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ORIGINAL RESEARCH

Patient-Reported Outcomes for Patients with Previously Treated Small Cell Lung Cancer Receiving Tarlatamab: Results from the DeLLphi-301 Phase 2 Trial

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ABSTRACT

Introduction: Tarlatamab demonstrated a durable response and promising survival outcomes in patients with previously treated small cell lung cancer (SCLC) in the phase 2, open-label DeLLphi-301 trial. Patient-reported outcomes (PROs) were evaluated to assess the benefit-risk profile of tarlatamab.

Methods: Patients received tarlatamab intravenously every 2 weeks at a dose of 10 mg (regulatory approved dose) or 100-mg until progression or loss of benefit. PROs, including European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC-QLQ-C30) and 13-item lung cancer

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module (LC13), Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and the GP5 question of the Functional Assessment of Cancer Therapy – General Form (FACT-GP5), were collected at Cycle 1 (days 1, 8, 22), Cycle 2 (days 1, 15) and every 6 weeks from Cycle 3 onwards. PROs were summarized descriptively alongside the amount and reason for missing data and analyzed using a mixed model for repeated measures. In addition, median time to deterioration (TTD) for symptom and functional scales was analyzed.

***Results*:** A total of 100 patients were PRO-evaluable at the selected target dose (10 mg). EORTC-QLQ-C30 and LC13 completion rates (proportion of PRO assessments expected to be completed) were high (> 80%) throughout the study. Least square mean changes from baseline showed a trend towards improvement for the QLQ-C30 subscale of global health status and stabilization for physical functioning. Patients experienced reduced symptom burden for dyspnea which was more pronounced for patients at later cycles (≥ 10 points), and stabilization for chest pain and cough. Median TTD exceeded 6 months for cough and dyspnea and was not estimable for chest pain. Overall, tarlatamab was well tolerated with the majority of patients reporting no bother or a little bit of bother from side effects post baseline. Patient-reported adverse events were generally of mild to moderate severity occurring rarely or occasionally.

***Conclusion*:** Alongside previously reported antitumor activity, tarlatamab demonstrated a positive benefit–risk profile in previously treated SCLC with favorable PROs across a range of functional outcomes and symptoms, while showing manageable and sustained tolerability.

***ClinicalTrials.gov Number*:** NCT05060016.

Keywords: DeLLphi-301; Patient reported outcomes; Phase 2 trial; Small cell lung cancer; Tarlatamab

Key Summary Points

Why carry out this study?

To explore patient-reported outcomes (PROs) in depth for patients with advanced small cell lung cancer previously treated with two or more lines of therapy receiving 10-mg tarlatamab in the DeLLphi-301 phase 2 trial.

To explore the change over time for disease-related symptoms, quality-of-life, and patient reported adverse events.

What was learned from the study?

Patients remaining on tarlatamab treatment experienced improvements across a range of quality-of-life outcomes.

PRO data, including patient reported adverse events, alongside progression-free survival and overall survival supports the use of 10-mg tarlatamab in this patient population.

INTRODUCTION

Extensive stage small cell lung cancer (ES-SCLC) is an aggressive form of lung cancer with a dismal 5-year overall survival rate not exceeding 12% [1]. Although ES-SCLC is usually sensitive to first-line standard of care treatment containing platinum, etoposide, and a program cell death ligand 1 (PD-L1) inhibitor, response is short-lived, and most patients relapse within months [2, 3]. Treatment options for relapsed small cell lung cancer (SCLC) are limited, resulting in poor outcomes with patients rarely surviving more than 8 months after their initial relapse [4–6].

Tarlatamab is a half-life extended bispecific T cell engager immuno-oncology therapy that dually binds to cluster of differentiation 3 on T cells and delta-ligand 3 on target tumor cells.

This leads to T cell activation and subsequent T cell-dependent killing of tumor cells [7]. The DeLLphi-301 phase 2, open label, multinational trial was designed to investigate the antitumor activity, safety, side-effect profile, and pharmacokinetics of tarlatamab in patients with advanced SCLC who were previously treated with two or more lines of therapy. The primary endpoint was an objective response assessed by blinded independent central review (BICR) according to the RECIST version 1.1. At the primary analysis data cutoff point, the percentage of patients with an objective response (BICR) was 40% [97.5% confidence interval (CI) 29, 52], the median progression-free survival was 4.9 months (95% CI 2.9, 6.7), and the median overall survival was 14.3 months [95% CI 10.8, not estimable (NE)] for patients receiving tarlatamab at the 10-mg dose [8]. A consistent overall survival was observed at a long-term follow-up data cutoff point with an estimated median overall survival of 15.2 months (95% CI 10.8, NE) [9].

The burden of SCLC is significant with patients experiencing a range of symptoms related to both the disease and side effects of anticancer treatments. Suboptimal disease control can result in rapid deteriorations of symptoms such as cough, dyspnea, chest pain, and fatigue. Concurrently, although the primary objective of treatment for patients with ES-SCLC is to prolong survival, treatment toxicity can at times surpass potential benefit [10]. Common toxicities associated with chemotherapies used in ES-SCLC include myelosuppression, alopecia, nausea, and vomiting. The overall symptom burden associated with SCLC can have a severe impact on physical, emotional, and social functioning. [11, 12] Evaluation of the patient's perspective of treatment is therefore recognized as a key component in oncology clinical trials and can therefore support the primary trial endpoints [13].

Complementary to the key efficacy and safety outcome of the DeLLphi-301 trial, the purpose of this analysis is to report the results for the exploratory patient-reported outcome (PRO) data that provide insight into patient-experienced treatment and disease burden on health-related quality of life, while undergoing treatment with tarlatamab.

METHODS

Study Design, Population, and Treatment

The design of the phase 2 DeLLphi-301 trial has been reported previously (Ahn et al.) [8]. Briefly, the study was performed in three parts. In Part 1 (dose selection), adult patients with histologically or cytologically confirmed SCLC that had relapsed after, or was refractory to, one platinum-based treatment regimen and at least one other line of therapy were randomly assigned 1:1 to receive intravenous tarlatamab at either 10 mg or 100 mg dose until disease progression. All patients received a step dose of 1-mg tarlatamab on Day 1 of Cycle 1, after which they received the target dose at Days 8 and 15 of Cycle 1 and every 2 weeks thereafter in 28-day cycles. Patients could continue tarlatamab after progression per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 if the investigator judged that continued treatment was clinically beneficial to the patient. In Part 2 (dose expansion), patients were enrolled at the selected dose, 10-mg, until 100 patients had been enrolled from Parts 1 and 2 combined. Part 3 evaluated the safety of tarlatamab when inpatient monitoring during Cycle 1 was reduced from 48 to 24 h after the infusion. The analysis described here was conducted on all patients randomized or enrolled during Parts 1 and 2 of the study.

The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki (WCG approval number 20233898). The protocol and

amendments were approved by the institutional review board at each participating site and by regulatory authorities in the participating countries. All the patients provided written informed consent. A data-review team external to the trial team provided oversight of safety throughout the trial.

Patient-Reported Endpoints

PROs were evaluated as exploratory endpoints and measured in Parts 1 and 2. PROs were collected at on-treatment visits at Cycle 1 (Days 1, 8, 22), Cycle 2 (Days 1, 15) then every 6 weeks until Week 48 and thereafter, collected every 12 weeks until end of treatment, and at the safety follow-up visit (6 weeks after the last tarlatamab dose). Patients completed PRO questionnaires at the clinic before any other clinical assessments, study medications, or before informed of their disease status.

Patient-reported symptoms, functioning, and quality of life (QoL) were measured using European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30) [14] and the 13-item lung cancer module (QLQ-LC13) [15, 16]. The pre-specified key subscales were symptoms of dyspnea [a 4-item composite score comprising one dyspnea item from QLQ-C30 (item 8) and three items of dyspnea from QLQ-LC13 (items 3, 4 and 5)], QLQ-LC13 chest pain and cough, QLQ-C30 global health status/quality of life (GHS/QoL) and physical functioning. Symptom burden for the pre-specified key symptoms (i.e., cough, chest pain, and dyspnea) was also measured by Patient Global Impression of Severity/Change (PGI-S and PGI-C) [17].

Patient-reported adverse events were measured using selected questions concerning arm or leg swelling, heart palpitations, headache, anxiety, shivering or shaking chills, rash, and problems with concentration from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [18]. Symptom burden was measured by the GP5 [19] question of the Functional Assessment of Cancer Therapy – General Form (FACT-G).

Statistical Methods

Details of the statistical analysis methods of DeLLphi-301 have been described previously [8]. PRO analyses were carried out in the intention-to-treat (ITT) population of the selected target dose (10-mg) without multiplicity adjustment. PRO assessments prior to first progressive disease, and before or on start of new anti-cancer therapy were used for the analysis. No imputation was carried out for the PRO analyses.

PRO completion rates were calculated as the number of assessments received divided by the number of assessments expected at each visit among all patients in the 10-mg cohort randomized or enrolled in Parts 1 and 2. Available data rates were calculated as the number of assessments received divided by the number of patients in the 10-mg cohort. Missing data investigations were conducted to assess the likely direction of any bias in the observed PRO scores. The extent of data missing at each visit was summarized by reason (death, disease progression, withdrawal of consent, etc.).

Change from baseline of the EORTC-QLQ-C30 and QLQ-LC13 subscales was summarized descriptively and analyzed using a mixed model for repeated measures. The dependent variable was the change from baseline in score up to Cycle 12 Day 1 as this was the last visit with at least 10 patients. The models included time [as a continuous variable defined as days since randomization (Part 1) or enrollment (Part 2)], treatment, and baseline score as fixed effects. The patient intercept and slope of time were random effects, and an unstructured covariance matrix was used. Estimates of the least squares (LS) mean and 95% CI at each visit were obtained from the model.

Time to deterioration (TTD) was defined as the time from randomization (Part 1) or enrollment (Part 2) to the first deterioration or death if no clinically meaningful deterioration was observed. A deterioration threshold of ± 10 points was used [20–22]. Death was only counted as an event if it occurred on or before the last scheduled PRO assessment. Patients with no clinically meaningful deterioration who were alive at the last scheduled PRO

assessment, or who died after two or more consecutive missed PRO visits, were censored at the time of the last available PRO assessment. The median TTD was estimated using Kaplan–Meier methods with 95% CI calculated using the Brookmeyer and Crowley method. TTD results were presented using Kaplan–Meier curves.

PGI-S and PGI-C scores for cough, dyspnea, and chest pain were summarized descriptively at each visit. For each symptom item, PRO-CTCAE scores at each visit were presented with a focus on the first two cycles where side effects of treatment are more likely to be prominent. The proportion of patients with each response category of the GP5 question of FACT-G was summarized at each visit.

Statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The CONSORT-PRO extension reporting checklist has been followed.

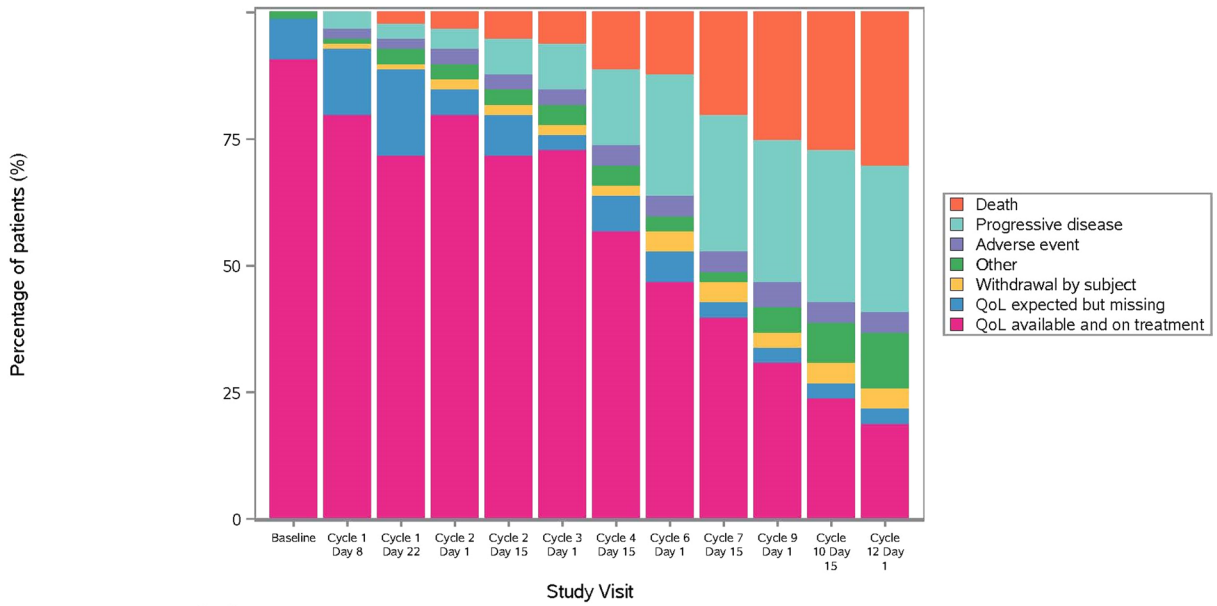
RESULTS

Patients

A total of 100 patients were included in the ITT analysis set for 10-mg tarlatamab. Demographic and clinical characteristics are summarized in Ahn et al. [8] Briefly, patients allocated to the 10-mg dose were 28% female and 72% male, with 41% of patients from Asia, 56% from Europe, and 3% from North America. Patients had an ECOG performance status of 0 (26%) or 1 (74%), and most patients had metastatic disease (98%). Patients had received a median of 2 prior lines of therapy (range 1–6).

PRO Completion Rates

Baseline PRO data were available for 91 (91%) patients for QLQ-LC13 and 92 (92%) patients for QLQ-C30 from the ITT analysis set. Available data rates (of the ITT population) were greater than 70% up to Cycle 3 and decreased to below



	Baseline	Cycle 1 Day 8	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 15	Cycle 6 Day 1	Cycle 7 Day 15	Cycle 9 Day 1	Cycle 10 Day 15	Cycle 12 Day 1
Death	0	0	2	3	5	6	11	12	20	25	27	30
Progressive disease	0	3	3	4	7	9	15	24	27	28	30	29
Adverse event	0	2	2	3	3	3	4	4	4	5	4	4
Other	1	1	3	3	3	4	4	3	2	5	8	11
Withdrawal by subject	0	1	1	2	2	2	2	4	4	3	4	4
QoL expected but missing	8	13	17	5	8	3	7	6	3	3	3	3
QoL available and on treatment	91	80	72	80	72	73	57	47	40	31	24	19

Fig. 1 Available data and reasons for missing QLQ-LC13 data. *QLQ-LC13* 13-item lung cancer module, *QoL* quality of life

50% by Cycle 6, which was expected due to the numbers of patients with disease progression by this visit. Completion rates (of those expected to have an assessment) for the QLQ-LC13 and QLQ-C30 were very high, greater than 80% for all cycles up to Cycle 12 Day 1. Available data rates were similar for the PRO-CTCAE and FACT-GP5 and are shown in Supplemental Table S1.

Reasons for missing QLQ-LC13 data are shown in Fig. 1. Most patients stopped PRO assessments due to disease progression before death. Reasons for missing data for QLQ-C30 were similar. Further investigation of the missing data using a logistic regression did not reveal any association between missing data and baseline score, previous score, or key clinical characteristics at baseline (data not shown).

QLQ-C30 and QLQ-LC13

Mean Baseline Scores and Comparison with Reference Population

The mean baseline scores together with the reference values for (all stage) patients with SCLC [16] are shown in Supplemental Table S2. The most severe symptoms at baseline were fatigue (QLQ-C30: 36.2), insomnia (QLQ-C30: 27.9), and dyspnea (QLQ-C30: 27.5). Low baseline values were reported for hemoptysis (QLQ-C13: 2.2), diarrhea (QLQ-C30: 5.8), and sore mouth (QLQ-C13: 5.9).

Baseline scores of the QLQ-C30 functional scales were generally aligned with the EORTC reference value for patients with SCLC except for GHS/QoL which was worse than the EORTC reference value (59.2 vs. 67.1)[16]. Likewise, most symptom scales were similar to SCLC reference means with the exception of pain (25.9 vs. 18.4) and constipation (22.8 vs. 15.6) which were worse than the reference values, and cough (26.7 vs. 34.2) and alopecia scores (26.7 vs. 36.6) which were better than the reference values.

Change from Baseline

Mean change from baseline analysis indicated that patients experienced improvement or stabilization in key disease-related symptoms and functional scales. LS mean changes from baseline for the QLQ-C30 GHS/QoL indicated an increasing trend toward improvement from Cycle 3 onwards with a LS mean change of 3.6 (95% CI 0.8, 6.3) at Cycle 4 and larger changes (≥ 10 points) observed for patients on treatment at Cycles 10 and 12 [Cycle 12 LS mean 12.3 (95% CI 7.1, 16.6)]. Least squares mean changes from baseline for the QLQ-C30 subscale of physical functioning indicated that scores were maintained over time (Fig. 2).

A decrease in symptom burden was observed for QLQ-C30/LC13 dyspnea composite score which decreased (improved) from Cycle 4 onwards with a LS mean change of – 3.9 (95% CI – 6.6, – 1.3) and a mean change ≥ 10 points for patients on treatment from Cycle 9 onwards (Cycle 12 LS mean – 14.4 [95% CI – 20.9, – 7.9]). QLQ-LC13 chest pain and cough remained more similar to baseline (Fig. 3). LS mean change results were aligned with the descriptive analysis which are shown in Supplementary Fig. 1.

Remaining QLQ-C30 and QLQ-LC13 subscales are shown in Supplementary Figs. 2 and 3. LS mean changes from baseline indicated a trend towards improvement in emotional and social functioning. For symptom subscales, LS means indicate improvements from baseline (≥ 10 points) for alopecia at all cycles, a deterioration for appetite loss at all cycles, and a deterioration for constipation for patients from Cycle 6 onwards. Other subscales were similar to baseline.

Time to Deterioration

Median TTD was not estimable for several subscales including the key subscale of chest pain. Other key symptoms scales of cough and dyspnea showed a median TTD of 7.3 and 6.0 months, respectively. Shorter median TTD were observed for GHS/QoL (1.9 months) and physical functioning (1.4 months). Kaplan–Meier curves are shown in Figs. 4 and 5 which show that most deteriorations occurred within the first 2 months of treatment. Median TTD for other subscales is presented in Supplementary

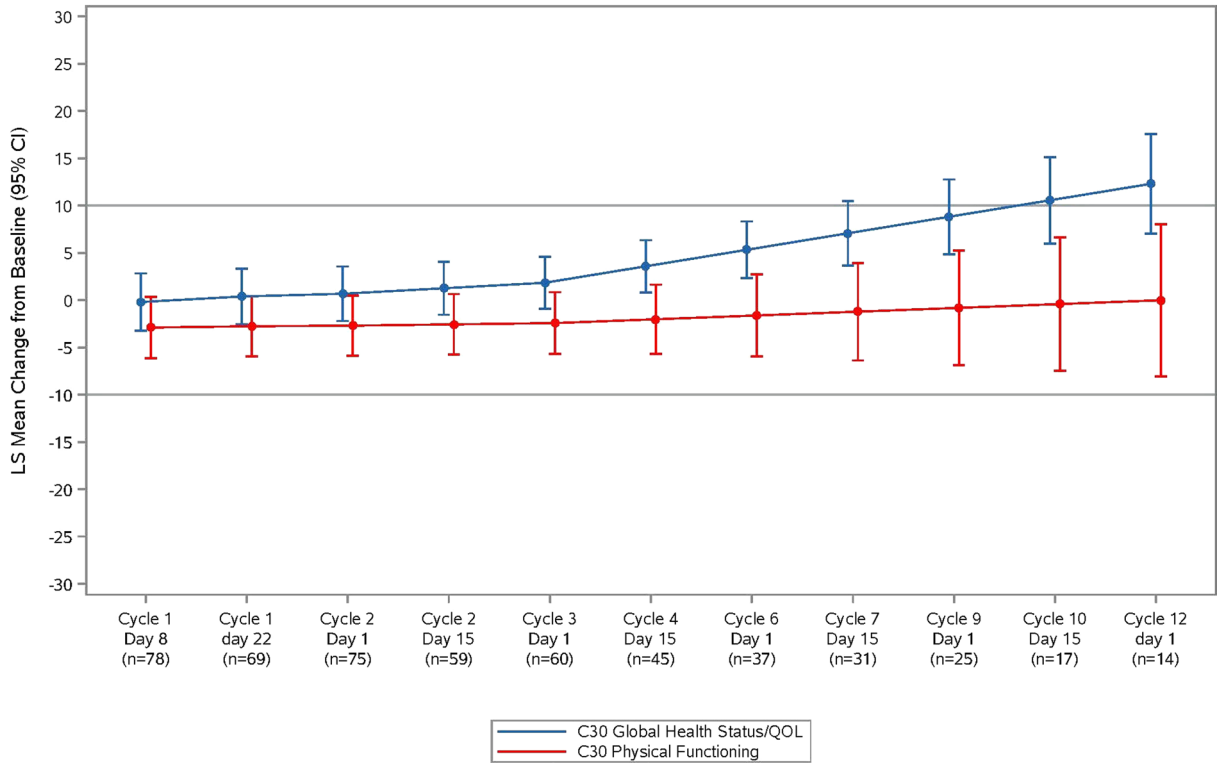


Fig. 2 QLQ-C30 GHS/QoL and physical functioning least squares mean change from baseline. For GHS/QoL and functioning scales, a positive change represents improvement. *CI* confidence interval, *GHS/QoL* global health status/quality of life, *LS* least squares, *QLQ-C30* 30-item Quality of Life Questionnaire

Table S3. The longest TTD were observed for diarrhea (12.9 months), pain in arm or shoulder, and pain in other parts (both 8.6 months); however, for all these symptoms, there were less than 50% of patients experiencing events.

Patient Global Impression of Severity And Change

At baseline, patients rated their cough, chest pain, and dyspnea, as moderate or severe in 18%, 8%, and 20% of cases, respectively. During treatment, symptoms improved, with fewer patients reporting moderate or severe cough (0–11%), chest pain (0–6%), and dyspnea (0% to 18%) (Fig. 6). Symptom improvements were also observed in PGI-C responses, with approximately 50% or more of patients rated their symptoms as "a little better" or "much better" compared to baseline. Fewer than 10% of patients rated their symptoms as worse compared to baseline, and these ratings were only observed up to Cycles 4 and 6, respectively (data not shown).

PRO-CTCAE and FACT-GP5 Assessment of Side Effects

PRO CTCAE Items at Baseline and Over Time

The proportion of patients completing the PRO CTCAE items at baseline was high (91%). During the first two treatment cycles, the frequencies of anxiety and headache were lower compared to baseline, with only up to 6% reporting

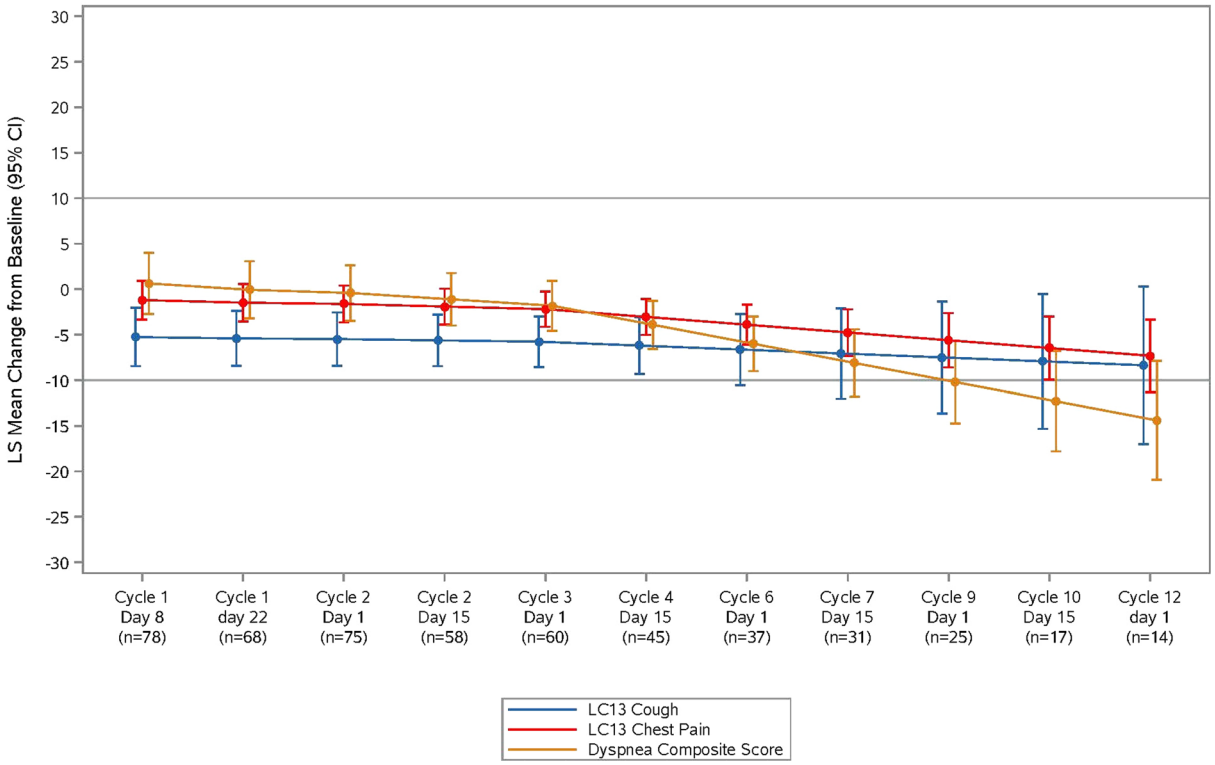


Fig. 3 QLQ-LC13/C30 cough, chest pain, and dyspnea least squares mean change from baseline. For symptom scales, a negative change represents improvement. *CI* confidence interval, *LS* least squares, *QLQ-LC13/C30* 13-item lung cancer module/30-item Quality of Life Questionnaire

anxiety and 3% reporting headache occurring "frequently" or "almost constantly". Anxiety severity and interference remained similar to baseline with only 4–8% of patients reporting severe or very severe anxiety, and 0–8% experiencing "quite a bit" or "very much" interference with daily life. Headache severity increased from baseline with up to 15% of patients experiencing severe headache, but inference was low with 0–8% reporting "quite a bit" or "very much" interference.

Palpitations and arm or leg swelling remained similar to baseline, with up to 1% of patients reporting palpitations and 6% reporting arm or leg swelling "frequently" or "almost constantly". Most palpitations were mild to moderate, none were severe, and one patient reported very severe palpations. Overall, arm or leg swelling severity remained similar from baseline with 7–29% of patients experienced severe or very severe swelling, and 7–21% reporting "quite a bit" or "very much" interference.

During the first two cycles, the frequency of shivering or shaking chills increased compared to baseline, but these were rated as "frequently" or "almost constantly" in less than 5% of patients. The severity of shivering reduced from baseline with 0–19% being rated as severe or very severe. The severity of problems with concentration (mild or higher) slightly increased from baseline, but only up to 7% of patients reported severe or very severe problems. The occurrence of rash was low and remained similar to baseline. The frequencies of adverse events during the study are presented in Supplementary Fig. 4, and severity and interference in Supplementary Figs. 5 and 6.

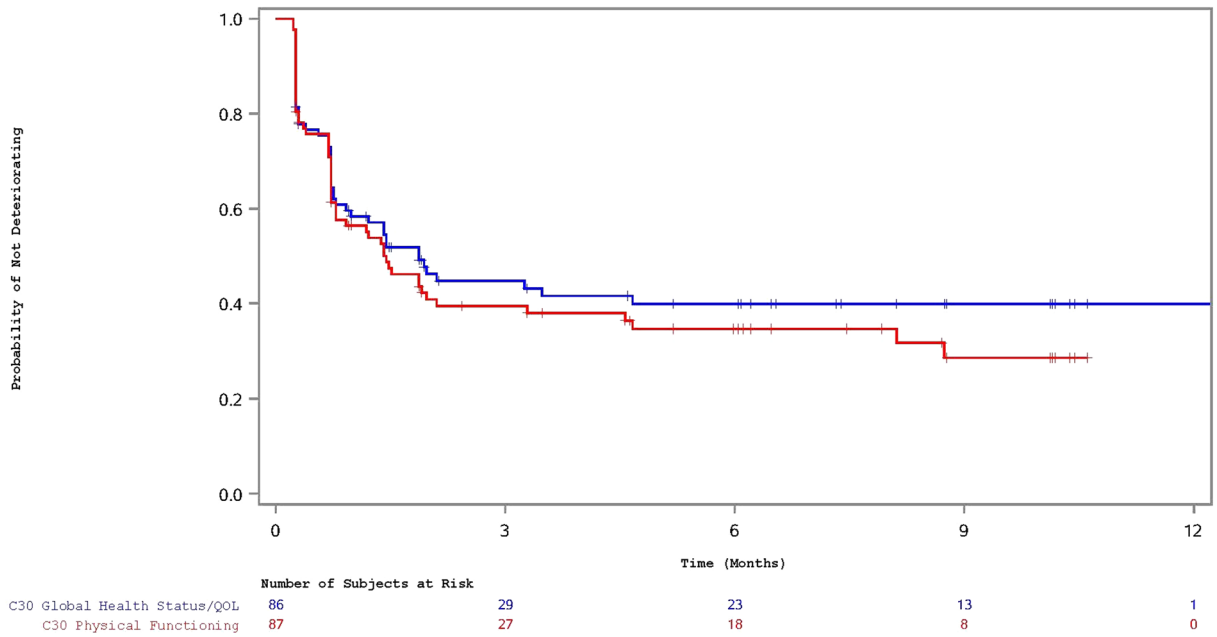


Fig. 4 Time to deterioration (TTD) in QLQ-C30 GHS/QoL and physical functioning. Median TTD was 1.9 months (95% CI 0.8, NE) for GHS/QoL and 1.4 (95% CI 0.8, 2.1) month for physical functioning. The median PFS was 4.9 months (95% CI 2.9, 6.7) and median OS was 14.3 months (95% CI 10.8, NE). *CI* confidence interval, *GHS/QoL* global health status/quality of life, *NE* not estimable, *OS* overall survival, *PFS* progression-free survival, *TTD* time to deterioration, *QLQ-C30* 30-item Quality of Life Questionnaire

FACT-GP5 At baseline, most patients (92%) reported that they were not or a little bit bothered by the side effects of treatment. During treatment, the bother with side effects increased only slightly. During the first two cycles, a maximum of 16% of patients reported being bothered by side effects "quite a bit" or "very much". From Cycle 3 onwards, fewer than 8% of patients reported being bothered by side effects of treatment "quite a bit" or "very much" (Fig. 7).

DISCUSSION

As previously reported, tarlatamab has shown a durable response, transformative survival outcomes, and a favorable safety profile in patients with heavily pretreated SCLC [8]. This comprehensive PRO analysis of a phase 2, open-label trial allows detailed interpretation and insight into patients' experience of treatment with tarlatamab, reflecting the totality of the treatment effect on patient reported symptoms, functioning and treatment-related adverse events.

PROs including cough, dyspnea and chest pain were generally improved or maintained whilst on treatment with tarlatamab supporting the overall efficacy benefits of tarlatamab on antitumor activities and survival. The patient population in the DeLLphi-301 trial was symptomatic at baseline with impaired physical function and quality of life. Levels of symptoms and functioning at baseline were generally similar to those expected for patients with SCLC previously reported (although this comparison was not matched by age and gender), highlighting generalizability of the sample. During tarlatamab treatment a trend toward symptom improvement or stability was observed for the key lung cancer symptoms of cough, dyspnea, and chest pain. Patients receiving tarlatamab also experienced alleviation of

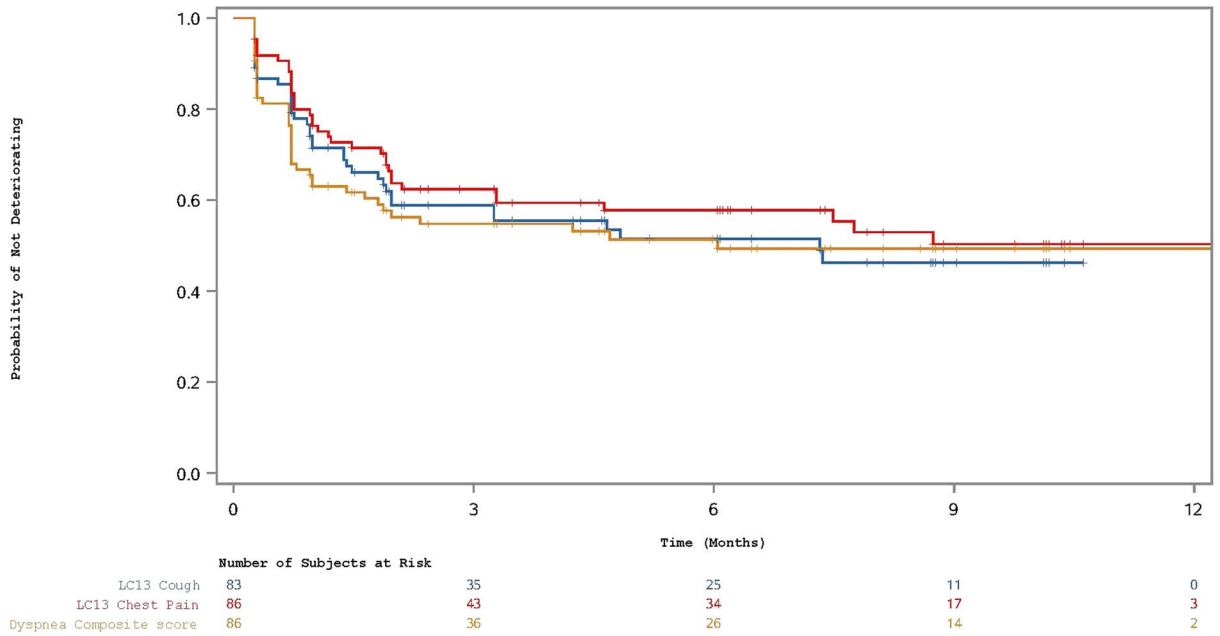


Fig. 5 Time to deterioration (TTD) in QLQ-C30/LC13 cough, chest pain, and dyspnea. Median TTD was 7.3 months (95% CI 2.0, NE) cough, NE (95% CI 3.3, NE) for chest pain, and 6.0 (95% CI 1.6, NE) for dyspnea. The median PFS was 4.9 months (95% CI 2.9, 6.7) and median OS was 14.3 months (95% CI 10.8, NE). *CI* confidence interval, *NE* not estimable, *OS* overall survival, *PFS* progression-free survival, *TTD* time to deterioration, *QLQ-C30/LC13* 30-item Quality of Life Questionnaire/13-item lung cancer module

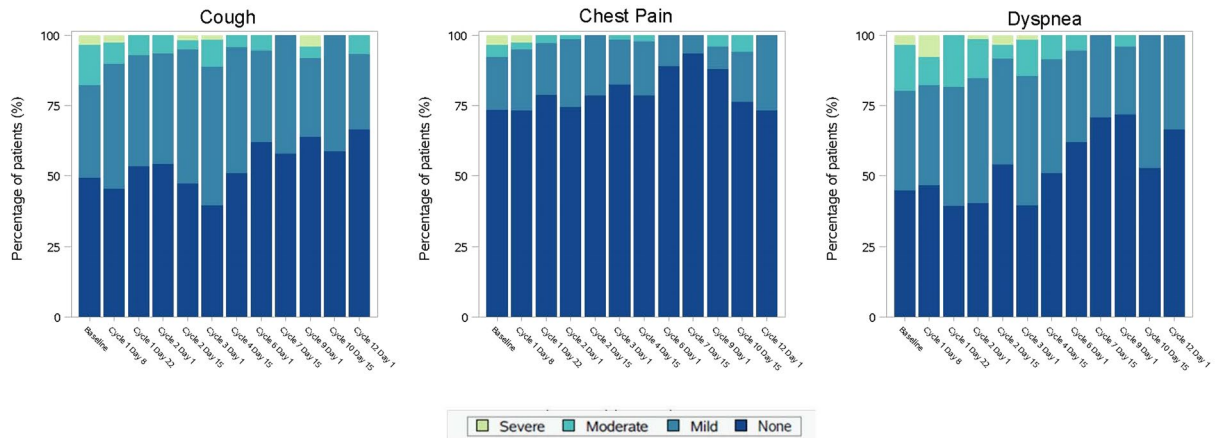


Fig. 6 Patient global impression of severity (PGIS) for cough, chest pain, and dyspnea

prior chemotherapy related side effects such as alopecia. A consistent trend towards improvement was also observed for global health status; physical functioning remained similar to baseline. Symptom improvement for cough, chest pain and dyspnea was also observed through different PRO instruments (QLQ-C30/LC13 and PGI-S/PGI-C responses) providing further confidence in the findings.

The median TTD (first deterioration or death if it occurred on or before the last scheduled PRO assessment) was not estimable or exceeded six months for key symptoms for cough, chest pain, dyspnea which is close to what has been

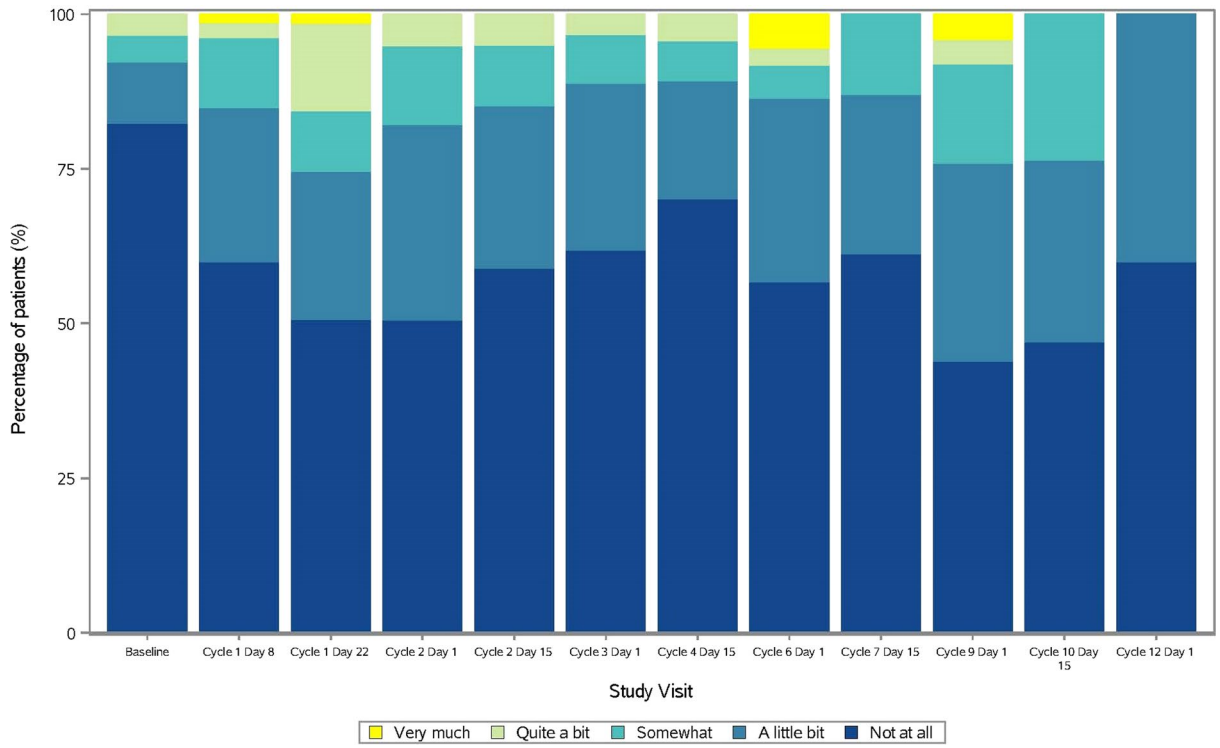


Fig. 7 FACT-GP5 bothered by side effects of treatment. *FACT-GP5* GP5 question of the Functional Assessment of Cancer Therapy – General Form

observed in the first-line ES-SCLC CASPIAN trial [20]. TTD for GHS/QoL and physical functioning was shorter than for symptoms, with median times less than two months. Early deterioration in GHS/QoL and physical functioning may be attributed to the inpatient monitoring required during the first treatment cycle of tarlatamab. Additionally, given its mechanism of action, the safety profile of tarlatamab includes risks of cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which occurred in 49% and 7% of patients, respectively. While most CRS and ICANS events were of low grade, they are often managed in an inpatient setting, potentially posing a transient yet negative impact on GHS/QoL and physical functioning. While most deteriorations occurred in early treatment cycles, patients treated for longer than two months did not have further clinical deterioration in GHS/QoL and physical functioning.

Most patients reported low levels of adverse events such as headache and arm or leg swelling at baseline. During the first two cycles of treatment there was an increase in the frequency of shivering or shaking chills, and a small increase in the severity of problems with concentration. FACT-GP5 showed that between 75 and 89% of patients reported 'no' or a 'little bit' of bother from the side effects of treatment. Overall, these results support the safety of 10 mg tarlatamab.

This analysis included all subscales of QLQ-C30 and LC13, providing valuable information about PRO scores at baseline in this study in heavily pre-treated patients with SCLC, as well as PRO outcomes during treatment with tarlatamab up to 12 cycles. We observed some ceiling effects (minimum symptoms or maximum function and baseline) affecting the ability to show change over time, particularly for QLQ-LC13 symptoms measured such as chest pain (where only 25% of patients had baseline scores with room for improvement, Supplementary Table S2). Researchers designing trials should consider their potential patient population

and include PRO scales which can measure low symptom levels more precisely (such as multiple items from an item bank).

Strengths of the study are that over 90% of the patients had baseline PRO data, and over 80% of expected assessments were completed at each visit, indicating very good compliance with planned PRO data collection. The observed PRO data is presented alongside the number of patients remaining in the study at each visit for context. In addition, PRO data were collected frequently, including mid- cycle. Despite the reduction in number of patients with PRO data over time, these data provide insight into the experience of patients receiving up to 12 cycles of 10-mg tarlatamab.

Limitations of the study include the uncontrolled design and the severity of the disease which leads to a high proportion of patients with unobserved PRO data. The study was designed to evaluate PRO data while on treatment and prior to disease progression or death, so observed data can only reflect the patient experience while on treatment. The most common reason for missing data was disease progression, aligning with the clinical outcomes observed in the study and in line with planned PRO data collection.

Considering the observed PRO results, patients remaining on tarlatamab experience improved function and symptom scores as seen across several of the QLQ-C30 and LC13 subscales with higher mean scores and change from baseline scores at later cycles. However, it must be noted that this effect at later cycles is likely to be due to the specific subgroup of patients who remained on tarlatamab, with patients with declining scores more likely to have dropped out of the study. Aligning with general improvements in symptoms observed, and some ceiling effects at baseline, fewer than 50% of patients experienced deterioration in symptoms over the course of the study, and therefore estimation of a TTD in symptoms is limited.

Further, this study provides insight into patient reported adverse events using selected items from the PRO-CTCAE item library. A subset of PRO-CTCAE items was included (up to six) which were not freely selected by the patients so may not have captured all relevant adverse events.

CONCLUSION

Alongside previously reported antitumor activity, patient-reported outcomes show potential benefits across a range of functional and symptom outcomes, including improvements in QoL and reduction in some key symptoms. The patient reported adverse events and impacts of side effects of treatment were generally mild, and therefore the patient-reported outcomes positively contribute supportive evidence for the benefit of treatment with 10-mg tarlatamab. The demonstration of benefit of tarlatamab with respect to PROs needs confirmation in a comparative phase 3 trial.

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Data Availability. The patient level data of the DeLLphi-301 trial is proprietary to Amgen and is not publicly available. Qualified researchers may request data from Amgen clinical studies. Complete details are available at https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

Declarations

Conflict of Interest. **Horst-Dieter Hummel** reports consultancy work and steering board membership, support for attending meetings, and participation on a data safety monitoring board with Amgen. **Myng-Ju Ahn** received consultancy fees from Amgen, Astra-Zeneca, Daiichi-Sankyo, Eli Lilly, F. Hoffman-La-Roche, Merck, Merck KGaA, and is employed as a professor of the Samsung Medical Centre. **Fiona Blackhall** reports consulting fees and payment or honoraria from Amgen and AstraZeneca. **Martin Reck** has been a paid member speaker bureau and/or consultant for Amgen, AstraZeneca AB, BeiGene USA Inc, Boehringer Ingelheim, Bristol Myers Squibb Company, Daiichi Sankyo Company LTD Eli Lilly F. Hoffmann-La Roche, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer, Regeneron Pharmaceuticals, and conducted Data and Safety Monitoring for Sanofi. **Hiroaki Akamatsu** received honoraria from Amgen Inc, AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Nippon Kayaku Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Pfizer Inc, Takeda Pharmatheutical Co. Ltd. and Taiho Pharmaceutical Co. Ltd.. He served as an advisor role for Amgen Inc, Janssen Pharmaceutical K.K., and Sandoz. He received research funding from Amgen Inc, Chugai Pharmaceutical Co. Ltd., and MSD K.K. **Suresh Ramalingan** reports consultancy fees from Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKine, Merck, Takeda Oncology. **Hossein Borghaei** reports research support (Clinical Trials) from BMS, Lilly, Amgen; Advisory16 Board/Consultant role for BMS, Lilly, Genentech, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTEO, Jazz, Janssen, DaVolterra; Data and Safety Monitoring Board participation with University of Pennsylvania: CAR T Program, Takeda, Incyte, Novartis; employment with Fox Chase Cancer Center; Scientific Advisory Board participation with Sonnetbio (Stock Options); Inspirna (formerly Rgenix, Stock Options); Nucleai (stock options); Honoraria from Amgen, Pfizer, Daiichi, Regeneron; Travel support from Amgen, BMS, Merck, Lilly, EMD-Serono, Genentech, Regeneron. **Melissa Johnson** reports a grant or contract for research on behalf of AbbVie, Acerta Pharma, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Array Biopharma, ArriVent BioPharma, Artios Pharma, AstraZeneca, Atreca, BeiGene, BerGenBio, BioAtla, Black Diamond, Boehringer Ingelheim, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics, City of Hope National Medical Center, Corvus Pharmaceuticals, Curis, CytomX, Daiichi Sankyo Company, Dracen Pharmaceuticals, Dynavax Technologies, Eli Lilly and Company, Elicio Therapeutics, EMD Serono, EQRx, Erasca, Exelixis, Fate Therapeutics, Genentech USA, Inc, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, Guardant Health, Harpoon, Helsinn Healthcare SA, Hengrui Therapeutics, Hutchinson MediPharma, IDEAYA Biosciences, IGM Biosciences, Immunitas Therapeutics, Immunocore, Incyte Corporation, Janssen Research & Development, LLC, Jounce Therapeutics, Kadmon Pharmaceuticals LLC, Kartos Therapeutics, LockBody Therapeutics, Loxo Oncology, Lycera, Memorial Sloan-Kettering Cancer Center, Merck, Merus, Mirati Therapeutics, Mythic Therapeutics, NeoImmune Tech, Neovia Oncology, Novartis, Numab Therapeutics, Nuvalent, OncoMed Pharmaceutical, Palleon Pharmaceuticals, Pfizer, PMV Pharmaceuticals, Rain Therapeutics, RasCal Therapeutics, Regeneron Pharmaceuticals, Inc, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, SANOFI US SERVICES INC, Seven and Eight Bipharmaceuticals, Shattuck Labs, Silicon Therapeutics, Stem Centrx, Syndax Pharmaceuticals, Takeda Pharmaceuticals America, Inc, Tarveda, TCR2 Therapeutics,

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Ethical Approval. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki (WCG (approval number 20233898). The protocol and amendments were approved by the institutional review board at each participating site and by regulatory authorities in the participating countries. All the patients provided written informed consent. A data-review team external to the trial team provided oversight of safety throughout the trial.

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