Clinical Study Report Synopsis	
Drug Substance	Durvalumab (MEDI4736)
Study Code	D419AC00002
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A Phase III Randomized, Open-Label, Multi-Center Study of Durvalumab Versus Standard of Care Platinum-Based Chemotherapy as First Line Treatment in Patients with PD-L1-High Expression Advanced Non Small-Cell Lung Cancer (NSCLC)

Study dates: First patient enrolled: 02 Jan 2017
Last patient enrolled: 25 Jan 2019
The analyses presented in this report are based on a database lock date of 30 Nov 2022 (data cut-off date: 27 Oct 2022)

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: PPD Guangdong 510080, China

China National Co-ordinating Investigator PPD Shanghai, China

Sponsor's Responsible Medical Officer: PPD Gaithersburg, MD 20878, USA

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

A total of 3075 patients were screened at 98 centers in 12 countries or regions: China (38 centers), Russia (12), Hungary (8), Poland (7), South Korea (7), Vietnam (7), Turkey (5), Australia (4), Taiwan (4), Thailand (4), United States of America (1), and Netherlands (1).

A total of 669 patients were randomized at 85 centers in 10 countries or regions: China (38 centers), Russia (12), Hungary (4), Poland (4), South Korea (7), Vietnam (6), Turkey (5), Australia (3), Taiwan (2), and Thailand (4).

Publications

At the time of writing this report, the following publication has been published:

Wu et al 2017

Wu Y, Lu S, Clarke K, Lactionov K, Li P, Kirkby M, et al. A phase 3 study of first-line durvalumab vs platinum-based chemotherapy in patients with advanced NSCLC and high PD-L1 expression: PEARL. Ann. Oncol. 2017;28 Suppl 5:v460-v96.

Objectives and criteria for evaluation

AstraZeneca developed and implemented a model intended to predict a patient's risk of early mortality to optimize the benefit:risk profile for treatment of patients with immune checkpoint inhibitors. Using this model, patients with a low risk of early mortality (LREM) were identified.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ≥ 25% (all randomized patients)	OS in patients with PD-L1 TC ≥ 25%
Primary	Efficacy	To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ≥ 25% low risk of early mortality (LREM)[a]	OS in patients with PD-L1 TC ≥ 25% LREM[a]
Secondary	Efficacy	To assess the efficacy of durvalumab compared to SoC in terms of OS	OS in patients with • PD-L1 TC ≥ 50% • PD-L1 TC ≥ 50% LREM[a]
Secondary	Efficacy	To further assess the efficacy of durvalumab compared to SoC in terms of PFS, ORR, DoR, OS18, OS24, APF12, and PFS2	PFS, ORR, DoR, APF12 using Investigator assessments according to RECIST 1.1, PFS2 using local standard clinical practice, OS18 and OS24 respectively in patients with • PD-L1 TC ≥ 25% • PD-L1 TC ≥ 25% LREM[a] • PD-L1 TC ≥ 50% • PD-L1 TC ≥ 50% LREM[a]

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	PRO	To assess disease-related symptoms and HRQoL in patients treated with durvalumab compared to SoC using the EORTC QLQ-C30 v3 and the LC13 module	EORTC QLQ-C30, EORTC QLQ-LC13, and changes in ECOG performance status in patients with • PD-L1 TC ≥ 25% • PD-L1 TC ≥ 25% LREM[a]
Secondary	Immuno-genicity	To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab in patients with • PD-L1 TC ≥ 25% • PD-L1 TC ≥ 25% LREM[a]
Secondary	Safety	To assess the safety and tolerability profile of durvalumab compared to SoC	AEs, physical examinations, laboratory findings, and vital signs

[a] The population at LREM consists of patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality

ADA, antidrug antibodies; AE, adverse event; APF12, alive and progression-free at 12 months; DoR, duration of response; ECOG, Easter Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; CCI HEOR, health economics and outcomes research; HRQoL, health-related quality of life; IFN, interferon; LREM, low risk of early mortality; ORR, objective response rate; OS, overall survival; OS18/24, overall survival at 18/24 months; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PFS2, time from randomization to second progression or death; PRO, patient-reported outcome; QLQ-30, 30-item core quality of life questionnaire version 3; QLQ-LS13, 13-item lung cancer quality of life questionnaire; RECIST, Response Evaluation Criteria for Solid Tumors; SoC, standard of care; TC, tumor cell

Study design

This was a randomized, open-label, multi-center, global Phase III study to determine the efficacy and safety of durvalumab versus platinum-based standard of care (SoC) chemotherapy in the first-line treatment of advanced NSCLC patients with tumors that lacked sensitizing epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement and with programmed cell death ligand 1 (PD-L1) high expression.

Patients were randomized in a 1:1 ratio to receive treatment with durvalumab or SoC. It is planned to use an interactive voice response system/interactive web response system (IVRS/IWRS) in the protocol, and IWRS was used in practice. Patients were stratified according to the following prognostic factors: PD-L1 tumor expression status (on tumor cell [TC] 25% to 49% versus TC ≥ 50%), histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker).

The dual primary objectives were to assess OS in patients with PD-L1 TC ≥ 25% (full analysis set [FAS]) and also in a population of patients with PD-L1 TC ≥ 25% LREM (PD-L1 TC ≥ 25% LREM analysis set). The secondary objectives include: 1) OS in patients with PD-L1 TC ≥ 50% (PD-L1 TC ≥ 50% analysis set) and patients with PD-L1 TC ≥ 50% LREM (PD-L1 TC ≥ 50% LREM analysis set); 2) PFS, ORR, DoR, OS18, OS24, APF12, and PFS2 in FAS, PD-L1 TC ≥ 25% LREM, PD-L1 TC ≥ 50%, and PD-L1 TC ≥ 50% LREM analysis

sets; 3) EORTC QLQ-C30, EORTC QLQ-LC13, and changes in Eastern Cooperative Oncology Group (ECOG) performance status in FAS and PD-L1 TC ≥ 25% LREM analysis set; 4) presence of ADAs for durvalumab in FAS and PD-L1 TC ≥ 25% LREM analysis set.

This study used an independent data monitoring committee (IDMC) to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The committee held its first meeting on 15 Sep 2017, approximately 6 months after the study had started, and more than 30 patients had been randomized and received at least 2 cycles of treatment. The IDMC met approximately every 6 months thereafter. Following each meeting, the IDMC reported to the Sponsor and could recommend changes in the conduct of the study. After the 7th IDMC meeting (28 May 2021), the IDMC agreed that no further meetings were required. This decision was based on there having been no safety concerns identified in the previous reviews, and the well established and recognized safety profile of durvalumab monotherapy, and there being fewer than 10% of the FAS patient population still receiving their assigned treatment across both treatment arms.

Target population and sample size

Patients had to be aged ≥ 18 years with Stage IV NSCLC (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology; IASLC Staging Manual in Thoracic Oncology). Patients were not to have received prior chemotherapy or any other systemic therapy for advanced NSCLC and had to have tumors that lacked a sensitizing EGFR mutation or ALK rearrangement. Patients had to have tumor cell PD-L1 high expression status, prior to randomization, defined as ≥ 25% PD-L1 membrane expression in tumoral tissue with the VENTANA PD-L1 (SP263) Assay.

The study planned to randomize approximately 650 patients across 2 study arms. This clinical study report (CSR) provides data for the cut-off date of 27 October 2022.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- **Durvalumab (MEDI4736):** 20 mg/kg durvalumab via intravenous (IV) infusion every 4 weeks (Q4W)

Standard of care: Investigator's choice of one of the following treatments:

- **Paclitaxel + carboplatin:** paclitaxel 175 mg/m^2 and carboplatin area under the plasma concentration curve (AUC) 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented progressive disease (PD) (if PD occurred before the 4 to 6 cycles were complete).
- **Gemcitabine + cisplatin (squamous patients only):** gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m^2 via IV

infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (if PD occurred before the 4 to 6 cycles were complete).

- **Gemcitabine + carboplatin (squamous patients only):** gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (if PD occurred before the 4 to 6 cycles were complete).
- **Pemetrexed + cisplatin (non-squamous patients only):** pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (if PD occurred before the 4 to 6 cycles were complete). Non-squamous patients who had not progressed after 4 cycles were eligible for pemetrexed maintenance therapy.
- **Pemetrexed + carboplatin (non-squamous patients only):** pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (if PD occurred before the 4 to 6 cycles were complete). Non-squamous patients who had not progressed after 4 cycles were eligible for pemetrexed maintenance therapy.

All SoC treatments were supplied locally, or centrally under certain circumstances when local sourcing was not feasible.

Duration of treatment

All treatments were administered until PD according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) unless specific treatment discontinuation criteria were met.

Patients in both arms with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continued to receive benefit from their assigned study treatment and who met the criteria for treatment in the setting of PD could continue to receive their assigned treatment for as long as they were gaining clinical benefit. However, patients in the immunotherapy arm were not permitted to continue immunotherapy if progression occurred after confirmed response (complete response [CR] or partial response [PR] as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the treatment period.

Statistical methods

A multiple testing procedure (MTP) with gatekeeping strategy was used to control type I error rate at 5% (2-sided) across the dual primary OS endpoints (OS in the intent-to-treat [ITT] population and OS in the PD-L1 TC ≥ 25% LREM population) and selected secondary endpoints (OS in the PD-L1 TC ≥ 50% population and PD-L1 TC ≥ 50% LREM population). As ITT population is the same as FAS population in this study, it will be directly referred to as "FAS" in the following text.

Primary analysis of OS in the FAS was performed using a stratified log-rank test, adjusting for level of PD-L1 expression (TC 25% to 49% versus ≥ 50%) and histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker) for generation of the p-value. The effect of durvalumab versus SoC was estimated by the hazard ratio (HR) from stratified Cox proportional hazards model together with its corresponding (1-adjusted alpha) × 100% confidence interval (CI) (with adjustments both without and with alpha recycling), 95% CI, with ties handled by Efron approach and the CI calculated using a profile likelihood approach. Primary analysis of OS in the PD-L1 TC ≥ 25% LREM analysis set was conducted in the same manner.

A secondary analysis of OS was performed using a stratified log-rank test, adjusting for only histology and smoking status using the PD-L1 TC ≥ 50% analysis set, and the PD-L1 TC ≥ 50% LREM analysis set. The corresponding HR and CI were estimated using a stratified Cox model.

Progression-free survival (PFS) was analyzed using a stratified log-rank test, adjusting for the same factors as the primary endpoint. The effect of durvalumab versus SoC was also estimated by the same methodology described for the primary endpoint. PFS2 was analyzed using the same methodology as PFS. Objective response rate (ORR) was summarized and compared between durvalumab versus SoC using logistic regression models adjusting for the same factors as the primary endpoint. The results of the analysis were presented in terms of an odds ratio (an odds ratio greater than 1 favoured durvalumab) together with its associated profile likelihood and p-value. Duration of response (DoR) was summarized descriptively. Kaplan-Meier plots of OS, PFS, PFS2, and DoR were presented by treatment group. The APF12, OS18, and OS24 were summarized (using the Kaplan-Meier plots) and presented by treatment arm.

Time to deterioration of EORTC QLQ-C30 and EORTC QLQ-LC13 were analyzed using the same methodology as OS. Kaplan-Meier plots were presented by treatment group.

The number and percentage of patients who developed detectable antidrug antibodies (ADA) to durvalumab was summarized.

Safety data were summarized from the treatment period for durvalumab alongside the SoC agents. The safety analysis set and the PD-L1 TC ≥ 25% LREM safety analysis set were used for reporting of safety data. Safety and tolerability were assessed in terms of adverse events (AEs) (including serious adverse events [SAEs]), physical examination, clinical chemistry, hematology, vital signs, electrocardiograms, and exposure. Time on study, dose delays/interruptions, and dose reductions were also summarized.

The China cohort analysis was performed using the same methodology as for the entire study population. All statistical analyses for the China cohort were considered exploratory. No adjustments for multiplicity were made.

Patient population

Global cohort

In the global FAS:

- 669 patients were randomized to receive durvalumab (n=335), or SoC (n=334). At DCO the majority of patients had discontinued study treatment with the main reason being worsening of condition under investigation. Also, there were 69 [21.1%] patients in SoC group who discontinued study treatment due to maximum cycle of chemotherapy reached.
- The reasons for discontinuation from study treatment did not raise any concerns about the conduct of the study.
- The COVID-19 pandemic caused no meaningful impact on the data integrity, the overall conduct or quality of the study, or with respect to the safety profile observed within the patient population described.
- The demographics and disease characteristics were generally well-balanced between the treatment groups.
  - The majority (80.0%) of patients were Asian with 20.0% being White.
  - The median age was 62.0 years (range, 20 to 85 years). Over half (62.2%) of patients were aged <65 years and 5.1% of patients were ≥75 years.
  - The majority of patients (80.3%) were male.
  - At baseline, 78.0% of patients had an ECOG PS of 1 (restricted). 73.8% and 26.2% of patients had an PD-L1 expression of ≥ 50% and 25% to 49% (from IWRS), respectively.
  - At diagnosis, 39.6% of patients had a histology type of squamous cell carcinoma, while 60.4% had non-squamous cell carcinoma including adenocarcinoma, large cell carcinoma, and others.
  - At diagnosis, most patients (93.3%) were AJCC stage IV.
  - As anticipated in this patient population, the majority of patients were former (57.8%) or current (20.6%) smokers.
- The relevant medical history of the study patients was representative of this patient population, and generally balanced between the treatment groups.
- A total of 28 (4.2%) patients received prohibited concomitant medications during the study (3.6% and 4.8% in the durvalumab and SoC groups, respectively). A total of 653 (97.6%) patients received permitted concomitant medications during the study treatment (97.3% and 97.9% in the durvalumab and SoC groups, respectively).
- Post-discontinuation anticancer treatment was administered in 48.3% of patients, and the proportion was higher in the SoC group than the durvalumab group (53.9% versus 42.7%, respectively).

  - 35.8% of patients in the durvalumab group and 32.3% of patients in the SoC group received cytotoxic chemotherapy, 18.2% of patients in the durvalumab group and 16.8% of patients in the SoC group received targeted therapy. The proportion of patients receiving immunotherapy was higher in the SoC group than the durvalumab group (26.3% and 7.5%, respectively). In addition, 13.4% of patients in the durvalumab group and 16.2% of patients in the SoC group received radiotherapy.
- The overall incidence of important protocol deviations was low. Their nature did not suggest an impact to the data integrity, the overall conduct of this study or the interpretation of the study results.

In the global PD-L1 TC ≥ 25% LREM analysis set:

- The PD-L1 TC ≥ 25% LREM analysis set included 549 randomized patients.
- The demographics and disease characteristics in the PD-L1 TC ≥ 25% LREM analysis set was consistent with the FAS.
  - The majority (82.0%) of patients were Asian with 18.0% being White.
  - The median age was 62.0 years (range, 20 to 85 years). Over half (62.7%) of patients were aged < 65 years and 5.6% of patients were ≥ 75 years.
  - The majority of patients (80.3%) were male.
  - At baseline, 77.2% of patients had an ECOG PS of 1 (restricted). 74.1% and 25.9% of patients had an PD-L1 expression of ≥ 50% and 25% to 49% (from IWRS), respectively.
  - At diagnosis, 40.4% of patients had a histology type of squamous cell carcinoma, while 59.6% had non-squamous cell carcinoma including adenocarcinoma, large cell carcinoma, and others.
  - At diagnosis, most patients (92.7%) were AJCC stage IV.
  - As anticipated in this patient population, the majority of patients were former (59.6%) or current (18.4%) smokers.
- The overall incidence of important protocol deviations was low.

China cohort

In the China FAS:

- 424 patients recruited from sites located in mainland China were randomized to receive durvalumab (n=208), or SoC (n=216). At DCO the majority of patients had discontinued study treatment with the main reason being worsening of condition under investigation. Also, there were 45 [21.4%] patients in SoC group who discontinued study treatment due to maximum cycle of chemotherapy reached.
- The reasons for discontinuation from study treatment did not raise any concerns about the conduct of the study.

- The demographics and disease characteristics were generally well-balanced between the treatment groups. The distribution of the demographics and disease characteristics in the China FAS were generally consistent with the global FAS.
  - All patients were Asian.
  - The median age was 63.0 years (range, 20 to 82 years). Over half (60.6%) of patients were aged < 65 years and 4.0% of patients were ≥ 75 years.
  - The majority of patients (82.3%) were male.
  - At baseline, 83.3% of patients had an ECOG PS of 1 (restricted). 78.5% and 21.5% of patients had an PD-L1 expression of ≥ 50% and 25% to 49% (from IWRS), respectively.
  - At diagnosis, 42.9% of patients had a histology type of squamous cell carcinoma, while 57.1% had non-squamous cell carcinoma including adenocarcinoma, large cell carcinoma, and others.
  - As anticipated in this patient population, the majority of patients were former (63.0%) or current (13.2%) smokers.
- Post-discontinuation anticancer treatment was administered in 52.8% of patients, and was comparable between the treatment groups (50.5% and 55.1%, respectively).
  - 40.9% of patients in the durvalumab group and 34.3% of patients in the SoC group received cytotoxic chemotherapy, 27.9% of patients in the durvalumab group and 22.7% of patients in the SoC group received targeted therapy. The proportion of patients receiving immunotherapy was higher in the SoC group than the durvalumab group (25.9% and 9.6%, respectively). In addition, 15.4% of patients in the durvalumab group and 17.1% of patients in the SoC group received radiotherapy.

In the China PD-L1 TC ≥ 25% LREM analysis set:

- The China PD-L1 TC ≥ 25% LREM analysis set included 369 randomized patients.
- The demographics and disease characteristics in the China PD-L1 TC ≥ 25% LREM analysis set was consistent with the China FAS, which was also consistent with the global PD-L1 TC ≥ 25% LREM analysis set.
  - All patients were Asian.
  - The median age was 62.0 years (range, 20 to 82 years). Over half (62.1%) of patients were aged < 65 years and 4.3% of patients were ≥ 75 years.
  - The majority of patients (81.6%) were male.
  - At baseline, 82.9% of patients had an ECOG PS of 1 (restricted). 78.3% and 21.7% of patients had an PD-L1 expression of ≥ 50% and 25% to 49% (from IWRS), respectively.
  - At diagnosis, 43.4% of patients had a histology type of squamous cell carcinoma, while 56.6% had non-squamous cell carcinoma including adenocarcinoma, large cell carcinoma, and others.

- As anticipated in this patient population, the majority of patients were former (63.4%) or current (12.2%) smokers.

Summary of efficacy results

PEARL did not show a statistically significant improvement based on pre-specified criteria in OS for either of the dual primary endpoints.

Global cohort

In the global FAS:

- There was a numerical improvement in OS for the durvalumab group compared with SoC; however, this difference was not statistically significant at the pre-specified level (HR: 0.84; 97.05% CI: 0.693, 1.008; 95% CI: 0.706, 0.989; p = 0.037). The alpha boundaries for FAS and PD-L1 TC ≥ 25% LREM populations are 0.029461 and 0.007445, respectively. These have been calculated by fixing the alpha spent at the interim analysis and lacking of significance for either primary endpoint at the final analysis.
  - Median OS was numerically higher in the durvalumab group (14.6 months, 95% CI: 12.2, 16.9) compared to the SoC group (12.8 months, 95% CI: 10.1, 14.7).
  - The estimated OS24 were 34.6% and 27.2% for the durvalumab and SoC groups, respectively; and OS36 were 23.6% and 17.6%, respectively.
  - Sensitivity analyses showed consistentency with the primary OS analysis.
  - Results of subgroup analyses showed that most of the estimated HRs were in favor of the durvalumab group (HRs < 1) with the exception of the patients with CNS metastases at baseline.
- PFS showed a numerical improvement with durvalumab compared with SoC (HR: 0.77; 95% CI: 0.650, 0.916; p = 0.003). Results of the sensitivity analyses were consistent with those of the main PFS analysis. Results of subgroup analyses showed that the estimated HRs were in favor of the durvalumab group (HRs < 1) except for the following patient subgroups: female patients, patients with PD-L1 TC 25% to 49%, non-squamous + never smoker, non-smoker, and CNS metastasis.
- The ORRs were 37.6% (95% CI: 32.4%, 43.0%) and 37.4% (95% CI: 32.2%, 42.9%) in the durvalumab and SoC groups, respectively.
- The median DoRs were 11.9 and 4.2 months in the durvalumab and SoC groups, respectively. The proportions of responders who remained in response at 18 months were 41.6% and 7.6%, respectively.
- The PFS2 analysis revealed a HR of 0.80 (95% CI: 0.675, 0.938) for durvalumab compared with SoC, which appeared to be predominantly driven by death events as compared to progression events.

In the global PD-L1 TC ≥ 25% LREM analysis set:

- There was no statistically significant difference in OS for the durvalumab group compared with SoC (HR: 0.96; 99.26% CI: 0.741, 1.233; 95% CI: 0.793, 1.151; p = 0.628) at the pre-specified level.
  - Median OS was 14.6 months in the durvalumab group (95% CI: 12.6, 17.2) and 15.0 months (95% CI: 13.1, 16.8) in the SoC group.
  - The estimated OS24 were 34.7% and 32.8% for the durvalumab and SoC groups, respectively; and OS36 were 23.6% and 21.1%, respectively.
  - Sensitivity analyses showed consistency with the primary OS analysis.
  - The results of subgroup analyses showed that the estimated HRs were in favor of the durvalumab group (HRs < 1) except for the following patient subgroups: age ≥ 65 at randomization, PD-L1 TC 25% to 49%, non-squamous + never smoker, non-squamous + former/current smoker, non-squamous, non-Asian, ECOG 0 at baseline, liver metastases at baseline, and CNS metastases at baseline.
- PFS showed a numerical improvement with durvalumab compared with SoC (HR: 0.85; 95% CI: 0.704, 1.030; p = 0.097). The results of subgroup analyses showed that the estimated HRs were in favor of the durvalumab group (HRs < 1) except for the following patient subgroups: female patients, patients with PD-L1 TC 25% to 49%, non-squamous + never smoker, non-smoker, non-Asian, liver metastases at baseline, and CNS metastasis.
- The ORRs were 38.5% (95% CI: 32.7%, 44.5%) and 40.2% (95% CI: 34.3%, 46.3%) in the durvalumab and SoC groups, respectively.
- The median DoRs were 11.6 and 4.2 months in the durvalumab and SoC groups respectively. The proportions of responders who remained in response at 18 months were 40.5% and 8.8%, respectively.
- The PFS2 analysis revealed a HR of 0.89 (95% CI: 0.740, 1.063) for durvalumab compared with SoC, which appeared to be predominantly driven by death events as compared to progression events.

In the global PD-L1 TC ≥ 50% analysis set:

- There was a numerical improvement in OS for the durvalumab group compared with SoC; however, this difference was not statistically significant (HR: 0.80; 96.58% CI: 0.649, 0.993; 95% CI: 0.659, 0.977; p = 0.028).
  - Median OS was numerically higher in the durvalumab group (14.6 months, 95% CI: 12.0, 17.7) compared to the SoC group (11.8 months, 95% CI: 9.8, 14.7).
  - The estimated OS24 were 37.0% and 27.0% for the durvalumab and SoC groups, respectively; and OS36 were 25.0% and 17.0%, respectively.
  - The stratified max-combo test was conducted as a sensitivity analysis and showed a similar result with the OS data in the PD-L1 TC ≥ 50% analysis set (p = 0.0259).
- PFS showed a numerical improvement with durvalumab compared to SoC (HR: 0.69; 95% CI: 0.569, 0.846; p < 0.001).

- The ORRs were 42.1% (95% CI: 35.9%, 48.5%) and 40.7% (95% CI: 34.5%, 47.1%) in the durvalumab and SoC groups, respectively.
- The median DoRs were 12.2 and 4.2 months, in the durvalumab and SoC groups, respectively. The proportions of responders who remained in response at 18 months were 43.3% and 6.3%, respectively.
- The PFS2 analysis revealed a HR of 0.79 (95% CI: 0.651, 0.956) for durvalumab compared with SoC, which appeared to be predominantly driven by death events as compared to progression events.

In the global PD-L1 TC ≥ 50% LREM analysis set:

- There was no improvement in OS for the durvalumab group compared with SoC (HR: 0.91; 96.67% CI: 0.719, 1.152; 95% CI: 0.732, 1.131; p = 0.391). In addition:
  - Median OS was 14.9 months in the durvalumab group (95% CI: 12.6, 19.0) and 14.9 months (95% CI: 11.8, 17.7) in the SoC group.
  - The estimated OS24 were 36.9% and 32.6% for the durvalumab and SoC groups, respectively; and OS36 were 24.9% and 20.3%, respectively.
  - The stratified max-combo test was conducted as a sensitivity analysis and showed a similar result with the OS data in the PD-L1 TC ≥ 50% LREM analysis set (p = 0.3746).
- PFS showed a numerical improvement with durvalumab compared with SoC (HR: 0.73; 95% CI: 0.584, 0.902; p = 0.004).
- The ORRs were 44.0% (95% CI: 37.1%, 51.0%) and 43.7% (95% CI: 36.7%, 50.9%) in the durvalumab and SoC groups, respectively.
- The median DoRs were 12.2 and 4.2 months in the durvalumab and SoC groups, respectively. The proportions of responders who remained in response at 18 months were 41.7% and 7.2%, respectively.
- The PFS2 analysis revealed a HR of 0.86 (95% CI: 0.698, 1.065) for durvalumab compared with SoC, which appeared to be predominantly driven by death events as compared to progression events.

China cohort

Overall, the results in the China cohort were consistent with the global cohort.

In the China FAS:

- There was a numerical improvement in OS for the durvalumab group compared with SoC (HR: 0.84; 95% CI: 0.677, 1.034; p = 0.098).
  - Median OS was numerically higher in the durvalumab group (15.6 months, 95% CI: 12.8, 19.5) over the SoC group (12.8 months, 95% CI: 9.8, 15.2).

  - The estimated OS18 were 44.5% and 37.4% for the durvalumab and SoC groups, respectively, and OS24 were 36.3% and 29.1%, respectively.
- PFS showed a numerical improvement with durvalumab compared with SoC (HR: 0.78; 95% CI: 0.625, 0.972; p = 0.026).
- The ORRs were 36.5% (95% CI: 30.0%, 43.5%) and 40.7% (95% CI: 34.1%, 47.6%) in the durvalumab and SoC groups, respectively.
- The median DoRs were 13.4 and 4.2 months in the durvalumab and SoC groups, respectively. The proportions of responders who remained in response at 18 months were 42.7% and 9.8%, respectively.

In the China PD-L1 TC ≥ 25% LREM analysis set:

- There was no statistically significant difference in OS for the durvalumab group compared with SoC (HR: 0.96; 95% CI: 0.765, 1.204; p = 0.722).
  - Median OS was 15.6 months in the durvalumab group (95% CI: 12.8, 19.0) and 15.2 months (95% CI: 11.2, 18.6) in the SoC group.
  - The estimated OS18 were 43.6% and 43.3% for the durvalumab and SoC groups, respectively, and OS24 were 34.8% and 33.6%, respectively.

In the China PD-L1 TC ≥ 50% analysis set:

- There was a numerical improvement in OS for the durvalumab group compared with SoC; however, this difference was not statistically significant (HR: 0.77; 95% CI: 0.608, 0.983; p = 0.035).
  - Median OS was 16.1 months in the durvalumab group (95% CI: 12.8, 21.6) and 12.8 months (95% CI: 9.3, 15.2) in the SoC group.
  - The estimated OS18 were 46.4% and 37.4% for the durvalumab and SoC groups, respectively, and OS24 were 39.5% and 28.8%, respectively.

In the China PD-L1 TC ≥ 50% LREM analysis set:

- There was no numerical improvement in OS for the durvalumab group compared with SoC (HR: 0.89; 95% CI: 0.688, 1.150; p = 0.373).
  - Median OS was 16.0 months in the durvalumab group (95% CI: 12.8, 21.0) and 14.9 months (95% CI: 11.0, 18.9) in the SoC group.
  - The estimated OS18 were 45.2% and 43.3% for the durvalumab and SoC groups, respectively, and OS24 were 37.4% and 33.2%, respectively.

Summary of patient reported outcomes/quality of life results

In the global FAS:

- Compliance rates for EORTC QLQ-C30 and EORTC QLQ-LC13 were high at baseline and decreased over time. The overall compliance rate was higher in the durvalumab group compared with SoC.
- EORTC QLQ-C30 global health status/QoL and functioning baseline scores were slightly lower (worse) in the durvalumab group. EORTC QLQ-C30 symptoms baseline scores were comparable between groups except fatigue and pain scores that were slightly higher (worse) in the durvalumab group. EORTC QLQ-LC13 baseline scores were comparable between treatment groups, except dyspnea, chest pain, and arm/shoulder pain that were slightly higher (worse) in the durvalumab group.
- There was a benefit of the durvalumab group compared with the SoC group for overall change from baseline in EORTC QLQ-C30 global health status/QoL while there was no significant difference between treatment groups in physical functioning.
- For all global health status/QoL, functioning and symptom scores, median time to deterioration was longer in durvalumab compared with SoC except for arm/shoulder pain.
- There was a benefit of durvalumab group compared with SoC on improvement rates for EORTC QLQ-C30 global health status/QoL and physical functioning, as well as the key symptoms of fatigue and appetite loss; however, there was no significant treatment effect on improvement rate for the key symptom of dyspnea. For EORTC QLQ-LC13, there were no significant difference between the two treatment groups in most scores, except for chest pain and dyspnea, where better improvement rates were observed in the durvalumab group compared with the SoC group.

In the global PD-L1 TC ≥ 25% LREM analysis set, similar evolution was observed compared with the global FAS for EORTC QLQ-C30 and EORTC QLQ-LC13.

Summary of Eastern Cooperative Oncology Group (ECOG) performance score results

ECOG performance status over time was comparable between treatment groups in the FAS and PD-L1 TC ≥ 25% LREM analysis set.

Summary of immunogenicity results

In the ADA evaluable analysis set, the incidence of ADA to durvalumab was low at 0.8% (2/236 patients). There is no clear evidence that the presence of ADAs has any potential impact on safety.

In the ADA evaluable LREM analysis set, the incidence of ADA to durvalumab was low at 1.0% (2/208 patients). There is no clear evidence that the presence of ADAs has any potential impact on safety.

Summary of safety results

- The total treatment duration was longer for the durvalumab group than the SoC group in global safety analysis set based on the study design. The duration of exposure to study treatment in the global PD-L1 TC ≥ 25% LREM safety analysis set and China cohort were generally consistent with the global cohort.

- Overall, the nature and incidence of AEs reported in the durvalumab group were consistent with the known safety profile of durvalumab and in keeping with AEs typically associated with immunotherapy. The safety profile of the SoC group were generally consistent with the known safety profiles of chemotherapy treatment regimens.
- In the global safety analysis set, 92.2% and 94.2% of patients treated with durvalumab and SoC experienced at least one AE. The most common AEs by PT reported (in > 10% of patients) in the durvalumab group were anaemia, decreased appetite, hypothyroidism, pneumonia, pyrexia, weight decreased, asthenia, hypoalbuminaemia, and upper respiratory tract infection. In addition to these AEs, the incidence of the following lab abnormalities frequently reported as AEs in the China cohort (> 10%), such as alanine aminotransferase increased, aspartate aminotransferase increased, hyponatraemia, hepatic function abnormal, and hypokalaemia.
- The incidence of maximum CTCAE Grade 3 or 4 AEs was lower in the durvalumab group compared to the SoC group (35.2% and 53.2%, respectively). Grade 3 or 4 hematological AEs were reported more frequently in the SoC group than the durvalumab group, which is consistent with the safety profile of SoC chemotherapy. The incidence of Grade 3 or 4 AEs was higher in the China cohort versus global which may be attributed to higher reporting of lab abnormalities as AEs.
- The rates of discontinuation of study drug due to AEs was similar in the durvalumab group (14.6%) and the SoC group (15.9%).
- SAEs occurred in a higher proportion of patients in the durvalumab group (39.4%) than in the SoC group (31.8%). The most frequently reported SAEs by PT (≥ 2% of patients) in the durvalumab group were pneumonia and death (death of unknown cause). In the SoC group, the most frequently reported SAEs by PT were anaemia, pneumonia, myelosuppression, and platelet count decreased.
- The incidence of AEs with an outcome of death was higher in the durvalumab group (11.0%) compared to the SoC group (3.1%). This could be explained by the longer duration of exposure in the durvalumab arm than in the SoC arm (median exposure 28 weeks versus 16 weeks, respectively). The most frequently reported (> 1 patients) AEs by PT leading to death in the durvalumab group were death (death of unknown cause;7 patients), disseminated intravascular coagulation and respiratory failure (each in 3 patients), pneumonia, completed suicide, dyspnoea, multiple organ dysfunction syndrome, and pulmonary embolism (each in 2 patients); the most frequently reported event leading to death in the SoC group was dyspnoea (2 patients). These events occurring in both arms were likely related to the complications of the underlying disease (NSCLC) or due to disease progression. The incidence of fatal AEs considered possibly related to treatment by the Investigator was low in both groups: 8 (2.4%) and 3 (0.9%) patients in the durvalumab and the SoC groups, respectively. In the China cohort, reports of AEs with an outcome of death were higher in the durvalumab group (10.6%) than the SoC group (1.4%) which was similar to the global cohort. The fatal AEs do not raise a safety concern and the safety profile observed in the durvalumab group in the study remains consistent with the overall durvalumab safety profile.
- Consistent with the immune-mediated mechanism of action for immunotherapy treatments, there was a higher incidence in the durvalumab group compared with the SoC group of AESIs or AEPIs (53.7% versus 39.8%, respectively) and imAEs (20.0% versus

1.2%, respectively). imAEs with a maximum CTCAE Grade 3 or 4 were reported in 5.7% of patients in the durvalumab group and 0.3% of patients in the SoC group. In the China cohort, the trends for AESI or AEPI were consistent with the global cohort.

- No major differences in all AE categories were noted between the PD-L1 TC ≥ 25% LREM patients of the safety analysis set and the overall safety analysis set in the global cohort. Safety data of the China cohort was generally consistent with the global cohort.

Conclusion(s)

- PEARL did not meet its dual primary objectives. No statistically significant improvement was observed in OS in patients who received durvalumab compared with SoC with PD-L1 TC ≥ 25% and PD-L1 TC ≥ 25% LREM at the pre-specified level; however, there was a numerical improvement in patients with PD-L1 TC ≥ 25%. OS HR of the China cohort in patients with PD-L1 TC ≥ 25% showed a similar trend as compared to the global cohort.
- While the results in PEARL did not reach the pre-specified statistical significance, the trial showed a numerical improvement in both OS and PFS with durvalumab monotherapy.
- The key secondary endpoints of OS in patients with PD-L1 ≥ 50% and in PD-L1 ≥ 50% LREM could not be statistically tested; however, there was a numerical improvement in patients with PD-L1 TC ≥ 50%. In addition, a numerical PFS improvement and longer DoR were observed in patients receiveing durvalumab compared with SoC. The results of China cohort were consistent with the results of the global cohort.
- Durvalumab demonstrated a tolerable and manageable safety profile for the treatment of patients with tumors that lacked sensitizing EGFR mutation and ALK rearrangement and with PD-L1 high expression. Generally, the safety profile in the patients receiving durvalumab were consistent with the established safety profile of durvalumab to date. No new safety signals were identified.