapy alone. Other secondary endpoints included PFS rate at 12 months, unconfirmed objective response rate, duration of response, safety and tolerability, and also PROs (reported here).

Secondary PRO endpoints were measurement of disease-related symptoms, functioning and HRQoL assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire, version 3 (QLQ-C30 v3) and its 13-item lung cancer module (QLQ-LC13) [26,27]. The QLQ-C30 v3 includes 30 questions that can be combined into five functional scales (cognitive, emotional, physical, role, and social); three symptom scales (fatigue, pain, and nausea/vomiting); six single-item symptom measures comprising appetite loss, constipation, diarrhea, dyspnea, insomnia, and (not reported here) perceived financial difficulties; and the global health status/QoL scale. The QLQ-LC13 includes 13 questions assessing lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain, reported here), as well as conventional chemoradiotherapy-related side effects (alopecia, neuropathy, sore mouth, and dysphagia) and pain medication, which are not reported. Global health status/QoL, physical functioning, fatigue, and appetite loss from QLQ-C30 and cough, dyspnea, and chest pain from QLQ-LC13 were pre-specified PRO measures of interest.

Patients used an electronic tablet (ePRO) to complete both questionnaires, unassisted, before any other study procedures at clinic visits, at baseline and on the first day of each treatment cycle received until disease progression, and then every 8 weeks until second progression or death. Patients who discontinued treatment before progression completed the questionnaires every 4 weeks after the last treatment dose until disease progression, and then every 8 weeks until second progression or death.

2.4. Statistical analysis

PRO analyses were conducted on an intent-to-treat (ITT) basis. Summary statistics were compiled for compliance over time, for both questionnaires. Scores for the QLQ-C30 and QLQ-LC13 questionnaires were calculated according to the EORTC Scoring Manual, with raw scores standardized by linear transformation to range from 0 to 100. A higher score represented a better level of functioning and global health status/QoL or greater symptom severity. For both questionnaires, a clinically meaningful change was prospectively defined as an absolute change (increase or decrease) in score from baseline of ≥ 10 points [28].

A hierarchical multiple testing procedure with gatekeeping strategy was used to strongly control the type I error at 5 % (2-sided) across the primary endpoints and alpha-controlled secondary endpoints; this procedure did not include PRO endpoints.

Time to deterioration (TTD) was assessed in patients from the ITT population whose baseline scores were ≥ 10 for global health status/QoL and functioning or ≤ 90 for symptoms. TTD was defined as the time from randomization to the first clinically meaningful deterioration that was confirmed at a subsequent assessment, or death from any cause in the absence of clinically meaningful deterioration. Patients with a single deterioration and with no further assessments were considered to have had a deterioration for the purposes of this analysis. TTD was analyzed using a log-rank test, stratified by tumor PD-L1 expression, disease stage, and histology. HRs and 95 % CIs were estimated using a Cox proportional hazards model, stratified as above, with the Efron method to control for ties. Median TTD was estimated using the Kaplan-Meier method.

Improvement rate was assessed in patients from the ITT population whose baseline scores were ≤ 90 for global health status/QoL and functioning or ≥ 10 for symptoms. The improvement rate was defined as the percentage of patients with two consecutive assessments at least 14 days apart who showed a clinically meaningful improvement from baseline (i.e., a ≥ 10-point decrease for symptoms or a ≥ 10-point increase for global health status/QoL and functioning). Odds ratios (ORs) and 95 % CIs were estimated using logistic regression, adjusting for tumor PD-L1 expression, disease stage, and histology.

3. Results

3.1. Patients and baseline QLQ-C30 and QLQ-LC13 scores

A total of 1013 patients were randomized to the study between June 27, 2017, and September 19, 2018, with 338 patients assigned to tremelimumab plus durvalumab and chemotherapy, 338 patients to durvalumab plus chemotherapy, and 337 patients to chemotherapy only. As previously reported, baseline demographics and disease characteristics were generally balanced between treatment arms [4].

Baseline PRO data including both QLQ-C30 and QLQ-LC13 questionnaires were completed by 325 (96.2 %), 326 (96.4 %), and 321 (95.3 %) patients, respectively, in the tremelimumab plus durvalumab and chemotherapy, durvalumab plus chemotherapy, and chemotherapy arms.

Compliance rates for both questionnaires were ≥ 60 % continuously from baseline to week 88 in the tremelimumab plus durvalumab and chemotherapy arm, to week 64 in the durvalumab plus chemotherapy arm, and to week 24 in the chemotherapy arm (Supplementary Fig. 1).

Baseline QLQ-C30 and QLQ-LC13 scores were generally comparable between treatment arms (Supplementary Fig. 2). In the tremelimumab plus durvalumab and chemotherapy, durvalumab plus chemotherapy, and chemotherapy only arms, respectively, mean baseline scores were 59.2, 59.1, and 59.7 for global health status/QoL; and 75.7, 75.6, and 75.2 for physical functioning. For the pre-specified symptoms of interest, mean baseline scores in the tremelimumab plus durvalumab and chemotherapy, durvalumab plus chemotherapy, and chemotherapy only arms, respectively, were 32.9, 32.3, and 33.9 for fatigue; 21.5, 21.2, and 24.5 for appetite loss; 36.1, 33.4, and 37.9 for cough; 27.5, 26.6, and 25.3 for dyspnea (QLQ-LC13); and 20.8, 18.5, and 24.0 for pain in chest.

Across all treatment arms, the most severe symptoms at baseline (mean score ≥ 25) were fatigue, pain (QLQ-C30), dyspnea (both scales), insomnia, and cough. The least severe symptoms at baseline (mean score < 10) in all three arms were diarrhea, hemoptysis, and nausea/vomiting.

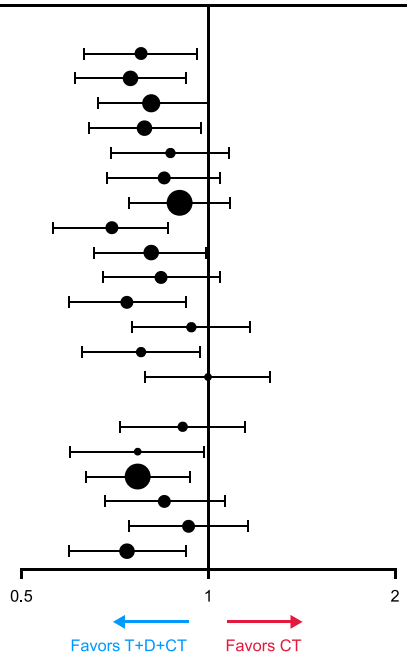
3.2. Time to deterioration

Longer median TTD was observed for patients in the tremelimumab plus durvalumab and chemotherapy arm versus the chemotherapy arm for global health status/QoL, all functioning scales, and all symptoms. HRs favored tremelimumab plus durvalumab and chemotherapy versus chemotherapy for global health status/QoL, all functioning scales, and all symptom scales except diarrhea (HR, 1.00; 95 % CI, 0.79–1.26) (Fig. 1A); the 95 % CI did not cross 1.0 for global health status/QoL, physical functioning, and cognitive functioning, as well as for the QLQ-C30 symptom scales pain, nausea/vomiting, insomnia, and constipation, and the QLQ-LC13 symptom scales hemoptysis, dyspnea, and pain in other parts.

Similarly, longer median TTD was observed for durvalumab plus chemotherapy versus chemotherapy for all scales except nausea/vomiting (median 5.6 months versus 5.6 months) and diarrhea (median 9.8 months versus 10.8 months), with HRs favoring durvalumab plus

A

	Tremelimumab + durvalumab + chemotherapy		Chemotherapy		HR (95% CI)
	Events/ patients, n/N	Median, months	Events/ patients, n/N	Median, months	
QLQ-C30					
Global health status/QoL	175/319	8.3	186/318	5.6	0.78 (0.63–0.96)
Physical functioning	189/323	7.7	193/320	5.3	0.75 (0.61–0.92)
Role functioning	196/314	6.6	192/304	4.8	0.81 (0.66–1.00)
Cognitive functioning	188/323	7.6	189/318	5.8	0.79 (0.64–0.97)
Emotional functioning	175/322	8.5	160/315	7.5	0.87 (0.70–1.08)
Social functioning	185/320	6.4	177/314	5.7	0.85 (0.69–1.04)
Fatigue	232/317	3.7	220/314	2.8	0.90 (0.75–1.08)
Pain	176/316	8.9	180/298	5.7	0.70 (0.56–0.86)
Nausea/vomiting	191/322	7.8	182/319	5.6	0.81 (0.65–0.99)
Dyspnea	180/310	7.9	164/301	6.7	0.84 (0.68–1.05)
Insomnia	176/311	8.3	170/301	5.8	0.74 (0.60–0.92)
Appetite loss	179/308	7.2	158/305	7.0	0.94 (0.75–1.17)
Constipation	173/315	9.2	165/306	6.1	0.78 (0.63–0.97)
Diarrhea	167/324	11.0	135/320	10.8	1.00 (0.79–1.26)
QLQ-LC13					
Cough	162/302	9.7	142/295	8.8	0.91 (0.72–1.15)
Hemoptysis	133/325	17.8	128/318	11.4	0.77 (0.60–0.98)
Dyspnea	220/325	5.4	211/316	3.6	0.77 (0.63–0.94)
Pain in chest	172/319	10.0	151/309	8.6	0.85 (0.68–1.07)
Pain in arm/shoulder	178/312	8.9	151/310	8.8	0.93 (0.74–1.16)
Pain in other parts	174/312	9.7	172/306	5.8	0.74 (0.60–0.92)



B

	Durvalumab + chemotherapy		Chemotherapy		HR (95% CI)
	Events/ patients, n/N	Median, months	Events/ patients, n/N	Median, months	
QLQ-C30					
Global health status/QoL	198/321	7.8	186/318	5.6	0.79 (0.64–0.96)
Physical functioning	195/325	8.3	193/320	5.3	0.70 (0.57–0.87)
Role functioning	198/313	7.4	192/304	4.8	0.75 (0.61–0.92)
Cognitive functioning	207/323	7.4	189/318	5.8	0.87 (0.71–1.06)
Emotional functioning	179/322	9.5	160/315	7.5	0.83 (0.66–1.03)
Social functioning	195/319	7.1	177/314	5.7	0.88 (0.72–1.09)
Fatigue	227/318	3.8	220/314	2.8	0.83 (0.69–1.00)
Pain	199/311	6.5	180/298	5.7	0.84 (0.68–1.03)
Nausea/vomiting	212/322	5.6	182/319	5.6	0.91 (0.74–1.12)
Dyspnea	182/310	6.9	164/301	6.7	0.86 (0.69–1.06)
Insomnia	186/304	7.4	170/301	5.8	0.84 (0.68–1.04)
Appetite loss	206/316	7.2	158/305	7.0	1.05 (0.85–1.31)
Constipation	188/314	8.7	165/306	6.1	0.84 (0.68–1.04)
Diarrhea	171/324	9.8	135/320	10.8	0.97 (0.77–1.22)
QLQ-LC13					
Cough	168/314	11.0	142/295	8.8	0.87 (0.69–1.09)
Hemoptysis	148/326	14.0	128/318	11.4	0.81 (0.63–1.03)
Dyspnea	220/325	5.0	211/316	3.6	0.81 (0.67–0.98)
Pain in chest	176/322	9.5	151/309	8.6	0.86 (0.69–1.08)
Pain in arm/shoulder	179/311	8.9	151/310	8.8	0.94 (0.75–1.17)
Pain in other parts	183/314	8.9	172/306	5.8	0.77 (0.62–0.96)

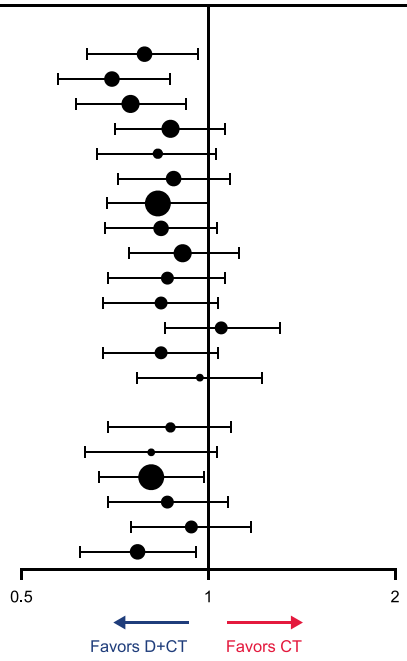


Fig. 1. Time to deterioration in global health status/QoL, functioning, and symptoms for (A) tremelimumab plus durvalumab and chemotherapy versus chemotherapy and (B) durvalumab plus chemotherapy versus chemotherapy. Global health status/QoL and functioning were assessed in patients with baseline scores ≥ 10 and symptoms were assessed in patients with baseline scores ≤ 90. The size of the circles is proportional to the number of events. A HR < 1.0 indicates longer time to deterioration with tremelimumab plus durvalumab and chemotherapy, or with durvalumab plus chemotherapy, versus chemotherapy alone. CI, confidence interval; CT, chemotherapy; D, durvalumab; HR, hazard ratio; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13; QoL, quality of life; T, tremelimumab.

chemotherapy versus chemotherapy for global health status/QoL, all functioning scales, and all symptoms, with the exception of appetite loss (HR, 1.05; 95 % CI, 0.85–1.31) (Fig. 1B). The 95 % CIs of the respective HRs for global health status/QoL, physical functioning, and role functioning, as well as for the QLQ-LC13 symptom scales dyspnea and pain in other parts, did not cross 1.0.

Kaplan-Meier curves for TTD are shown in Fig. 2 for the pre-specified endpoints of interest and in Supplementary Fig. 3 for all other functioning and symptom scales.

3.3. Improvement rates

Consistently higher rates of improvement in global health/QoL, all functioning scales and all symptoms were observed for both immunotherapy plus chemotherapy arms versus the chemotherapy arm, with ORs > 1 (Fig. 3). For tremelimumab plus durvalumab and chemotherapy versus chemotherapy, the 95 % CIs of the respective ORs for physical functioning and emotional functioning, as well as for the symptoms pain, nausea/vomiting, constipation (all QLQ-C30), and pain in arm/

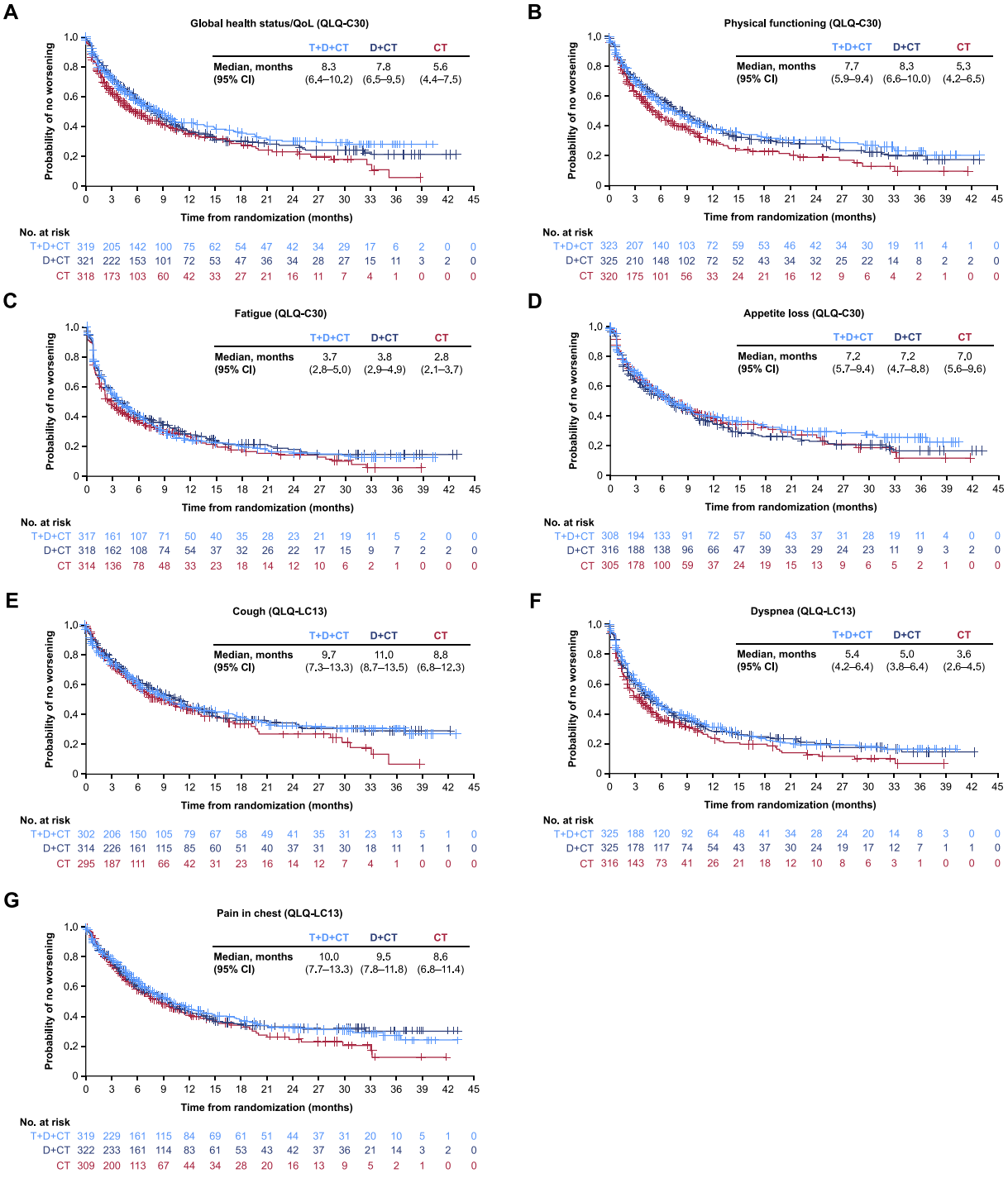


Fig. 2. Kaplan-Meier analysis of time to deterioration in pre-specified endpoints of interest: (A) global health status/QoL, (B) physical functioning, (C) fatigue, (D) appetite loss, (E) cough, (F) dyspnea, and (G) pain in chest. Global health status/QoL and functioning were assessed in patients with baseline scores ≥ 10 and symptoms were assessed in patients with baseline scores ≤ 90. CI, confidence interval; CT, chemotherapy; D, durvalumab; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13; QoL, quality of life; T, tremelimumab.

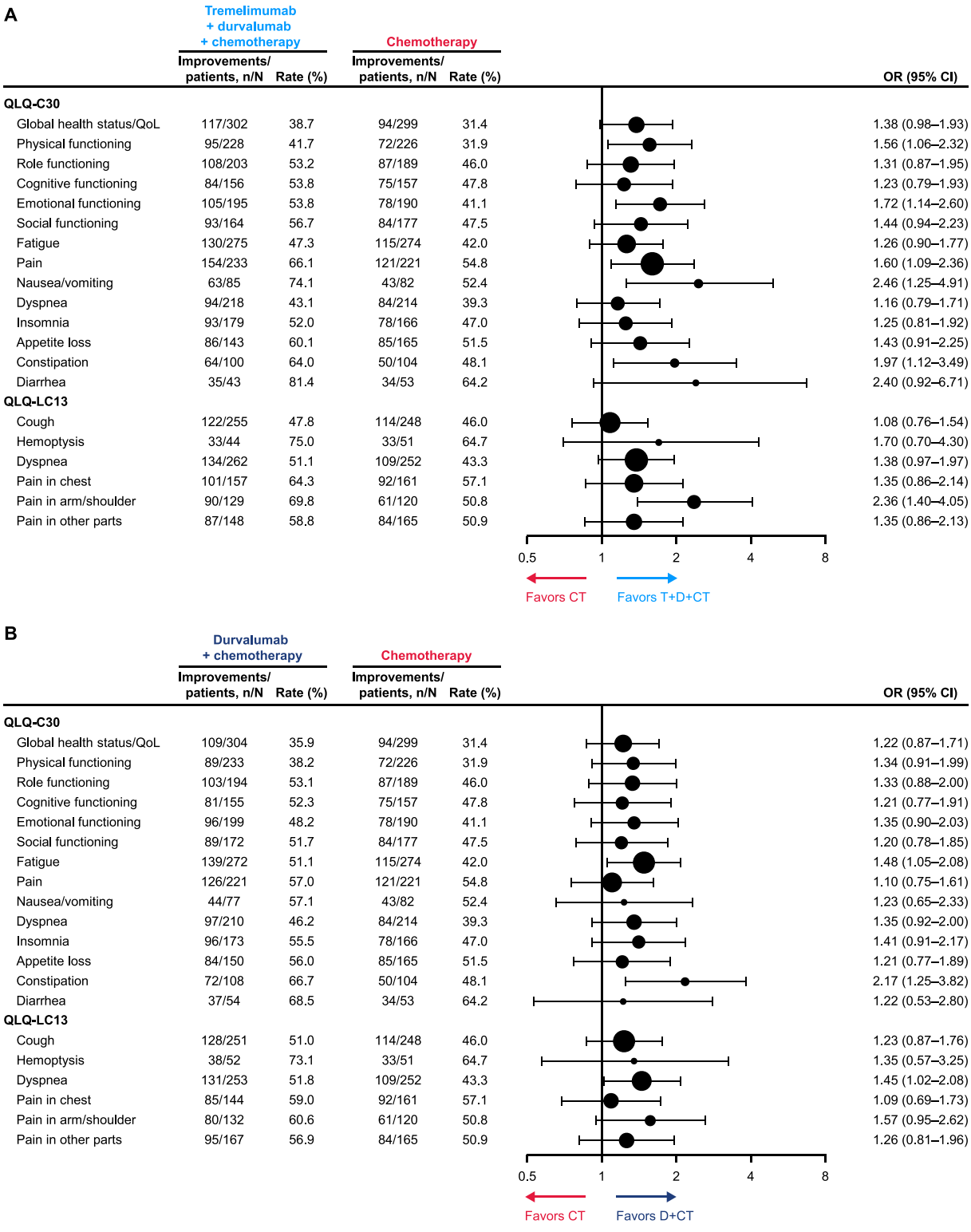


Fig. 3. Improvement rates in global health status/QoL, functioning, and symptoms for (A) tremelimumab plus durvalumab and chemotherapy versus chemotherapy and (B) durvalumab plus chemotherapy versus chemotherapy. Global health status/QoL and functioning were assessed in patients with baseline scores ≥ 10 and symptoms were assessed in patients with baseline scores ≤ 90. An improvement was defined as two consecutive assessments, at least 14 days apart, that show a clinically meaningful improvement from baseline (i.e., a ≥ 10-point increase for global health status/QoL and functioning or a ≥ 10-point decrease for symptoms). The size of the circles is proportional to the number of patients with an improvement. An odds ratio > 1.0 indicates a higher probability of improvement with tremelimumab plus durvalumab and chemotherapy, or with durvalumab plus chemotherapy, versus chemotherapy alone. CI, confidence interval; CT, chemotherapy; D, durvalumab; OR, odds ratio; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13; QoL, quality of life; T, tremelimumab.

shoulder (QLQ-LC13), did not cross 1.0. For durvalumab plus chemotherapy versus chemotherapy, the 95 % CIs of the respective ORs for the symptoms fatigue, constipation (both QLQ-C30), and dyspnea (QLQ-LC13), did not cross 1.0.

4. Discussion

Our results show that patients receiving either tremelimumab plus durvalumab and chemotherapy or durvalumab plus chemotherapy in the POSEIDON study had longer median TTD (except for nausea/vomiting and diarrhea in patients treated with durvalumab plus chemotherapy) and greater rates of improvement in patient-reported global health status/QoL, functioning, and symptoms than those receiving chemotherapy alone, as measured throughout their treatment course and afterwards until second disease progression or death. A trend for HRs (TTD) and ORs (improvement rate) favoring both immunotherapy plus chemotherapy arms compared with the chemotherapy arm was observed across almost all symptoms and domains, with the exception of the HRs for TTD in diarrhea, for which there was no difference between the tremelimumab plus durvalumab and chemotherapy arm and the chemotherapy arm, and appetite loss, which favored the chemotherapy arm versus the durvalumab plus chemotherapy arm. There is no obvious biological explanation for this result, which deviates from the general trends observed. The pattern of delay in TTD was similar in the tremelimumab plus durvalumab and chemotherapy arm and the durvalumab plus chemotherapy arm, suggesting there was no substantial worsening in PROs with the addition of tremelimumab. With tremelimumab plus durvalumab and chemotherapy versus chemotherapy, the 95 % CIs of both the HR for TTD and the OR for improvement rate did not cross 1 for physical functioning, pain, nausea/vomiting, and constipation [all QLQ-C30], potentially indicative of particular benefit with the combination regimen in those PRO items. The same was true for dyspnea (QLQ-LC13) with durvalumab plus chemotherapy versus chemotherapy.

As expected for a study population of patients with ECOG performance status 0 or 1, baseline PRO scores suggested slightly better baseline health status in POSEIDON compared with available reference values for patients with stage III-IV lung cancer [29]; global health status/QoL and functioning scores from study patients were generally slightly higher, and symptom scores generally slightly lower, than the reference values. However, since baseline scores in POSEIDON were similar across treatment arms, the between-arm differences seen during and after treatment should be a reflection of differences in the impact of treatment on PROs. The longer TTD generally seen in both immunotherapy plus chemotherapy arms versus the chemotherapy alone arm was consistent with the longer PFS and OS and improved response rates of these arms [4]. Although TTD might intuitively be expected to be linked to disease progression, it is possible that deterioration in any of the PROs assessed could occur after initial disease progression; in POSEIDON, we collected PRO data up to second disease progression in an attempt to capture deterioration at a later time point.

The value of collecting post-treatment PRO data to monitor long-term effects of treatment is increasingly recognized by payers and regulatory agencies, although the barriers to doing so are also acknowledged [30,31]. As expected in cancer studies, compliance with the PRO questionnaires decreased over time, which may be related to disease progression accompanied by reduced motivation to complete questionnaires, patient dropout, starting new treatment after progression, or death. We collected PRO data digitally via electronic tablets to facilitate questionnaire completion and to allow for remote compliance monitoring. The more rapid drop-off in compliance in the chemotherapy alone arm compared with the immunotherapy plus chemotherapy arms was likely a reflection of the shorter duration of treatment and generally shorter time to progression for patients in this treatment arm. However, compliance in the study was acceptable to good ($\geq$ 60 %) for approximately 15 months or more in the immunotherapy plus chemotherapy arms and approaching 6 months in the chemotherapy alone arm, resulting in a substantial PRO dataset.

Our results, showing generally longer TTD and greater improvement in PROs with immunotherapy plus chemotherapy versus chemotherapy alone, are consistent with those previously reported for first-line treatment with PD-1/PD-L1 inhibitors, with or without chemotherapy, in patients with metastatic NSCLC [17,20–23,31]. Detailed comparison is confounded by differences in study design (e.g., open-label versus placebo-controlled), the PRO instruments used, and the timing of the assessments; however, the overall picture is one of improved or maintained PROs with immunotherapy-based regimens compared with chemotherapy alone, with the exception of the atezolizumab IMpower150 study which had similar PROs across all three treatment arms (although in this study patients received bevacizumab in addition to chemotherapy) [23]. Trials of first-line treatment with a combination of anti-PD-(L)1 and anti-CTLA-4, with or without chemotherapy, in patients with metastatic NSCLC also indicated alleviated symptom burden and improved health status compared with chemotherapy alone [17–19]. Thus, improvement in PROs with immune checkpoint inhibitor-based regimens compared with chemotherapy alone generally seem to go hand-in-hand with improved efficacy outcomes.

To our knowledge, POSEIDON and MYSTIC (durvalumab or durvalumab plus tremelimumab versus chemotherapy; NCT02453282) are the only studies in the first-line metastatic NSCLC setting to provide PRO results for anti-PD-(L)1 both alone/with chemotherapy and in combination with anti-CTLA-4 therapy. The CheckMate 9LA study included only nivolumab plus ipilimumab plus chemotherapy and chemotherapy arms [18]; while CheckMate 227 did include a nivolumab monotherapy arm, PRO data from this arm have not been presented [19]. The results from both POSEIDON and MYSTIC suggested that the addition of tremelimumab to durvalumab (plus chemotherapy in POSEIDON) did not compromise patient-reported global health status/QoL, functioning, and symptom burden [17], although it should be noted that the two immunotherapy arms were not formally compared within these trials.

Commonly used tools for measuring PROs with immunotherapy-based regimens in lung cancer clinical trials have included the EORTC QLQ-C30 v3 and QLQ-LC13 (used in this study), the European Quality of Life 5 Dimensions-3 Level questionnaire, and the Lung Cancer Symptom Scale average symptom burden index and 3-item global index [18–23,26,27,32–36]. These PRO questionnaires were designed in the era of chemotherapy, with the primary focus being on general HRQoL and symptoms of cancer. In response to the emergence of immunotherapy, novel tools (e.g., the V-Care platform and the Utrecht Symptom Diary Immunotherapy) are being developed to improve the assessment of symptoms related to immune-mediated adverse events (e.g., feeling cold, rash, or changes in weight) [37–41]. Nonetheless, to date most PRO data in this setting have been derived using established tools such as the EORTC QLQ-C30/LC13 (which have been extensively validated) [36].

Further limitations to the PRO analyses presented here include the open-label treatment assignment in POSEIDON, which may have introduced bias in the subjective assessment of PROs. However, if such bias exists, it is possible that it may not meaningfully alter outcomes (e.g., PROs) in clinical trials and/or that it may not affect all PRO domains equally [42,43]; for example, it is believed that physical functioning may potentially be less subject to open-label bias than emotional functioning [44]. As mentioned above, compliance was unbalanced between treatment arms with a smaller sample size in the chemotherapy arm at the later timepoints. However, if non-compliance in the chemotherapy arm was potentially associated with declining health status/function or increased symptom burden, it would tend to bias the data in favor of this arm. Finally, the TTD analysis, in the absence of analysis of changes in PROs from baseline, could in theory miss any improvement in symptoms or functioning after initial deterioration.

In conclusion, the phase 3 POSEIDON study showed that first-line treatment with tremelimumab plus durvalumab and chemotherapy delayed deterioration in symptoms, functioning, and global health

status/QoL compared with chemotherapy alone, with similar patterns observed to the durvalumab plus chemotherapy arm. This is a meaningful benefit from the patient perspective which, together with previously reported statistically significant improvements in survival and manageable tolerability, support the use of tremelimumab plus durvalumab and chemotherapy as a potential first-line treatment option in patients with metastatic NSCLC.

Data sharing statement

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. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Edward B. Garon: Investigation, Writing – review & editing. **Byoung Chul Cho:** Investigation, Writing – review & editing. **Alexander Luft:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Jorge Alatorre-Alexander:** Investigation, Supervision, Writing – review & editing. **Sarayut Lucien Geater:** Data curation, Investigation, Writing – review & editing. **Sang-We Kim:** Investigation, Writing – review & editing. **Grygorii Ursol:** Investigation, Writing – review & editing. **Maen Hussein:** Investigation, Writing – review & editing. **Farah Louise Lim:** Data curation, Investigation, Writing – review & editing. **Cheng-Ta Yang:** Investigation, Writing – review & editing. **Luiz Henrique Araujo:** Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Haruhiro Saito:** Data curation, Investigation, Writing – review & editing. **Niels Reinmuth:** Investigation, Resources, Supervision, Writing – review & editing. **Nenad Medic:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Helen Mann:** Formal analysis, Writing – review & editing. **Xiaojin Shi:** Formal analysis, Supervision, Writing – review & editing. **Solange Peters:** Conceptualization, Formal analysis, Methodology, Validation, Writing – review & editing. **Tony Mok:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **Melissa Johnson:** Investigation, Writing – review & editing.

Declaration of Competing Interest

Edward B. Garon reports grants or contracts from ABL Bio, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Dynavax Technologies, Eli Lilly, EMD Serono, Genentech, Gilead, Iovance Biotherapeutics, Merck, Mirati Therapeutics, Neon, and Novartis; consulting fees from AbbVie, ABL Bio, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dracen Pharmaceuticals, EMD Serono, Eisai, Eli Lilly, Gilead, GlaxoSmithKline, Merck, Natera, Novartis, Personalis, Regeneron, Sanofi, Shionogi, Xilio, and Zymeworks; and travel support from A2 Bio and Novartis.

Byoung Chul Cho reports consulting fees from Abion, AstraZeneca, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Bridgebio Therapeutics, Bristol-Myers Squibb, CJ, CureLogen, Cyrus Therapeutics, Eli Lilly, GI-Cell, Hanmi, HK Inno-N, Imnewrun Biosciences, Janssen, KANAPH Therapeutic, Medpacto, MSD, Novartis, Ono Pharmaceutical, Onegene Biotechnology, Oscotec, Pfizer, RandBio, Roche, Takeda, and Yuhan; advisory board participation for Bridgebio Therapeutics, Cyrus Therapeutics, Guardant Health, Kanaph Therapeutics, and Oscotec; honoraria from ASCO, AstraZeneca, ESMO, Guardant Health, IASLC, Korean Cancer Association, Korean Cancer Study Group, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, MSD, Novartis, Pfizer, Roche, and The Chinese Thoracic Oncology Society; research funding from AbbVie, Abion, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bridgebio Therapeutics, CHA Bundang Medical Center, Champions Oncology, CJ Bioscience, CJ Blossom Park, Cyrus Therapeutics, Dizal Pharma, Dong-A ST, Eli Lilly, Genexine, GI-Cell, GIInnovation, Hanmi, Illumina, ImmuneOncia, Interpark Bio, Janssen, J Ints Bio, Kanaph Therapeutics, LG Chem, Medpacto, MOGAM Institute, MSD, Novartis, Nuvalent, Oncternal, Ono Pharmaceutical, Oscotec, Regeneron, Therapex, and Yuhan; royalties from Champions Oncology, Crown Bioscience, and Imagen; board membership for Interpark Bio and J Ints Bio; stock ownership in Bridgebio Therapeutics, Cyrus Therapeutics, Gencurix, Interpark Bio, Kanaph Therapeutics, J Ints Bio, and TheraCanVac; and other relationships for DAAN Biotherapeutics (Founder) and Korean University Health System (Employment).

Alexander Luft has nothing to disclose.

Jorge Alatorre-Alexander reports advisory board participation for Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, MSD, and Roche; travel support from AstraZeneca, MSD, and Roche; and honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, MSD, and Roche.

Sarayut Lucien Geater reports research funding (to institution) from AstraZeneca, Boehringer Ingelheim, MSD, Novartis and Roche; honoraria from AstraZeneca, and Boehringer Ingelheim; and advisory board participation for Pfizer.

Sang-We Kim reports research funding (to institution) from Yuhan; and travel support from AstraZeneca.

Grygorii Ursol has nothing to disclose.

Maen Hussein reports consulting fees from AbbVie, Aptitude Health, AstraZeneca, Athenex, Biopharma, Bristol-Myers Squibb, Coherus Biosciences, CTI BioPharma, Exelixis, GIntrinsiQ, IntegraConnect, Integra PrecisionQ, IntrinsiQ, Karyopharm Therapeutics, Mirati Therapeutics, National Community Oncology Dispensing Association, and Oncocyte.

Farah Louise Lim has nothing to disclose.

Cheng-Ta Yang has nothing to disclose.

Luiz Henrique Araujo reports consulting fees from AstraZeneca, Bristol-Myers Squibb, Illumina, Lilly, MSD, Roche, and Sanofi; honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck, MSD, Pfizer, and Roche; travel support from AstraZeneca, Bristol-Myers Squibb, and Daiichi-Sankyo; and grants or contracts from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck, MSD, Novartis, Pfizer, and Roche.

Haruhiro Saito reports honoraria from AstraZeneca and ONO Pharmaceutical; and grants or contracts from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, and ONO Pharmaceutical.

Niels Reinmuth reports honoraria from AstraZeneca, Bristol-Myers Squibb, Lilly, MSD, and Roche; and consulting fees from AstraZeneca, Bristol-Myers Squibb, MSD, and Roche.

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Solange Peters reports honoraria (to institution) from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, ecancer, Eli Lilly, Fishawack, Imedex, IQVIA, Medscape, MSD, Novartis, Oncology Education, PER, Pfizer, Prime Oncology, RMEI Medical Education, Research to Practice, Roche/Genentech, and Takeda; advisory board participation for AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Biocartis, Bioinvent, Bristol-Myers Squibb, Clovis Oncology, Daiichi-Sankyo, Debiopharm Group, Eli Lilly, Foundation Medicine, Illumina, Incyte, Janssen, Merck Serono, MSD, Merrimack, Novartis, Pfizer, PharmaMar, Phosplatin Therapeutics, Regeneron, Roche/Genentech, Sanofi, Seattle Genetics, and Takeda; and research funding (to institution) from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Illumina, Iovance Biotherapeutics, Lilly, Merck Serono, MSD, Novartis, Pharma Mar, Pfizer, Phosplatin Therapeutics,

Takeda, Sanofi, Seattle Genetics, and Roche/Genentech.

Tony Mok reports honoraria from ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca (before 1/1/19), BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Daz, Fishawack Facilitate, InMed Medical Communication, Janssen, Jiahui Holdings, LiangYiHui Healthcare, Lilly, Lucence Health, MD Health Brazil, Medscape, Merck, MiRXES, MSD, Novartis, OrigiMed, P. Permanyer SL, PeerVoice, PER, Pfizer, Prime Oncology, Research to Practice, Roche Pharmaceuticals/Diagnostics/Foundation One, Sanofi-Aventis, Shanghai BeBirds Translation & Consulting, Taiho Pharmaceutical, Takeda, and Touch Independent Medical Education; consulting fees from for AbbVie, ACEA Pharma, Adagene, Alpha Biopharma, Amgen, Amoy Diagnostics, Bayer, BeiGene, Berry Oncology, Boehringer Ingelheim, Blueprint Medicines, Bristol-Myers Squibb, Covidien, C4 Therapeutics, Cirina, CStone Pharmaceuticals, Curio Science, D3 Bio, Da Volterra, Daiichi-Sankyo, Eisai, Elevation Oncology, G1 Therapeutics, geneDecode, Gilead, Gritstone Oncology, Guardant Health, Hengrui Therapeutics, HutchMed, Ignyta, Inivata, IQVIA, Janssen, Lilly, Lunit USA, Loxo Oncology, Lucence Health, Medscape/WebMD, Merck Serono, MSD, Mirati Therapeutics, MiRXES, MoreHealth, Novartis, Omega Therapeutics, OrigiMed, OSE Immunotherapeutics, PeerVoice, Pfizer, Prime Oncology, Puma Biotechnology, Qiming Development, Roche/Genetech, Roche Pharmaceuticals/Diagnostics/Foundation One, Sanofi-Aventis, SFJ Pharmaceutical, Simcere of America, Synergy Research, Takeda, Tigermed, Vertex Pharmaceuticals, Virtus Medical Group, and Yuhan; advisory board participation for AbbVie, ACEA Pharma, Amgen, AstraZeneca, Berry Oncology, Blueprint Medicines, Boehringer Ingelheim, Bowtie Life Insurance, Bristol-Myers Squibb, C4 Therapeutics, Covidien, CStone Pharmaceuticals, Curio Science, D3 Bio, Daiichi-Sankyo, Eisai, Fishawack Facilitate, G1 Therapeutics, Gilead, Gritstone Oncology, Guardant Health, geneDecode (uncompensated), Hengrui Therapeutics, HutchMed, Ignyta, Incyte, Inivata, IQVIA, Janssen, Lakeshore Biotech, Lilly, Loxo Oncology, Lunit, Merck Serono, Mirati Therapeutics, MiRXES, MSD, Novartis, OrigiMed, Pfizer, Puma Biotechnology, Roche/Genentech, Sanofi-Aventis, SFJ Pharmaceutical, Simcere of America, Takeda, Vertex Pharmaceuticals, Virtus Medical Group, Yuhan; leadership roles for ACT Genomics-Sanomics, AstraZeneca, Aurora Tele-Oncology, HutchMed, and Lunit USA; stock/stock options in Act Genomics-Sanomics, AstraZeneca, Aurora Tele-Oncology, Biolidics, and HutchMed; research funding (to institution) from AstraZeneca, Bristol-Myers Squibb, G1 Therapeutics, MSD, Merck Serono, Novartis, Pfizer, Roche, SFJ, Takeda, and XCovery; and travel support (some to institution) from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, MiRXES, MSD, Novartis, Pfizer, Roche.

Melissa Johnson reports research funding (paid to institution) from AbbVie, Acerta, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Array BioPharma, Artios Pharma, AstraZeneca, Atreca, BeiGene, BergenBio, BioAtla, Black Diamond, Boehringer Ingelheim, Bristol-Myers Squibb, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics, City of Hope National Medical Center, Corvus Pharmaceuticals, Curis, CytomX, Daiichi-Sankyo, Dracen Pharmaceuticals, Dynavax, Lilly, Elicio Therapeutics, EMD Serono, Erasca, EQRx, Exelixis, Fate Therapeutics, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, Guardant Health, Harpoon, Helsinn Healthcare, Hengrui Therapeutics, Hutchison MediPharma, IDEAYA Biosciences, IGM Biosciences, Immunitas Therapeutics, Immunocore, Incyte, Janssen, Jounce Therapeutics, Kadmon Pharmaceuticals, Kartos Therapeutics, Loxo Oncology, Lycera, Memorial-Sloan Kettering, Merck, Merus, Mirati Therapeutics, Mythic Therapeutics, NeoImmune Tech, Neovia Oncology, Novartis, Numab Therapeutics, OncoMed Pharmaceuticals, Palleon Pharmaceuticals, Pfizer, PMV Pharmaceuticals, Rain Therapeutics, RasCal Therapeutics, Regeneron Pharmaceuticals, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals/Birdie Biopharmaceuticals, Shattuck Labs, Silicon Therapeutics, StemCentRx, Syndax Pharmaceuticals, Takeda, Tarveda, TCR2 Therapeutics, Tempest, Therapeutics, Tizona Therapeutics, TMUNITY Therapeutics, Turning Point Therapeutics, University of Michigan, Vyriad, WindMIL, and Y-mAbs Therapeutics; and consulting fees (paid to institution) from AbbVie, Arcus Biosciences, Amgen, Arrivent, Astellas, AstraZeneca, Axelia Oncology, Black Diamond, Calithera, Daiichi-Sankyo, EcoR1, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, Ideaya Biosciences, Immunocore, iTeos, Janssen, Jazz Pharmaceuticals, Merck, Mirati Therapeutics, Molecular Axiom, Novartis, Oncorus, Pyramid Biosciences, Regeneron Pharmaceuticals, Revolution Medicines, SeaGen, Sanofi-Aventis, Takeda, Turning Point Therapeutics, Synethekine, and VBL Therapeutics.

Acknowledgments

The study was funded by AstraZeneca. The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, under the direction of the authors, was provided by Jean Scott, PhD, James Holland, PhD, and Samantha Holmes, DPhil, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by AstraZeneca.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107422.

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