Clinical Study Report Synopsis

Drug Substance	Durvalumab (MEDI4736)
Study Code	D4191C00001
Edition Number	01
Date	20 Jul 2017
EudraCT Number	2014-000336-42

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Study dates: First patient enrolled: 9 May 2014
Last patient enrolled: 22 April 2016
Data cut-off: 13 February 2017 (study ongoing)

Phase of development: III

International Co-ordinating Investigator: PPD
Tampa, FL 33612, United States.

Sponsor's Responsible Medical Officer: PPD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

This ongoing study is being conducted at study centers in North and Latin America, Europe, and Asia Pacific. A total of 308 study centers in 28 countries were selected for this study, of which 235 study centers in 26 countries enrolled patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of durvalumab (MEDI4736) treatment compared with placebo in terms of OS and PFS	PFS using BICR assessments according to RECIST 1.1[a] OS

a The co-primary analysis of PFS is based upon programmatically derived PFS using BICR assessments according to RECIST 1.1. See Section 12.2.2 of the CSP for further details (Appendix 12.1.1).
BICR Blinded Independent Central Review; CSP clinical study protocol; OS overall survival; PFS progression-free survival; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 11.

Table S2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of durvalumab compared with placebo in terms of: OS24, ORR, DoR, APF12, APF18, PFS2, and TTDM	OS24 ORR using BICR assessments according to RECIST 1.1[a] DoR using BICR assessments according to RECIST 1.1[a] APF12 and APF18 using BICR assessments according to RECIST 1.1 PFS2 as defined by local standard clinical practice TTDM using BICR assessments according to RECIST 1.1
To assess the safety and tolerability profile of durvalumab compared with placebo	AEs, physical examinations, vital signs including blood pressure, pulse, ECGs, and laboratory findings including clinical chemistry, hematology, and urinalysis
To assess the PK of durvalumab	Concentration of durvalumab in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of durvalumab	ADA (confirmatory results: positive or negative; titers [ADA neutralizing antibodies will also be assessed])

Secondary Objective:	Outcome Measure:
To assess symptoms and health-related quality of life in patients treated with durvalumab compared with placebo using EORTC QLQ-C30 and EORTC QLQ-LC13	EORTC QLQ-C30: Time to symptom deterioration (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Time to QoL/function deterioration (physical function; role function; emotional function; cognitive function; social function, and global health status/QoL) EORTC QLQ-LC13: Time to symptom deterioration (dyspnea, cough, hemoptysis, and pain) Changes in World Health Organization Performance Status will also be assessed

a Analysis of ORR and DoR is based upon BICR assessment according to RECIST 1.1. See Sections 12.2.3 and 12.2.5 of the CSP for further details (Appendix 12.1.1).

Note: Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

ADA antidrug antibody; AE adverse event; APF12 proportion of patients alive and progression free at 12 months from randomization; APF18 proportion of patients alive and progression free at 18 months from randomization; BICR Blinded Independent Central Review; CSP clinical study protocol; DoR duration of response; ECG electrocardiogram; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and Lung Cancer Module; ORR objective response rate; OS24 proportion of patients alive at 24 months from randomization; PFS2 time from randomization to second progression; PK pharmacokinetic(s); QoL quality of life; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1; TTDM time to death or distant metastasis.

Table S3 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To explore irRC criteria as an assessment methodology for clinical benefit of durvalumab compared with placebo by BICR	PFS and ORR using BICR assessments according to irRC
To investigate the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs and/or safety parameters, if deemed appropriate	A graphical and/or a data modelling approach will be used to analyze durvalumab PK exposure and the relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate
To describe and evaluate resource use associated with durvalumab treatment and underlying disease	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data
To investigate the relationship between a patient's PD-L1 expression and spatial distribution within the tumor microenvironment and efficacy outcomes with durvalumab	Tumoral expression of PD-L1 and spatial distribution within the tumor microenvironment relative to efficacy outcomes (OS, PFS, and ORR)

Exploratory Objective:	Outcome Measure:
To collect blood and tissue samples for analysis of peripheral and tumoral biomarkers	Biomarker analysis of blood and tissue to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles within the peripheral and tumoral compartments, the presence of IFN-γ, TNF-α, IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumor, self, or viral antigens, expression of PD-L1 and the number and phenotype of immune cells such as T-cells
To explore the relationship(s) between a patient's biomarker status and durvalumab PK exposure and clinical outcomes before and after treatment	Biomarker status before and after treatment and durvalumab PK exposure and relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate
To explore potential biomarkers in residual biological samples (eg, tumor, plasma and/or serum), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to durvalumab treatment	Correlation of biomarkers with response to durvalumab treatment and/or the progression of cancer
To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study drugs and/or susceptibility to disease (optional)	Correlation of polymorphisms with variation in PK, PDx, safety or response parameters observed in patients treated with durvalumab and/or susceptibility to disease

AE adverse event; BICR Blinded Independent Central Review; EQ-5D-5L EuroQoL 5 Dimension, 5 Level Health State Utility Index; IFN interferon; IL interleukin; irRC immune-related response criteria; ORR objective response rate; PD-L1 programmed death ligand 1; PDx pharmacodynamic(s); PFS progression free survival; PK pharmacokinetic(s); TNF tumor necrosis factor.

Study design

This is an ongoing randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable Stage III Non-Small Cell Lung Cancer (NSCLC), who have not progressed following definitive, platinum-based cCRT (concurrent chemoradiotherapy).

Patients were randomized in 2:1 ratio to durvalumab or placebo, and stratified according to age (<65 vs ≥65 years of age), sex (male vs female), and smoking history (smoker vs non-smoker). Patients in the durvalumab monotherapy group were to receive durvalumab intravenously at 10 mg/kg every 2 weeks (Q2W) for up to 12 months. Patients in the placebo group were to receive matching placebo infusion Q2W for up to 12 months.

Target subject population and sample size

Approximately 880 patients with locally advanced, unresectable Stage III NSCLC were planned to be recruited to randomize 702 patients at 260 to 330 sites in Australia, Asia, Europe, North and South America, and South Africa.

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

Durvalumab (MEDI4736), manufactured by the Sponsor, was provided at a concentration of 200 mg/vial for intravenous infusion after dilution to 50 mg/mL. Batch numbers used in this study were CCI [redacted] Placebo, which was sourced locally, was provided as a matching saline solution for intravenous infusion.

Duration of treatment

Administration of study treatment (ie, durvalumab or placebo) was started on Day 1 following randomization to durvalumab or placebo after confirmation of eligibility and continued Q2W for a maximum duration of 12 months (maximum of 26 doses, last dose at Week 50). Study treatment was to be discontinued prior to 12 months if there was confirmed progression of disease (unless the Investigator considered that the patient continued to receive benefit from the study drug), upon initiation of alternative cancer therapy, unacceptable toxicity, upon withdrawal of consent, or when other reasons to discontinue the study drug occurred.

For all patients who completed the first 12-month period of treatment with study drug and had complete response (CR), partial response (PR), or stable disease (SD) at completion, retreatment (ie, with the same blinded study drug that the patient received in the first 12 months) during follow-up was offered as an option on the basis of a patient having objective Response Evaluation Criteria In Solid Tumors (RECIST 1.1) PD, with or without confirmation subsequently.

For all patients who were treated through progression, or patients who achieved disease control [ie, CR, PR, or SD] at 12 months and restarted treatment upon evidence of PD during follow-up, the Investigator should have ensured that patients did not have any significant, unacceptable, or irreversible toxicities that indicated that continuing or restarting treatment would not further benefit the patient. The maximum duration of retreatment was 12 months.

Statistical methods

The clinical study report provides data from the first data cut-off of 13 February 2017, which was a planned interim analysis of progression free survival (PFS). The interim PFS analysis was conducted when 371 events (81%) of the target 458 events were observed. Since the study achieved statistical significance based on this analysis, this is now considered as the final PFS analysis.

Statistical analyses were performed in accordance with the comprehensive Statistical Analysis Plan, which details all analyses to be performed and summaries to be produced, and the analysis sets upon which they were to be based.

<u>Full Analysis Set</u>

The primary statistical analysis of the efficacy of durvalumab vs placebo included all randomized patients and compared the treatment groups on the basis of randomized treatment,

regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study drug were included in the full analysis set (FAS - also called Intent-to-treat [ITT]) population. Therefore, all efficacy and health-related Quality of Life data were analyzed using the FAS on an ITT basis.

Safety Analysis Set

All patients who received at least 1 dose of randomized study drug durvalumab or placebo (regardless of whether that was the randomized therapy intended or indeed whether, in rare cases, they received therapy without being randomized) were included in the safety population. Erroneously treated patients (eg, those randomized to Treatment A but given Treatment B) were accounted for by the actual treatment administered.

Pharmacokinetics analysis set

All patients who received at least 1 dose of durvalumab per the protocol, for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the pharmacokinetics (PK) analyses, were included in the PK analysis set.

In general, for efficacy and patient-reported outcome (PRO) endpoints, the last observed measurement prior to randomization was considered to be the baseline measurement. However, if an evaluable assessment was available only after randomization but before the first dose of randomized treatment, then this assessment was used as baseline. For safety endpoints, the last observation before the first dose of study treatment was considered the baseline measurement unless otherwise specified.

Efficacy and PRO data were summarized and analyzed based on the FAS. Safety data were summarized and analyzed based on the Safety Analysis Set. PK data were summarized and analyzed based on the PK Analysis Set. Study population and demography summaries were summarized by FAS.

Subject population

A total of 983 patients were enrolled in 235 study centers across 26 countries. Of these, 713 patients were randomized in 2:1 ratio to receive either durvalumab 10 mg/kg Q2W (476 patients) or placebo (237 patients).

Of the 713 patients, 709 (473 [99.4%] in the durvalumab group and 236 [99.6%] in the placebo group) received study treatment. Four patients (3 [0.6%] in the durvalumab group and 1 [0.4%] in the placebo group) were randomized but did not receive study treatment because of patient decision (2 patients), neutropenia (1 patient), and worsening chronic obstructive pulmonary disease (1 patient).

The first patient was randomized into the study on 09 May 2014, and the last patient was randomized on 22 April 2016. At the time of the cut-off date of 13 February 2017, 273 patients (202 [42.7%] in the durvalumab group and 71 [30.1%] in the placebo group) had

completed the protocol-defined 12 months of treatment. Treatment had been discontinued prior to the defined 12 months of treatment in 241 (51.0%) patients in the durvalumab group and 153 (64.8%) patients in the placebo group. Main reasons for discontinuation of study treatment were worsening of disease progression (148 [31.3%] and 116 [49.2%] of patients in the durvalumab and placebo groups, respectively), adverse events (AEs) (73 [15.4%] and 23 [9.7%] of patients in the durvalumab and placebo groups, respectively) and patient decision (14 [3.0%] and 12 [5.1%] of patients in the durvalumab and placebo groups, respectively). Treatment was ongoing in 30 (6.3%)patients in the durvalumab group and 12 (5.1%) patients in the placebo group.

The demographics were representative of the intended patient population and were well balanced between randomized treatment groups. Specifically, patients had a median age of 64 years, 70.1% were male, and, in terms of Race, 69.3% were White. Most (91%) were current or former smokers.

The disease characteristics were also representative of the intended patient population and were well balanced between the durvalumab and placebo treatment groups: baseline WHO performance status of 0 (49.2% vs 48.1%, respectively), squamous histology (47.1% vs 43.0%, respectively); and stage (Stage IIIA [52.9% vs 52.7%, respectively] and Stage IIIB [44.5% vs 45.1%, respectively]).

Specific molecular characteristics (PD-L1 and epidermal growth factor receptor [EGFR]) were generally well balanced between the 2 treatment groups:

- PD-L1 status was retrospectively analyzed in patients with available samples. These samples were obtained prior to cCRT. Of the 713 patients, 451 (63.3%) patients had a PD-L1 status result. The overall prevalence was 35.3% (159/451) for PD-L1 TC ≥25% (≥25% tumor cells [TC] expressing PD-L1 on the membrane) and 64.7% (292/451) for PD-L1 TC<25% (<25% of TC expressing PD-L1 on the membrane).

- The percentage of patients with PD-L1 TC ≥25% was 24.2% (115/713) were in the durvalumab group and 18.6% (44/713) were in the placebo group. The percentage of patients with PD-L1 TC <25% was 39.3% (187/713) in the durvalumab group and 44.3% (105/713) in the placebo group. The percentage of patients with PD-L1 unknown status was balanced between the 2 treatment groups (36.6% [174/713] for durvalumab and 37.1% [88/713] for placebo).

- Of the 713 patients, 523 (73.3%) had available EGFR test result (combined local and central testing results). The overall prevalence of EGFR mutation rate was 8.2% (43/523). EGFR mutations were observed in 6.0% of patients (6.1% in the durvalumab group and 5.9% in the placebo group), whereas 67.3% of patients' tumors were EGFR wild-type (66.2% in the durvalumab group and 69.6% in the placebo group). The EGFR status was unknown in 27.7% of patients in the durvalumab group and 24.5% of patients in the placebo group. Considering the patients in this study were predominantly smokers, 70.1% male, 69.3% White

Caucasian, and 45.7% with tumor squamous histology, the EGFR mutation rate prevalence was as expected

Over 90% of patients received the protocol-intended cCRT of at least 2 cycles of platinum-based doublet chemotherapy concurrent with radiation therapy (54 to 66 Gy) prior to randomization in the study and was well balanced between the groups. Response to prior cCRT was well balanced between the 2 groups (best response to prior therapy: 1.9% vs 3.0% of patients with CR, 48.7% vs 46.8% of patients with PR, and 46.6% vs 48.1% of patients with SD in the durvalumab and placebo groups, respectively).

The medical and surgical history as well as the types of concomitant medication used were typical for this population.

The incidence of important protocol deviations was low (2.9% of the total population) and those observed do not raise any concerns regarding the overall conduct or quality of the study.

Summary of efficacy results

- Durvalumab treatment demonstrated a statistically significant (HR: 0.52; 98.9% CI: 0.39, 0.70; p-value less than 0.0001) and clinically meaningful prolongation of PFS (according to BICR assessment of RECIST 1.1) compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.
  - The risk of progression or death was reduced by 48% on the durvalumab treatment compared with placebo.
  - The durvalumab treatment demonstrated a median PFS improvement of 11.2 months when compared with placebo (the median PFS was 16.8 months in the durvalumab group and 5.6 months in the placebo group).
  - The treatment effects were observed early and sustained over time, as supported by the estimates of the PFS rates at 12 months (55.9% in the durvalumab group and 35.3% in the placebo group) and 18 months (44.2% and 27.0%, respectively). The 95% CIs for both APF12 and APF18 did not overlap, demonstrating a substantial increase in progression-free rates at 12 and 18 months of durvalumab over placebo.
- The PFS was robust and consistent in favor of durvalumab across all prespecified sensitivity analyses, including the PFS analysis based on Investigator's assessment.
- The PFS benefit of the durvalumab treatment was observed consistently across subgroups defined by region, demographics, prior chemo-radiation, and baseline characteristics.

- The PFS benefit in favor of durvalumab was observed irrespective of PD-L1 expression (HR: 0.59; 95% CI: 0.43, 0.82 for less than 25% and HR: 0.41, 95% CI: 0.26, 0.65 for at least 25%).

- The numbers of patients with EGFR mutation positive tumors was small with few events; thus interpretation of this subgroup should be with caution, nevertheless the HR for the EGFR mutant subgroup was 0.76, in favor of durvalumab, with a wide confidence interval that crossed 1.0.

- The improvement of PFS is supported by the clinical meaningful incremental ORR of 12% over placebo (28.4% in the durvalumab group vs 16.0% in the placebo group; nominal p-value less than 0.001).

- The responses were durable with the median DoR not reached in the durvalumab group, compared to 13.8 months in the placebo group.

- TTDM was longer for the durvalumab group compared to the placebo group (HR: 0.52; 95% CI: 0.39, 0.69; nominal p-value less than 0.0001). The median TTDM was 23.2 months in the durvalumab group, compared to 14.6 months in the placebo group.

- Patient reported outcome data showed high level of compliance (greater than 80%) for both groups for up to 60 weeks. Results across all sub-scales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.

- The data on OS were immature at the time of the interim analysis of the PFS, as the number of events required for the planned first OS interim analysis had not been reached at the time of this PFS analysis.

Summary of pharmacokinetic results

The PK concentration of durvalumab in this patient population was in line with PK observations from previous studies and typical of a fully human immunoglobulin (Ig)G1 monoclonal antibody at the intravenous dose of 10 mg/kg Q2W. Based on previous studies, the concentration in this study is expected to be sufficient to achieve soluble PD-L1 suppression.

Overall, PK exposure of durvalumab were similar between antidrug antibody (ADA) evaluable patients and ADA negative patients, indicating that the impact of immunogenicity on PK exposure of durvalumab was minimal.

Summary of immunogenicity results

From the data, there is no clear evidence that the presence of ADAs or neutralizing antibodies has any potential impact to safety. The impact of ADAs on the clinical efficacy of durvalumab in NSCLC patients was not evaluable.

Summary of safety results

- All patients were required to have completed definitive platinum-based cCRT prior to study entry. Given the nature of cCRT and variable time for resolution of cCRT-associated toxicities, patients receiving placebo played an important role in the interpretation of toxicities in this study. The placebo-control study design provided an accurate assessment of safety of durvalumab in the appropriate context of background AEs as seen in patients receiving placebo.

- At the time of interim PFS analysis, the extent of exposure and follow-up was adequate to characterize the safety profile of durvalumab 10 mg/kg Q2W. The mean relative dose intensity was similar between the treatment groups, indicating most patients were able to tolerate durvalumab treatment.

- Overall, durvalumab was well-tolerated and had a manageable safety profile relative to the standard of care for the population under study. Generally, the type, incidence, and severity of AEs were comparable between the treatment groups. Where not comparable, the type, incidence, and severity of events were consistent with the established durvalumab safety profile to date, with the exception of the events of pneumonitis/radiation pneumonitis.

- In general, as expected in this patient population, there was a high background incidence of radiation pneumonitis and pneumonitis. Technically, these events were difficult to distinguish from each other radiologically or clinically. The report terms of individual events were based on Investigators' judgment. These events were then carefully assessed through collecting additional information and a Sponsor adjudication of all cases independently from the study team and prior to unblinding.

- Pneumonitis and radiation pneumonitis were notable events in multiple AE categories. There was a numerical increase in these events for patients receiving durvalumab over those receiving placebo, however most of these events were low grade. Clinically important CTCAE Grade 3 or 4 events were infrequent and balanced between the 2 treatment groups.

- The AESIs/imAEs were generally manageable and/or reversible with appropriate medical management, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

- The most common AEs included cough (35.4% vs 25.2% for durvalumab and placebo, respectively), fatigue (23.8% vs 20.5%), dyspnea (22.3% vs 23.9%), radiation pneumonitis (20.2% vs 15.4%), and diarrhea (18.3% vs 18.8%).

- AEs of CTCAE Grade 3 or 4 were reported in 32% of patients treated with durvalumab and 27.8% of patients treated with placebo. The most common CTCAE Grade 3 or 4 AEs included pneumonia (4.4% vs 4.3% for durvalumab and placebo, respectively), anemia (2.9% vs 3.4%), hypertension (2.1% vs 0.9%), and pneumonitis (1.7% vs 2.1%).

- SAEs were reported in 28.6% and 22.6% of patients receiving durvalumab and placebo, respectively. The SAEs most frequently reported were pneumonia (5.7% vs 5.1% for durvalumab and placebo groups, respectively), pneumonitis (3.4% vs 3.0%, respectively), and radiation pneumonitis (3.6% vs 1.3%. respectively).

- AEs leading to discontinuation were reported in 15.4% and 9.8% of patients receiving durvalumab and placebo, respectively. AEs leading to discontinuation reported in 2 or more patients were pneumonitis (4.8% vs 2.6% of patients receiving durvalumab and placebo, respectively), radiation pneumonitis (1.3% vs 1.3%, respectively), and pneumonia (1.1% vs 1.3%, respectively).

- AEs with an outcome of death were comparable between treatment groups (4.4% vs 6.0% of patients receiving durvalumab and placebo, respectively).

- AESIs were reported in 66.1% 48.7% of patients treated with durvalumab and placebo, respectively.

  – The most frequently reported AESIs were dermatitis or rash (32.6% vs 17.9%), diarrhea (18.3% vs 19.2%), pneumonitis (13.7% vs 9.4%), and hypothyroidism (13.3% vs 3.0%) for patients receiving durvalumab and placebo, respectively.

  – Thyroid dysfunction was manageable with endocrine therapies and steroids, as applicable. Rash was generally manageable with short courses of topical or systemic steroids.

  – AESIs of maximum CTCAE Grade 3 or 4 were reported in 8.2% and 3.8% of patients treated with durvalumab and placebo, respectively. AESIs that led to discontinuation of study medication occurred in 7.4% and 3.8% of patients treated with durvalumab and placebo, respectively. AESIs that resulted in at least 1 dose delay occurred in 13.7% patients treated with durvalumab and 5.6% of patients treated with placebo.

  – AESIs with an outcome of death occurred in 4 (0.8%) patients treated with durvalumab (4 pneumonitis) and 4 (1.7%) patients treated with placebo (3 pneumonitis and 1 eosinophilic myocarditis).

- AESIs requiring concomitant treatment were reported in 42.1% and 17.1% of patients treated with durvalumab and placebo, respectively. Concomitant treatments for AESIs included steroids (15.2% vs 6.8% for durvalumab and placebo, respectively), high-dose steroids (8.8% vs 5.1%), endocrine therapy (11.6% vs 1.3%) or other immunosuppressants (0.4% for both treatment groups).

- Infusion-related reactions were reported in 5 (1.1%) patients receiving durvalumab. No patient receiving placebo reported an infusion-related reaction.

- The AESI of pneumonitis was reported in 13.7% and 9.4% of patients receiving durvalumab and placebo, respectively. Radiation pneumonitis was reported in 20.2% and 15.4% of patients treated with durvalumab and placebo, respectively. An event of either pneumonitis or radiation pneumonitis was reported for 33.9% of patients receiving durvalumab and 24.8% of patients receiving placebo.

- Clinically important CTCAE Grade 3 pneumonitis or radiation pneumonitis was balanced between the 2 treatment groups, and occurred in 3.4% and 2.6% of patients receiving durvalumab and placebo, respectively. No Grade 4 events of pneumonitis or radiation pneumonitis were reported in either treatment group. Fatal events of pneumonitis or radiation pneumonitis were also balanced between the 2 treatment groups, and occurred in 1.1% of patients treated with durvalumab and 1.7% of patients treated with placebo.

- Consistent with the immune-mediated mechanism of action for durvalumab, there was a higher incidence of imAEs for patients receiving durvalumab (24.2% of patients) compared with patients receiving placebo (8.1% of patients).

  - imAEs of CTCAE Grade 3 or 4 were reported for 3.4% and 2.6% of patients receiving durvalumab and placebo, respectively.

  - imAEs for patients on durvalumab required systemic steroids (for 14.3% of patients), high-dose steroids (8.2%), endocrine therapy (10.7%) and other immunosuppressants (0.4%). For imAEs in patients on placebo, systemic steroids, high-dose steroids, endocrine therapy and other immunosuppressants were required in 5.6%, 4.3%, 1.3%, and 0.4% of patients, respectively.

- There was a slight increase in the overall AEs in the SOC of infections and infestations regardless of causality (56.0% and 46.6% for patients receiving durvalumab and placebo, respectively). For the majority of patients, infection AEs were CTCAE Grade 1 or 2. Grade 3 or higher infection AEs, infection SAEs, as well as infection AEs that led to discontinuation were similar between the treatment groups.

- With regard to clinical laboratory evaluations:
  - No clinically important changes from baseline or trends in hematology values over time were observed in either treatment group.
  - Sixteen (3.4%) patients receiving durvalumab and 1 (0.4%) patient receiving placebo had a Grade 3 ALT or AST value greater than 5 ×ULN. Four patients (all receiving durvalumab) had an ALT or AST value greater than 10 x ULN. There were no patients who met the biochemical criteria for a potential Hy's Law case. Two patients receiving durvalumab discontinued due to increases in Grade 3 transaminases.
  - No patient in either treatment group had post-baseline changes in creatinine values greater than CTCAE Grade 2.
  - TSH values greater than 10 x ULN were reported for 4.8% patients of treated with durvalumab and 0.4% of patients treated with placebo.
- No notable changes from baseline in vital signs were observed in either treatment group.
- There was no clear evidence of any potential impact of ADA status on safety. AEs were reported for 17 of 18 ADA positive patients compared with 373 of the 383 ADA negative patients.

Conclusions

- Durvalumab treatment demonstrated a statistically significant (HR: 0.52; 98.9% CI: 0.39, 0.70; p-value less than 0.0001) and clinically meaningful prolongation of PFS compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after platinum-based cCRT.
  - The risk of progression or death was reduced by 48% on the durvalumab treatment compared with placebo.
  - The durvalumab treatment demonstrated a median PFS improvement of 11.2 months when compared with placebo (the median PFS was 16.8 months in the durvalumab group and 5.6 months in the placebo group).
  - The treatment effects were sustained over time, as supported by the estimates of the 12-month PFS (55.9% in the durvalumab group and 35.3% in the placebo group) and 18-month PFS (44.2% and 27.0%, respectively). The CIs for both APF12 and APF18 didn't overlap, demonstrating a substantial increase of progression-free rates at 12 and 18 months of durvalumab over placebo.

  - The PFS benefit with durvalumab was consistent across all subgroups, including tumor PD-L1 expression levels.

- The PFS benefits was supported by the incremental increase of 12% in ORR, longer duration of response, and prolonged TTDM

- Durvalumab treatment demonstrated a well-tolerated and manageable safety profile. In general, the safety profile observed in this study was consistent with the established safety profile to date with the exception of the events of pneumonitis/radiation pneumonitis. Pneumonitis and radiation pneumonitis were notable events in multiple AE categories. There was a numerical increase in these events in the durvalumab group over placebo, but most of these events were low grade and manageable. Clinically important CTCAE Grade 3 and above events were infrequent and balanced between the 2 groups.

- In addition to pneumonitis, the other AESIs and imAEs reported in the study were typical of the PD-1/PD-L1 class of immunotherapies and were generally manageable and/or reversible with appropriate treatment guidelines, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

- Taken together, the overall benefit/risk of durvalumab treatment is highly favorable in the indicated patient population.

Clinical Study Report Addendum

Drug Substance	Durvalumab
Study Code	D4191C00001
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Date	17 August 2018
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A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Study dates:	First patient randomized: 09 May 2014 Last patient randomized: 22 April 2016 Data cut-off date: 22 March 2018 (study ongoing)
Phase of development:	III
International Co-ordinating Investigator:	PPD Tampa, FL 33612, United States.
Sponsor's Responsible Medical Officer:	PPD AstraZeneca LP PPD Gaithersburg, MD 20878

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

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12.2 Patient Data Listings

If required by a regulatory authority, Appendices 12.3 Case Report Forms and 12.4 Individual Patient Data (listings) will be included in the appropriate section of the application.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APF12	proportion of patients alive and progression-free at 12 months from randomization
APF18	proportion of patients alive and progression-free at 18 months from randomization
AST	aspartate aminotransferase
BICR	blinded independent central review
cCRT	concurrent chemoradiation therapy
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor DNA
CV	coefficient of variance
DoR	duration of response
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer quality of life questionnaire and lung cancer module
FAS	full analysis set
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase

Abbreviation or special term	Explanation
HR	hazard ratio
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LS	least squares means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
nAb	neutralizing antibody
NR	not reached/not reported
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
Q2W	every 2 weeks
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RT	radiotherapy
SAE	serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SD	stable disease or standard deviation
SOC	system organ class
TC	tumor cell
$t_{½}$	half-life
TFST	time to first subsequent therapy or death
TSH	thyroid stimulating hormone
TTDM	time to death or distant metastasis
ULN	upper limit of normal
WHO	World Health Organization

1. ETHICS

For information on ethics, please refer to Section 1, PACIFIC Interim CSR, Module 5.3.5.1.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

For information on study personnel and administrative structure, please refer to Section 2, PACIFIC Interim CSR, Module 5.3.5.1.

3. INTRODUCTION

PACIFIC (D4191C00001) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multi-center, global clinical study designed to evaluate the efficacy and safety of durvalumab (IMFINZI™) compared with placebo in patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemoradiation. The primary objective is to assess the efficacy of durvalumab compared with placebo in terms of progression-free survival (PFS; based on blinded independent central review [BICR]) and overall survival (OS). Secondary efficacy endpoints included OS at 24 months, objective response rate (ORR), duration of response (DoR), time to death or distant metastases (TTDM), time to second progression or death (PFS2), and patient-reported outcome (PRO). Time to first subsequent therapy or death (TFST) was derived as a supportive summary to PFS and time to second subsequent therapy or death (TSST) was derived as a supportive summary to PFS2.

Three interim analysis were planned for this study: 1 for PFS and 2 for OS. The planned interim analysis of PFS was conducted after 371 events (80%) of the target 458 events were observed (DCO: 13 February 2017). Based on the review of that interim analysis, the Sponsor unblinded the study for PFS and safety. Since the study achieved statistical significance based on this analysis, that analysis was considered to be the final PFS analysis.

The first planned interim analysis of OS was conducted after 299 (61%) of the target 491 deaths were observed (DCO: 22 March 2018). Results from the interim OS analysis were reviewed by the IDMC on 21 May 2018. Since the study achieved the statistical significance level of ≤ 0.00274 that met the predefined criterion for unblinding the OS data, the results of this first interim OS analysis (as presented in this addendum) will now be considered as the final OS analysis. Patients will continue to be followed for long-term survival and updated OS analyses will be presented in future reports, as needed.

This CSR addendum reports updated efficacy and safety data from the planned interim analysis of OS at the data cut-off (DCO) date of 22 March 2018, when 299 events (60.9%) of the target 491 events were observed.

The PACIFIC Interim CSR provides complete information on study design, plan and procedures, etc. To avoid repetition, this information is not included in this Addendum. All tables, figures and listings that were generated based on the 22 March 2018 DCO are shown in Section 11, including new outputs for the OS results and secondary endpoints of time to PFS2 and TSST; updated results for the secondary/supportive efficacy parameters of OS24, ORR, DoR, TFST, TDDM, and patient-reported outcomes (PRO); and updated results for the primary safety parameters (ie, adverse events [AEs], serious adverse events [SAEs], deaths). Due to the small number of patients still ongoing study treatment at the time of the initial data cut-off (42 patients: 30 in the durvalumab group, 12 in the placebo group), the additional safety data are limited, thus other safety sections will primarily refer to the full results in the Interim CSR.

4. STUDY OBJECTIVES

4.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of durvalumab treatment compared with placebo in terms of OS and PFS	PFS using BICR assessments according to RECIST 1.1[a] OS

BICR = blinded independent central review; OS = overall survival; PFS = progression-free survival; RECIST 1.1= Response Evaluation Criteria In Solid Tumors version 1.1.

a The primary analysis of PFS is based on programmatically derived PFS using BICR assessments according to RECIST 1.1. For further details, see Section 12.2.2 of the CSP (Appendix 12.1.1).

4.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of durvalumab compared with placebo in terms of: OS24, ORR, DoR, APF12, APF18, PFS2, and TTDM	OS24 ORR using BICR assessments according to RECIST 1.1a DoR using BICR assessments according to RECIST 1.1a APF12 and APF18 using BICR assessments according to RECIST 1.1 PFS2 as defined by local standard clinical practice TTDM using BICR assessments according to RECIST 1.1
To assess the safety and tolerability profile of durvalumab compared with placebo	AEs, physical examinations, vital signs including blood pressure, pulse, ECG, and laboratory findings including clinical chemistry, hematology, and urinalysis
To assess the PK of durvalumab	Concentration of durvalumab in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of durvalumab	ADA (confirmatory results: positive or negative; titers [ADA neutralizing antibodies will also be assessed])

Secondary Objective:	Outcome Measure:
To assess symptoms and health-related quality of life in patients treated with durvalumab compared with placebo using EORTC QLQ-C30 and EORTC QLQ-LC13	EORTC QLQ-C30: Time to symptom deterioration (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Time to QoL/function deterioration (physical function; role function; emotional function; cognitive function; social function, and global health status/QoL) EORTC QLQ-LC13: Time to symptom deterioration (dyspnea, cough, hemoptysis, and pain) Changes in WHO performance status will also be assessed

ADA = antidrug antibody; AE = adverse event; APF12 = proportion of patients alive and progression-free at 12 months from randomization; APF18 = proportion of patients alive and progression-free at 18 months from randomization; BICR = blinded independent central review; CSP = clinical study protocol; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer ; EORTC QLQ-C30 = 30-item core quality of life questionnaire; EORTC QLQ-LC13 = quality of life questionnaire and lung cancer module; ORR = objective response rate; OS24 = proportion of patients alive at 24 months from randomization; PFS2 = time from randomization to second progression; PK = pharmacokinetic(s); QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; TTDM = time to death or distant metastasis; WHO = World Health Organization.

a Analysis of ORR and DoR is based upon BICR assessment according to RECIST 1.1. See Sections 12.2.3 and 12.2.5 of the CSP for further details (Appendix 12.1.1).

Note: Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

4.3 Exploratory objectives

Appendix 12.1.14 presents results of efficacy analyses from exploratory *post hoc* biomarker (PD-L1) subgroup analyses.

5. STUDY PLAN AND PROCEDURES

5.1 Overall study design and flow chart

This is an ongoing, randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable Stage III NSCLC, who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy (cCRT).

For details on the study design, see Section 5.1, PACIFIC Interim CSR, Module 5.3.5.1.

5.2 Rationale for study design, doses, and control groups

See Section 5.2, PACIFIC Interim CSR, Module 5.3.5.1.

5.3 Selection of study population

See Section 5.3, PACIFIC Interim CSR, Module 5.3.5.1.

5.4 Treatments

See Section 5.4, PACIFIC Interim CSR, Module 5.3.5.1.

5.5 Measurements of study variables and definitions of outcome variables

See Section 5.5, PACIFIC Interim CSR, Module 5.3.5.1.

5.6 Data management and quality assurance

See Section 5.6, PACIFIC Interim CSR, Module 5.3.5.1.

5.7 Statistical methods and determination of sample size

See Section 5.7, PACIFIC Interim CSR, Module 5.3.5.1.

5.8 Clinical study protocol amendments and other changes in the conduct of the study or planned analyses

5.8.1 Changes in the conduct of the study

For important amendments to the original study protocol, including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct, see Section 5.8.1, PACIFIC Interim CSR, Module 5.3.5.1. Important amendments implemented since the time of the 13 February 2017 DCO are shown in Table 1. See CSR Appendix 12.1.1 for full details of all protocol amendments.

Table 1 Protocol amendments and other significant changes to study conduct

Number (date of internal approval)	Key details of amendment	Reason for amendment	Person(s) / group(s) responsible for amendment[a]
Amendment 5 9 Oct 2017	Clarified that the IDMC will review the unblinded interim analysis summaries of efficacy data	To further clarify requirements for IDMC reviews	Sponsor
	Specified that patients whose disease progressed after completing 12 months of durvalumab treatment could be re-treated with durvalumab for as long as they are gaining clinical benefit	To allow patients to receive the maximum benefit from treatment	Sponsor
	Added text throughout the protocol regarding procedures for patients who continue in follow-up or retreatment following the final DCO	To add guidance for the Investigators regarding treatment and data collection for these patients	Sponsor
	Revised Appendix H (Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions)	To match updated toxicity management guidelines from August 2016	Sponsor
Amendment 6 7 Dec 2017	Revised Appendix H (Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions)	To match updated toxicity management guidelines from November 2017	Sponsor
	Updated the list of AESIs	To align with the current durvalumab Investigator Brochure	Sponsor
	Updated the study timetable and end-of-study procedures	To clarify the circumstances under which the study may continue if the study reaches statistical significance for OS at the interim or final analyses	Sponsor

a All protocol amendments were approved by the Sponsor before being submitted to a regulatory authority and/or an Institutional Review Board/Independent Ethics Committee.

AESI = adverse event of special interest; DCO = data cut-off; IDMC = Independent Data Monitoring Committee
OS = overall survival.

5.8.2 Changes to planned analyses

No additional changes have been made to the planned analyses from those outlined in the PACIFIC Interim CSR (see Section 5.8.2, PACIFIC Interim CSR, Module 5.3.5.1).

6. STUDY PATIENTS

Summary tables and figures pertaining to this section are presented in Section 11.1 and CSR Appendix 12.2.

6.1 Disposition

A total of 983 patients were enrolled in 235 study centers across 26 countries worldwide. Of these, 713 patients were randomized in 2:1 ratio to receive either durvalumab 10 mg/kg Q2W (476 patients) or placebo (237 patients; FAS; Table 2).

Of the 713 patients, 709 (473 [99.4%] in the durvalumab group and 236 [99.6%] in the placebo group) received study treatment (Figure 1). The other 4 patients (3 [0.6%] in the durvalumab group and 1 [0.4%] in the placebo group) were randomized but did not receive study treatment because of patient decision (2 patients), neutropenia (1 patient), and worsening chronic obstructive pulmonary disease (COPD) (1 patient) (see Section 6.1, PACIFIC Interim CSR, Module 5.3.5.1).

The first patient was randomized into the study on 09 May 2014, and the last patient was randomized on 22 April 2016. At the time of the data cut-off date of 22 March 2018 for this addendum, 314 patients had completed the protocol-defined 12 months of treatment: 232 (49.0%) patients in the durvalumab group and 82 (34.7%) patients in the placebo group. Treatment had been discontinued prior to the defined 12 months of treatment in the other 241 (51.0%) patients in the durvalumab group and 154 (65.3%) patients in the placebo group.

The most frequently reported (ie, with an incidence of greater than 1%) reasons for discontinuing study treatment, were worsening of condition under investigation (148 [31.3%] patients and 117 [49.6%] patients in the durvalumab and placebo groups, respectively), AEs (73 [15.4%] patients and 23 [9.7%] patients, respectively), and patient decision (14 [3.0%] patients and 12 [5.1%] patients, respectively) (Table 2).

This was a global study with sites in Australia, Asia, Europe, North and South America, and South Africa (Table 11.1.6 and Section 6.1, PACIFIC Interim CSR, Module 5.3.5.1).

Table 2 Patient disposition (all patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Patients enrolled [a]			983
Patients randomized	476 (48.4)	237 (24.1)	713 (72.5)
Patients who were not randomized			270 (27.5)
Patient decision	--	--	35 (3.6)
Eligibility criteria not fulfilled	--	--	225 (22.9)
Death	--	--	6 (0.6)
Other	--	--	4 (0.4)
Full analysis set	476 (100.0)	237 (100.0)	713 (100.0)
Patients who received study treatment [b]	473 (99.4)	236 (99.6)	709 (99.4)
Patients who did not receive study treatment [b]	3 (0.6)	1 (0.4)	4 (0.6)
Patients who completed 12 months of treatment [c,d]	232 (49.0)	82 (34.7)	314 (44.3)
Patients who discontinued study treatment [c]	241 (51.0)	154 (65.3)	395 (55.7)
Patient decision	14 (3.0)	12 (5.1)	26 (3.7)
Adverse event	73 (15.4)	23 (9.7)	96 (13.5)
Severe non-compliance to protocol	1 (0.2)	1 (0.4)	2 (0.3)
Condition under investigation worsened	148 (31.3)	117 (49.6)	265 (37.4)
Development of study specific discontinuation criteria	1 (0.2)	1 (0.4)	2 (0.3)
Other [e]	4 (0.8)	0	4 (0.6)
Patients ongoing study at data cut-off date [b]	273 (57.4)	108 (45.6)	381 (53.4)
Patients who terminated study [c]	203 (42.6)	129 (54.4)	332 (46.6)
Subject decision [f]	22 (4.6)	14 (5.9)	36 (5.0)
Death	180 (37.8)	115 (48.5)	295 (41.4)
Subject lost to follow-up	1 (0.2)	0	1 (0.1)

a Informed consent received.

b In this section, percentages are calculated from number of patients in the full analysis set.

c In this section, percentages are calculated from number of patients who received treatment.

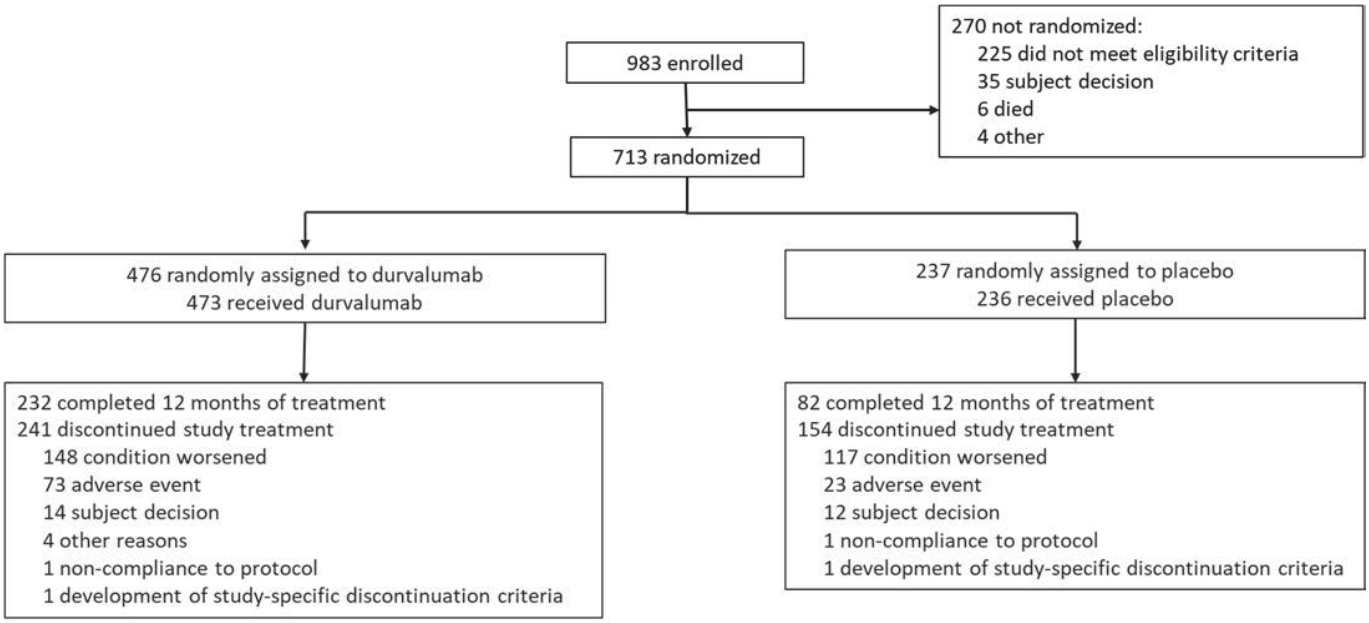
d Patients who completed 12 months of treatment have reported maximum cycle of immunotherapy reached on the case report form.

e PPD

f Four patients who terminated study due to patient decision have died.

Source: Table 11.1.1.OS

Figure 1 Patient disposition at final analysis of overall survival



Source: Table 11.1.1.OS

6.2 Protocol deviations

No additional important protocol deviations were identified between the 13 February 2017 and the 22 March 2018 DCOs. See Section 6.2, PACIFIC Interim CSR, Module 5.3.5.1 for more information regarding important protocol deviations.

6.3 Patients analyzed (analysis sets)

The analysis set used for each outcome variable is shown in Table 3 and are unchanged from the 13 February 2017 data cut-off.

Table 3 Analysis sets

	Number of patients		
	Durvalumab	**Placebo**	**Total**
Patients randomized	476	237	713
Patients included in full analysis set [a]	476	237	713
Patients included in safety analysis set [b]	475	234	709
Patients excluded from safety analysis set	3	1	4
Did not receive at least 1 dose of randomized study treatment	3	1	4

Table 3 Analysis sets

	Number of patients		
	Durvalumab	**Placebo**	**Total**
Patients included in PK analysis set [c]	473		473
Patients excluded from PK analysis set	3		3
Did not receive at least 1 dose of durvalumab	3		3

ITT = intent-to-treat; PK = pharmacokinetic(s)
a Full analysis set = all randomized patients analyzed on an ITT basis.
b Safety analysis set = all patients who received at least 1 dose of randomized study treatment, durvalumab or placebo. Two patients PPD in the placebo group inadvertently received a single infusion of durvalumab therapy at Week 8 and Week 28, respectively, and thus were included in the safety analysis set for durvalumab. This deviation was discovered after unblinding; the integrity of the blind remained intact.
c PK analysis set = all patients who received at least 1 dose of durvalumab per the protocol, had any post-dose data, and did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The 2 patients randomized to placebo who received 1 dose of durvalumab and were excluded from the PK analysis due to protocol violation.
Source: See Table 11.1.3.OS, PACIFIC Interim CSR, Module 5.3.5.1

6.4 Demographic and other patient characteristics

For a full presentation of the demographic and key baseline characteristics of study patients, including prior therapies, see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1.

Demographics and baseline characteristics were representative of the intended patient population, and well balanced between the 2 treatment groups. Note that data for the following 2 disease characteristics changed slightly between the 13 February 2017 and 22 March 2018 DCOs (Table 11.1.12.OS and see Table 11.1.12, PACIFIC Interim CSR, Module 5.3.5.1):

- The best response to prior therapy was revised from Non-evaluable or Not Applicable to PR or SD for 6 patients in the durvalumab group and 2 patients in the placebo group.
- The EGFR status for 2 patients in the durvalumab group changed from unknown to negative, as the results for these 2 patients were analyzed after the previous DCO.

6.4.1 Concomitant medication after study entry

A total of 696 (97.6%) patients received allowed concomitant medications during the study treatment (Table 11.1.16.OS). Concomitant medication use was consistent between the 2 treatment groups (98.1% of patients in the durvalumab group and 96.6% of patients in the

placebo group). Concomitant medication prescribed was balanced between the 2 treatment groups and generally in keeping with the supportive treatment given to this patient population.

A total of 16 patients received prohibited concomitant medications during the study treatment (Table 11.1.15.OS). The proportion of patients who used prohibited medications was 1.9% in the durvalumab group, compared to 3.0% in the placebo group. The prohibited concomitant medications (primarily glucocorticoids) do not raise any concerns on the outcome measures of the study.

6.4.2 Post-discontinuation disease-related anti-cancer therapy

A total of 195 (41.0%) patients in the durvalumab group and 128 (54.0%) patients in the placebo group received post-discontinuation disease-related, anti-cancer therapy (Table 11.1.18.OS). Most patients in both treatment groups received cytotoxic chemotherapy (eg, carboplatin and pemetrexed): 128 (26.9%) patients in the durvalumab group and 71 (30.0%) patients in the placebo group. Other systemic therapy (eg, targeted therapies) was administered in 47 (9.9%) of patients in the durvalumab group and 31 (13.1%) in the placebo group. Fewer patients in the durvalumab group than the placebo group received immunotherapy: 38 (8.0%) vs 53 (22.4%), respectively. A total of 82 (17.2%) patients in the durvalumab group and 56 (23.6%) patients in the placebo group received radiotherapy.

6.5 Conclusions on study patients

Demographics and disease characteristics were representative of the intended patient population and were well balanced between the durvalumab and placebo groups (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1). Disease characteristics related to best response to previous therapy and the proportion of patients with EGFR negative status changed slightly between the 13 February 2017 and 22 March 2018 DCOs, but these differences were not expected to have any clinically meaningful effect on study results.

7. EFFICACY EVALUATION

7.1 Efficacy results

Additional summary tables and figures pertaining to efficacy results are presented in Section 11.2 and Appendix 12.2.6.

7.1.1 Primary efficacy variables

7.1.1.1 Progression-free survival

At the time of the interim PFS analysis based on BICR assessments according to RECIST 1.1 (13 February 2017 DCO), the study met the pre-defined criteria of the PFS interim analysis.

Durvalumab demonstrated a statistically significant and clinically meaningful benefit in PFS over placebo (HR: 0.52; 98.9% confidence interval [CI]: 0.39, 0.70; p-value <0.0001). The Kaplan-Meier estimate of median duration of PFS was 16.8 months in the durvalumab group (95% CI: 13.0, 18.1), compared to 5.6 months (95% CI: 4.6, 7.8) in the placebo group. The separation in the Kaplan-Meier curves between the treatment groups was observed early, sustained over the treatment period, and supported by the estimates of the 12-month and 18-month PFS rates. For a detailed description of the final PFS results, see Section 7.1.1, PACIFIC Interim CSR, Module 5.3.5.1.

7.1.1.2 Overall survival

At the time of the OS interim analysis (22 March 2018 DCO), the study met the pre-defined criteria of the interim OS analysis (ie, statistical significance level of ≤0.00274).

Durvalumab demonstrated a statistically significant and clinically meaningful benefit in OS over placebo, with a 32% reduction in the risk of death (HR: 0.68; 99.73% CI: 0.469, 0.997; p-value=0.00251; see Table 4). The Kaplan-Meier estimate of the median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group.

Table 4 Overall survival, primary analysis (Full analysis set)

Survival status	Durvalumab (N=476)	Placebo (N=237)
Death, n (%)	183 (38.4)	116 (48.9)
Median overall survival (months) [a]	NR	28.7
95% CI for median overall survival [a]	34.7, NR	22.9, NR
Survival rate at 12 months (%) [a]	83.1	75.3
95% CI for survival rate at 12 months [a]	79.4, 86.2	69.2, 80.4
Survival rate at 24 months (%) [a]	66.3	55.6
95% CI for survival rate at 24 months [a]	61.7, 70.4	48.9, 61.8

Table 4 Overall survival, primary analysis (Full analysis set)

Survival status	Durvalumab (N=476)	Placebo (N=237)
2-sided p-value [b]	0.005	
Hazard ratio, comparing durvalumab vs. placebo [c]	0.68	
99.73% CI for hazard ratio [c,d]	0.469, 0.997	
95% CI for hazard ratio [c]	0.53, 0.87	
97.5% CI for hazard ratio [c]	0.52, 0.91	
2-sided p-value [e]	0.00251	

CI = Confidence interval, NR = Not reached.

a Calculated using the Kaplan-Meier technique.

b The p-value is generated based on z-test where z-test statistic is the ratio of the log-transformed ratio of the cumulative hazards in the two treatment arms divided by the sqrt of the variance calculated for each strata and combined by weighting inversely proportionately according to each within stratum variance. The variance is estimated using the delta method and Greenwood's formula.

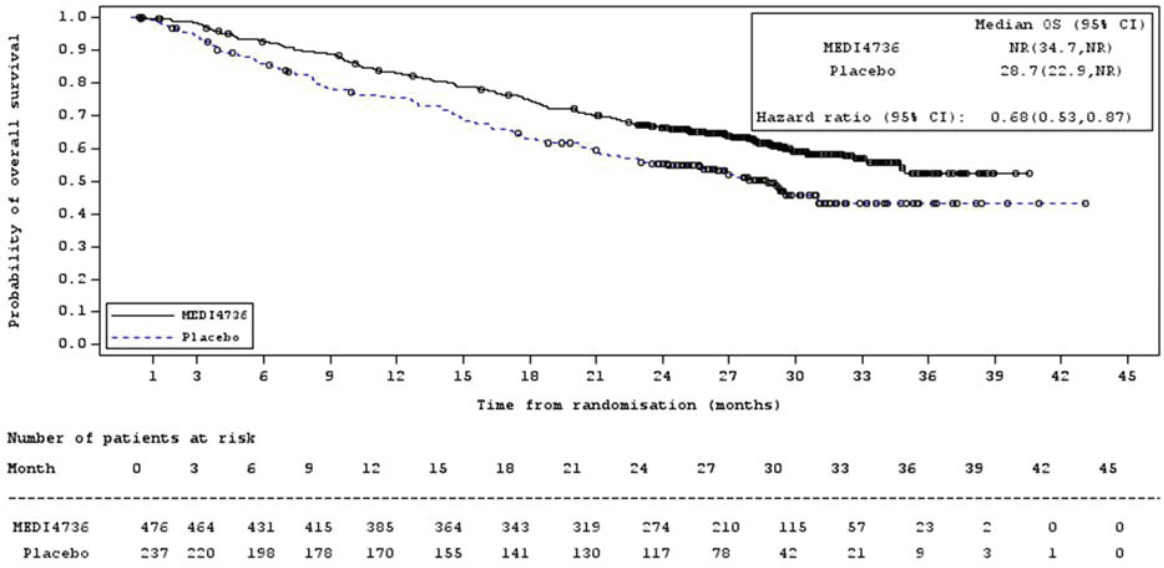
c The analysis was performed using stratified log-rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

d The adjusted alpha levels for the treatment comparison was derived based upon the exact number of overall survival events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function.

Source: Table 11.2.1.1.OS

The separation of OS curves between the durvalumab and placebo groups was observed early and was sustained over the treatment period (Figure 2). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at both the OS12 (83.1% vs. 75.3%, respectively) and OS24 (66.3% vs. 55.6%, respectively) landmarks, as shown in Table 4.

Figure 2 Kaplan-Meier plot of overall survival (Full analysis set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
MEDI4736	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Circles indicate a censored observation
Source: Figure 11.2.1.1.OS

The duration of follow-up in all patients was balanced between the 2 treatment groups, with a median of 25.9 months (range: 0.2 to 40.5) in the durvalumab group and 23.8 months (range: 0.3 to 43.1) in the placebo group (Table 11.2.1.2.OS). A total of 414 patients (293 durvalumab and 121 placebo) were censored at the last date they were known to be alive. The duration of follow-up for OS in the censored patients was balanced between the 2 treatment groups, with a median of 28.8 months (range: 0.4 to 40.5) in the durvalumab group and 28.2 (range: 0.5 to 43.1) in the placebo group. The majority (90%) of patients who were censored at the time of the analysis had their latest follow-up for survival within 8 weeks of the DCO date; therefore, the status of the majority of patients was known at the time of the analysis.

Sensitivity analysis

A sensitivity analysis was performed using stratification factors as determined by the baseline CRF variables instead of the IVRS values in the stratified log-rank test (Table 11.2.1.1.1.OS). These results (HR: 0.67; 95% CI: 0.53, 0.86) were consistent with the primary analysis of OS.

Two multivariate Cox regression models were used to adjust for the following prespecified covariates:

- Covariates for model 1: sex, age at randomization, and smoking history
- Covariates for model 2: sex, age at randomization, smoking history, stage of disease at study entry (Stage IIIA vs Stage IIIB), histology (squamous vs all other), best response to prior anticancer therapy (CR vs PR vs SD), WHO performance status

(normal vs restricted activity), region (Asia vs Europe vs North America and South America), and race (White vs Black/African-American vs Asian vs Other).

The results demonstrated consistency with the primary analyses: model 1, HR: 0.69, 95% CI: 0.55, 0.87; model 2, HR: 0.66, 95% CI: 0.52, 0.84 (Table 11.2.1.4.OS).

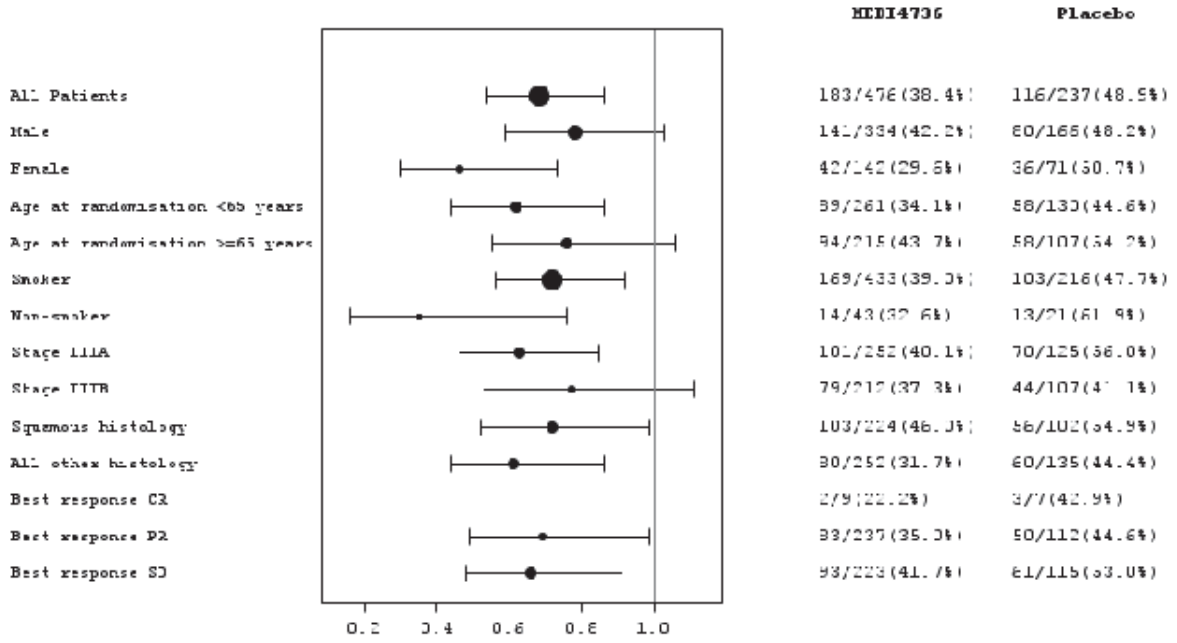
There was no interaction between treatment and stratification based on the Gail and Simon test (Table 11.2.1.5.OS). There was no indication of the violation to the proportional hazards assumption (Figure 11.2.1.2.OS).

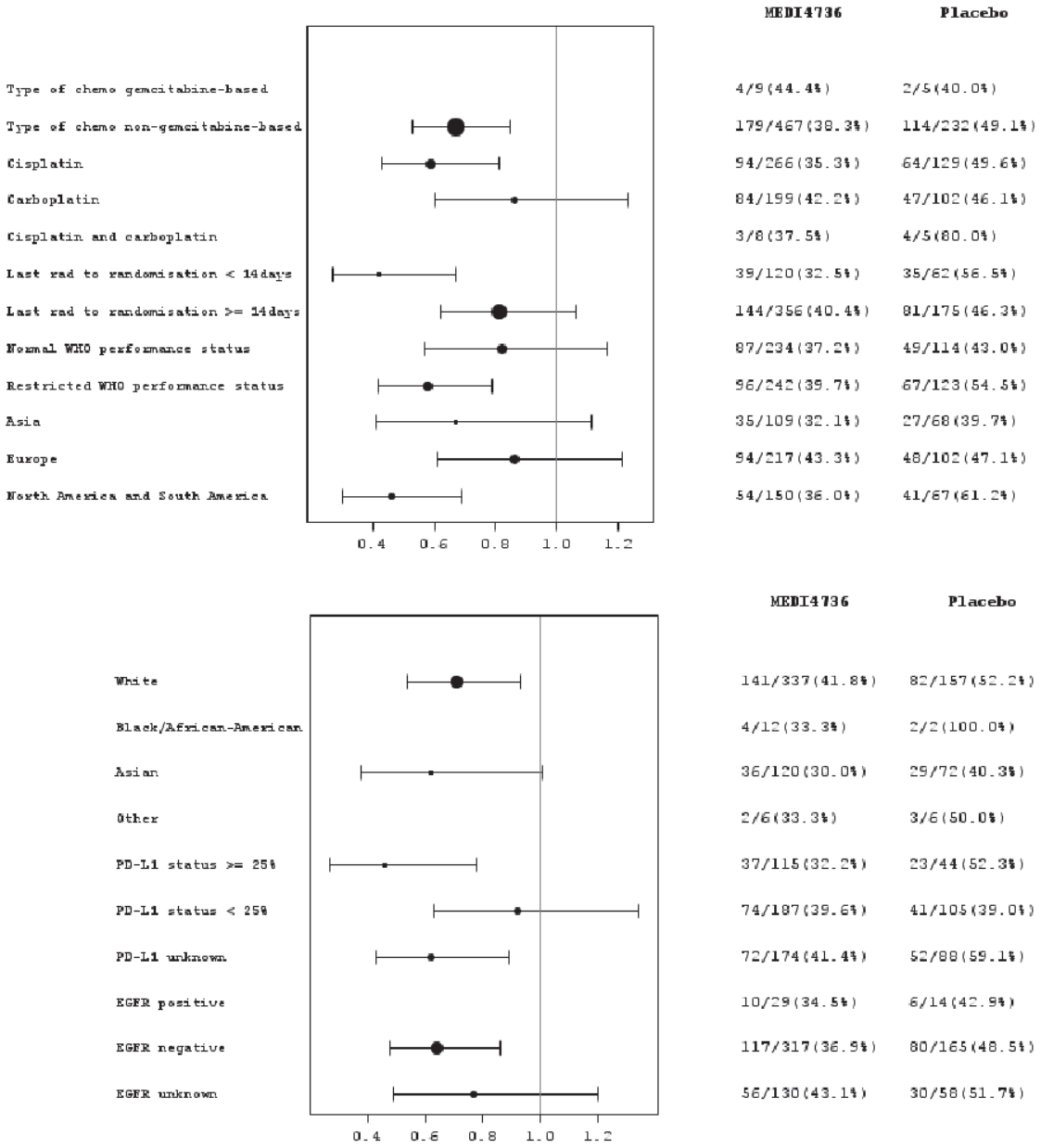
A KM plot of the time to censoring in which the censoring indicator of the primary OS analysis was reversed did not show any meaningful difference between the 2 treatment groups, indicating there was no attrition bias (Figure 11.2.1.3.OS).

Subgroup analysis

Improvements in OS favoring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, and baseline disease characteristics (Figure 3 and Table 11.2.1.3.OS). For further discussion on exploratory post-hoc subgroup biomarker analysis by PD-L1 status, refer to Appendix 12.1.14.

Figure 3 Overall survival Forest plot, by subgroup (Full analysis set)





CI=Confidence interval, WHO=World Health Organisation, CR=Complete response, PR=Partial response, SD=Stable disease, Chemo=chemotherapy

Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has fewer than 20 events.

The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.

Unknown is either insufficient tumour tissue, not able to be analyzed or analyzed but results were not interpretable.

Size of circle is proportional to the number of events.

Source: Figure 11.2.1.4.OS

7.1.2 Secondary efficacy variables

7.1.2.1 Overall survival at 24 months (OS24)

The proportion of patients alive at 24 months was higher for the durvalumab group than for the placebo group (66.3% vs. 55.6%; p-value=0.005; Table 4 and Figure 2).

7.1.2.2 Objective response rate (ORR)

Of the 476 and 237 patients in the durvalumab and placebo groups, 443 and 213 patients, respectively, had measurable disease at baseline according to BICR. The ORR to treatment for these patients is provided in Table 5.

At the date of OS interim analysis (DCO of 22 March 2018), treatment with durvalumab resulted in a clinically meaningful improvement in ORR compared to placebo, based on BICR assessments according to RECIST 1.1: 30.0% in the durvalumab group vs 17.8% in the placebo group; nominal p-value <0.001. The proportion of patients with a CR was 8 (1.8%) patients in the durvalumab group compared to 1 (0.5%) patient in the placebo group (Table 11.2.6.5.OS). These results were consistent with those from the analysis based on the 13 February 2017 DCO (see Section 7.1.2.1, PACIFIC Interim CSR, Module 5.3.5.3).

Table 5 Analysis of objective response rate based on BICR assessments (Full analysis set with measurable disease at baseline)

	Durvalumab (N=443)	Placebo (N=213)
Patients with objective response [a], n(%)	133 (30.0)	38 (17.8)
95% CI (%) [b]	25.79, 34.53	12.95, 23.65
p-value [c]	<0.001	

BICR = blinded independent central review
a Responses include unconfirmed responses.
b 95% confidence intervals are calculated using the Clopper Pearson method.
c The analysis was performed using Fisher's exact test with mid p-value modification by subtracting half of the probability of the observed table from Fisher's p-value.
Source: Table 11.2.6.1.OS

7.1.2.3 Duration of response (DoR)

As of the 22 March 2018 DCO, treatment with durvalumab resulted in a longer DoR compared to placebo (Table 6). The median DoR for patients in the durvalumab group was not reached (25th percentile: 15.4 months; 75th percentile was not reached), compared to 18.4 months (25th percentile: 5.9 months; 75th percentile was not reached) for patients in the placebo group. Based on Kaplan-Meier estimates, 86.9% and 69.7% of patients, respectively, were estimated to remain in response beyond 6 months (Figure 11.2.1.11). The proportion of patients in the durvalumab and placebo groups who remained in response was 81.3% and 60.2%, respectively, at 12 months and 73.5% and 52.2%, respectively, at 18 months.

These results were consistent with the analysis based on the 13 February 2017 DCO, with an additional 10 responders in the durvalumab group and 6 responders in the placebo group who subsequently progressed or died (see Section 7.1.2.2, PACIFIC Interim CSR, Module 5.3.5.3).

Table 6 Duration of objective response based on BICR assessments according to RECIST 1.1 (Full analysis set, patients with objective response)

Statistic	Durvalumab (N=133)	Placebo (N=38)
Number of responders who subsequently progressed or died, n(%)	34 (25.6)	20 (52.6)
Duration of response from onset of response (months) [a,b]		
25th percentile and 95% CI	15.4 (10.3, 27.4)	5.9 (1.9, 9.4)
Median and 95% CI	NR (27.4, NR)	18.4 (6.7, 24.5)
75th percentile and 95% CI	NR (NR, NR)	NR (21.9, NR)
Percentage remaining in response at [b]		
6 months	86.9	69.7
12 months	81.3	60.2
18 months	73.5	52.2

BICR = blinded independent central review, NR = Not reached.

a Duration of response is the time from the first documentation of CR/PR until the date of progression, death, or the last non-missing RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits.

b Calculated using the Kaplan-Meier technique.

Source: Table 11.2.7.1.OS

7.1.2.4 Time to first subsequent therapy or death (TFST)

Time to the start of first subsequent therapy or death (TFST) was derived as a supportive summary to PFS. As of the 22 March 2018 DCO, treatment with durvalumab prolonged the TFST compared to placebo (HR: 0.58; 95% CI: 0.47, 0.72; Table 7 and Figure 4). The median TFST was 21.0 months in the durvalumab group, compared to 10.4 months in the placebo group.

In addition, a lower proportion of patients in the durvalumab group than the placebo group started subsequent therapy in < 1 month (13.3% vs 24.8%) and in ≥ 1 to < 2 months (9.1% vs 16.2%) from treatment discontinuation (Table 11.3.12.OS).

These results were consistent with those from the analysis based on the 13 February 2017 DCO (see Section 7.1.2.3, PACIFIC Interim CSR, Module 5.3.5.3).

Table 7 Time to first subsequent therapy or death (Full analysis set)

	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n (%)	267 (56.1)	169 (71.3)
Subsequent therapy [b]	196 (41.2)	130 (54.9)
Death	71 (14.9)	39 (16.5)
Median time to first subsequent therapy or death (months) [c]	21.0	10.4
95% CI for Median time to first subsequent therapy or death [c]	16.6, 25.5	8.3, 12.5
Hazard ratio	0.58	
95% CI for hazard ratio	0.47, 0.72	
2-sided p-value	<0.0001	

a Patients with first subsequent therapy or death (TFST). TFST is defined as the time from randomization to the start date of the first subsequent therapy after discontinuation of treatment, or death.

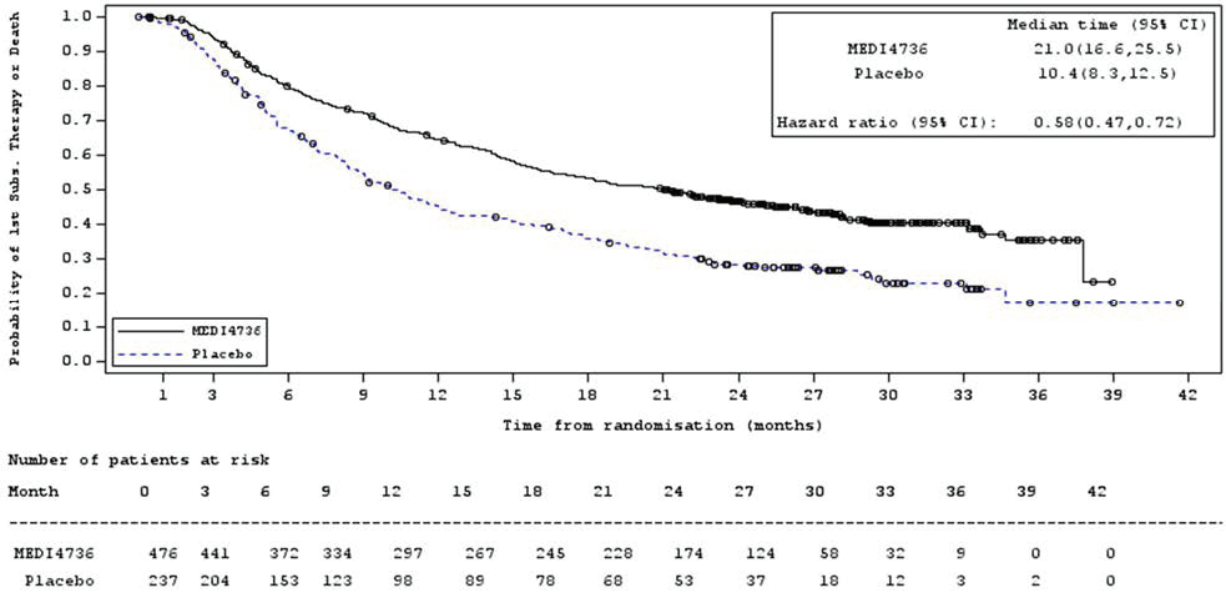
b An additional patient in the durvalumab group and 2 patients in the placebo received concurrent palliative radiotherapy (allowed per protocol) prior to discontinuing study treatment that was incorrectly recorded on the time to first subsequent therapy CRF.

c Calculated using the Kaplan-Meier technique.

The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Source: Table 11.2.5.1.OS

Figure 4 **Kaplan-Meier plot of time to first subsequent therapy or death (Full analysis set)**



Circles indicate a censored observation.
Source: Figure 11.2.1.10.OS

7.1.2.5 Time to death or distant metastasis (TTDM)

As of the 22 March 2018 DCO, treatment with durvalumab resulted in fewer events compared to placebo and a longer TTDM, based on BICR (median 28.3 vs 16.2 months, respectively; HR: 0.53; 95% CI: 0.41, 0.68; nominal p-value <0.0001; Table 8 and Figure 5).

These results were consistent with the analysis based on the 13 February 2017 DCO, with 51 additional total events in the durvalumab group and 28 additional total events in the placebo group (see Section 7.1.2.4, PACIFIC Interim CSR, Module 5.3.5.3).

Table 8 **Time to death or distant metastasis based on BICR assessments according to RECIST 1.1 (Full analysis set)**

	Durvalumab (N=476)	Placebo (N=237)
Total events,[a] n (%)	182 (38.2)	126 (53.2)
Distant metastasis [b]	75 (15.8)	62 (26.2)
Death in the absence of distant metastasis	107 (22.5)	64 (27.0)
Median time to death or distant metastasis (months) [e]	28.3	16.2
95% CI for time to death or distant metastasis [e]	24.0, 34.9	12.5, 21.1

Table 8 Time to death or distant metastasis based on BICR assessments according to RECIST 1.1 (Full analysis set)

	Durvalumab (N=476)	Placebo (N=237)
Hazard ratio [f]	0.53	
95% CI for hazard ratio [f]	0.41, 0.68	
2-sided p-value [f]	<0.0001	

BICR = blinded independent central review; CI = Confidence interval; NR = not reported; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1

a Patients who have not died or have distant metastasis, or who die or get distant metastasis after 2 or more missed visits, are censored at the latest non-missing RECIST assessment, or Day 1 if there are no non-missing visits or baseline data unless they die within 2 visits of baseline.

b Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy.

c Distant metastasis event occurred after 2 or more missed visits or the patient has no non-missing visits or does not have a baseline assessment.

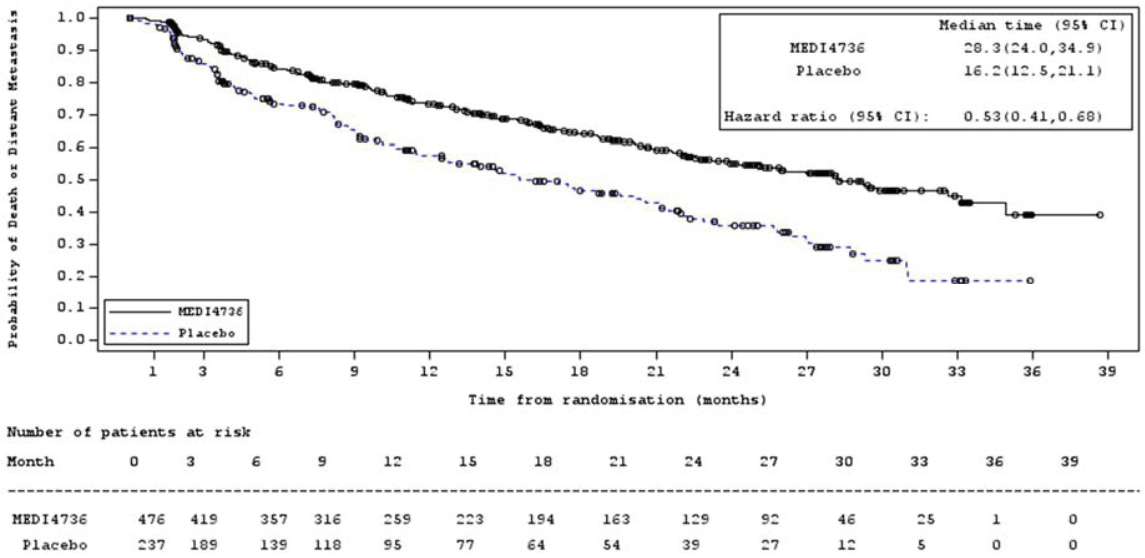
d Death that occurred after 2 or more missed visits in the absence of distant metastasis.

e Calculated using the Kaplan-Meier technique.

f The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Source: Table 11.2.11.1.OS

Figure 5 Kaplan-Meier plot of time to death or distant metastasis (Full analysis set)



Circles indicate a censored observation.
CI = confidence interval; MEDI4736 = durvalumab
Source: Figure 11.2.1.15.OS

7.1.2.6 Time to second progression or death (PFS2)

PFS2 was defined as the time from randomization to the time of the second progression or death (see Section 3.2.2.6, Statistical Analysis Plan, PACIFIC interim CSR, Module 5.3.5.1). The date of the first progression was programmatically determined from Investigator-assessed data. The date of second progression was recorded by the Investigator and defined according to local standard clinical practice, and could have involved any of the following: objective radiological, symptomatic progression, or death. Patients who were alive and for whom a second disease progression had not been observed were censored at the last time they were known to be alive and without a second disease progression(ie, censored at the latest PFS or PFS2 assessment date at which the patient did not have a second progression or death).

At the 22 March 2018 DCO, a clinically meaningful 11.2-month delay in PFS2 was observed in patients on durvalumab when compared with those on placebo (HR: 0.58; 95% CI: 0.46,0.73; nominal p<0.0001). The KM estimate of median PFS2 was 28.3 months in the durvalumab group (95% CI: 25.1, 34.7), compared with 17.1 months (95% CI: 14.5, 20.7) in the placebo group.

Table 9 Time from randomization to second progression or death, summary and stratified log-rank test (Full analysis set)

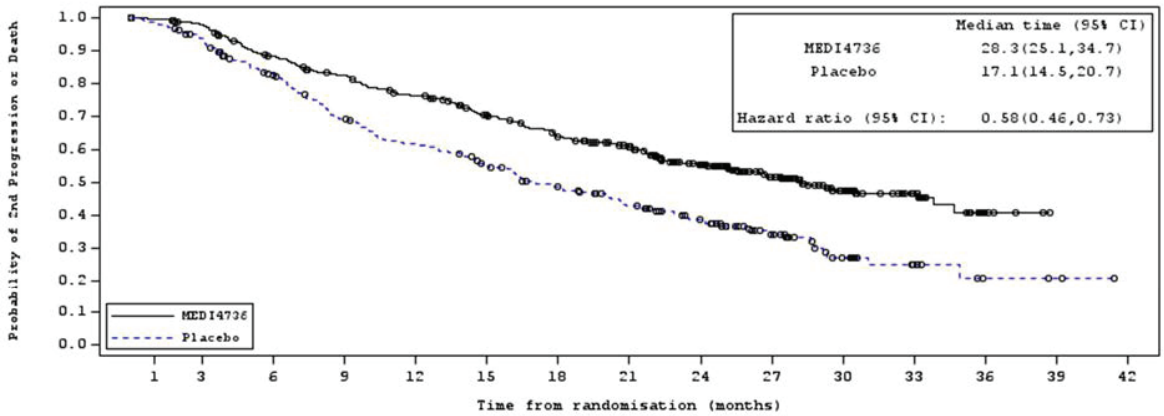
	Durvalumab (N=476)	**Placebo (N=237)**
Total events [a], n(%)	217 (45.6)	144 (60.8)
Second Progression	116 (24.4)	78 (32.9)
Objective progression by RECIST	78 (16.4)	48 (20.3)
Symptomatic Progression	13 (2.7)	15 (6.3)
New or worsening of soft tissue/visceral or bone metastases	22 (4.6)	13 (5.5)
Other	3 (0.6)	2 (0.8)
Death in the absence of second progression	101 (21.2)	66 (27.8)
Median time to second progression or death (months)[b]	28.3	17.1
95% CI for median time to second progression or death [b]	25.1, 34.7	14.5, 20.7
Hazard ratio [c]	0.58	
95% CI for hazard ratio [c]	0.46, 0.73	
2-sided p-value [c]	<0.0001	

Table 9 **Time from randomization to second progression or death, summary and stratified log-rank test (Full analysis set)**

	Durvalumab (N=476)	Placebo (N=237)

Progression is determined by investigator assessments. CI=Confidence interval.
a Patients who have not progressed the second time or died, are censored at the latest progression assessment, or day 1 if there are no progression assessments.
b Calculated using the Kaplan-Meier technique.
c The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (male vs female) and smoking history (smoker vs non-smoker), with ties handled using the Breslow approach.
Source: Table 11.2.10.1.OS

Figure 6 **Kaplan-Meier plot of time to second progression or death (Full analysis set)**



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
MEDI4736	476	455	404	373	342	307	274	249	192	126	65	36	5	0	0
Placebo	237	216	183	150	131	114	96	80	63	38	19	10	3	2	0

Circles indicate a censored observation
Progression is determined by investigator assessment.
Source: Figure 11.2.1.14.OS

Time to second subsequent therapy or death

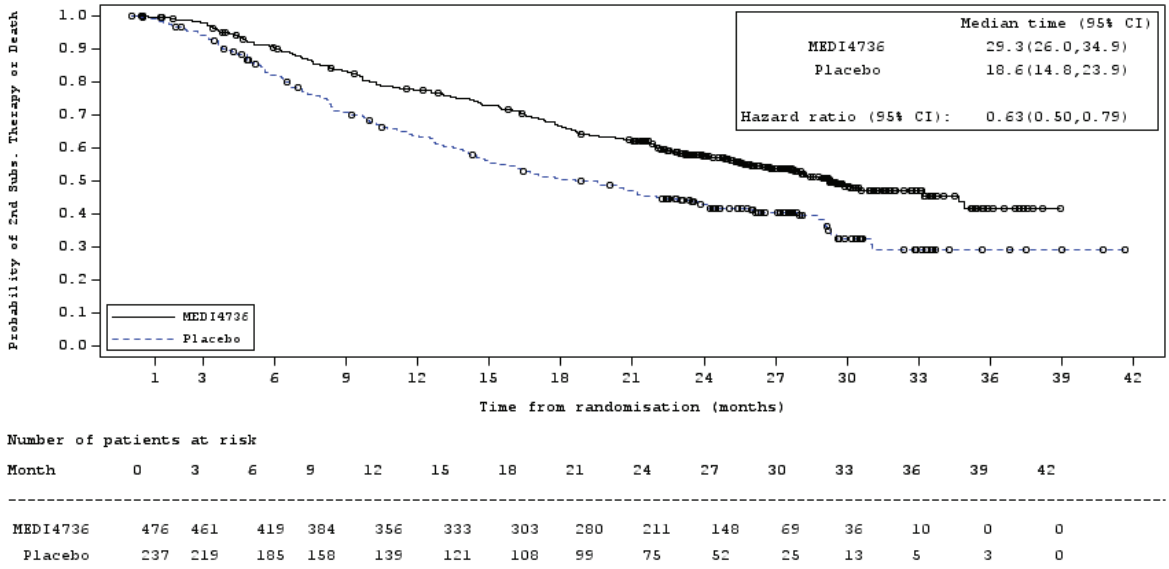
Time to start of second subsequent therapy or death (TSST) was derived as a supportive summary to PFS2. At the time of the OS interim analysis (DCO of 22 March 2018), treatment with durvalumab prolonged the time to start of second subsequent therapy or death compared to placebo (HR: 0.63; 95% CI: 0.50, 0.79; Table 10 and Figure 7). The median TSST was 29.3 months in the durvalumab group, compared to 18.6 months in the placebo group.

Table 10 Time to second subsequent therapy or death, stratified log test (Full analysis set)

	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n (%)	221 (46.4)	139 (58.6)
Subsequent therapy	83 (17.4)	61 (25.7)
Death	138 (29.0)	78 (32.9)
Median time to first subsequent therapy or death (months) [b]	29.3	18.6
95% CI for median time to first subsequent therapy or death [b]	26.0, 34.9	14.8, 23.9
Hazard ratio	0.63	
95% CI for hazard ratio	0.50, 0.79	
2-sided p-value	<0.0001	

a Patients with second subsequent therapy or death. TSST is defined as the time from randomization to the start date of the second subsequent therapy after discontinuation of treatment, or death.
b Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
Source: Table 11.2.9.1.OS

Figure 7 Kaplan-Meier plot of time to second subsequent therapy or death (Full analysis set)



Circles indicate a censored observation.
Source: Figure 11.2.1.13.OS

7.1.2.7 Patient-report outcomes (PRO) and health-related quality of life (HRQoL)

Patient-reported symptoms and HRQoL were collected using the European Organization for Research and Treatment of Cancer 30-item core QoL questionnaire (EORTC QLQ-C30) and its lung cancer module, European Organization for Research and Treatment of Cancer QoL lung cancer module (EORTC QLQ-LC13).

Patient-reported-outcome data showed a high level of compliance (>80%) for both groups for up to 48 weeks. Results across all sub-scales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.

The results from the DCO of 22 March 2018 were consistent with those from the 13 February 2017 DCO (Table 11.2.12.1.OS, Table 11.2.12.2.OS, Figure 11.2.2.2.OS, Figure 11.2.2.4.OS, and see Section 7.1.2.5, PACIFIC Interim CSR, Module 5.3.5.1).

7.2 Pharmacokinetic results

As of the DCO of 22 March 2018, PK data were available for a total of 473 patients (PK analysis set) following treatment with durvalumab 10 mg/kg Q2W administered as an IV infusion over 60 minutes. There are 25 new PK concentration data points (1 Week 24 trough concentration and 24 Week 48 trough concentrations) included in the 22 March 2018 DCO compared to the 13 February 2017 DCO. The summary of durvalumab serum concentrations are similar between the 22 March 2018 and 13 February 2017 DCOs, with no change in the overall PK conclusions (Table 11.3.10.8.2.OS, and see Section 7.2, PACIFIC Interim CSR, Module 5.3.5.1). Overall, PK exposure of durvalumab was similar between ADA treatment-emergent positive and the ADA-negative patients, indicating the effect of immunogenicity on PK exposure of durvalumab was minimal. The individual durvalumab serum concentrations are provided in Table 11.3.10.8.1.OS. The statistics of durvalumab serum concentrations are presented in Table 11.3.10.8.2.OS.

7.3 Immunogenicity results

As of the data cut-off date of 22 March 2018, immunogenicity data were available for a total of 620 patients who had valid baseline and at least 1 valid post-baseline ADA result (ADA-Evaluable Population). These 620 patients included 416 patients in the durvalumab 10 mg/kg Q2W dose group and 204 patients in the placebo group. The testing approach and validation methods are as described in the interim CSR (see Section 7.3, PACIFIC Interim CSR, Module 5.3.5.1). A summary of ADA responses during the study by treatment group is presented in Table 11. A listing of ADA results (ADA status, titer value, and the presence of nAb) of all patients in the safety analysis set is presented in Table 11.3.10.8.3.OS.

As shown in Table 11, ADA prevalence of the durvalumab 10 mg/kg Q2W dose group and the placebo group were 4.6% (19 of 416 patients) and 4.9% (10 of 204 patients), respectively.

ADA incidence of the durvalumab 10 mg/kg Q2W dose group and the placebo group were 1.9% (8 of 416 patients) and 2.5% (5 of 204 patients), respectively. Thus, the number of ADA-positive patients in the study was largely unchanged from that presented in the Interim CSR, with the addition of 1 patient in the durvalumab group PPD whose ADA status was reclassified from non-ADA evaluable to ADA-transiently positive (Table 11.3.10.8.4.OS, and see Section 7.3, PACIFIC Interim CSR, Module 5.3.5.1). The number of nAb-positive patients remained unchanged at 3 (of 416 patients, 0.7%).

Table 11 Summary of anti-drug antibody responses during the study (ADA-evaluable population)

	Number (% of patients)	
ADA Categories	**Durvalumab 10 mg/kg Q2W (N=416)**	**Placebo Q2W (N=204)**
ADA prevalence[a,f]	19 (4.6)	10 (4.9)
ADA incidence (treatment-emergent)[b,f]	8 (1.9)	5 (2.5)
ADA-positive at baseline and post-baseline[f]	2 (0.5)	2 (1.0)
ADA-positive post-baseline only[f]	8 (1.9)	5 (2.5)
ADA-positive at baseline only[f]	9 (2.2)	3 (1.5)
Treatment-boosted ADA[c,f]	0	0
ADA-persistently-positive[d,f]	5 (1.2)	5 (2.5)
ADA-transient-positive[e,f]	5 (1.2)	2 (1.0)
nAbs-positive at any visit[f]	3 (0.7)	0

a ADA prevalence is the proportion of study population having a ADA-positive result at any point in time, baseline or post-baseline.
b ADA incidence (treatment-emergent ADA) is the sum of both treatment-induced (post-baseline ADA-positive only) and treatment-boosted ADA-positive patients as a proportion of the evaluable patient population.
c Treatment-boosted ADA is defined as baseline ADA titer that was boosted by ≥4 fold following drug administration.
d Persistently positive is defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment.
e Transiently positive is defined as having at least 1 post-baseline ADA-positive assessment and not fulfilling the conditions of persistently positive.
f Denominator is the number of ADA-evaluable patients in the treatment group.
ADA antidrug antibody; N number of ADA-evaluable patients, nAb neutralizing antibody; Q2W every 2 weeks.
Source: Table 11.3.10.8.4.OS

The analysis of PFS and OS by ADA status was conducted based on data from the respective DCOs (PFS: 13 February 2017; OS: 22 March 2018) and are summarised below:

Given that there were fewer than 30 patients who were ADA positive (19 patients in the durvalumab group [of whom 18 were determined to be ADA positive at the time of the PFS analysis] with 11 PFS and 10 OS events; 10 patients in the placebo group with only 7 PFS and 6 OS events) formal efficacy analyses for PFS and OS are not considered meaningful. A review of the patient-level efficacy data showed that the majority of durvalumab-treated, ADA-positive patients (15 out of 19 patients) had an OS duration of 1 year or longer; 8 out of these 19 patients were alive for 2 years or longer (Table 11.3.10.8.3.OS). Similarly, 6 of the 18 durvalumab treated, ADA-positive patients had a PFS duration of 1 year or longer. While the small number of patients precludes definitive clinical interpretation, these results do not suggest a lack of benefit in ADA-positive patients compared to those from the overall population.

7.4 Efficacy evaluation conclusions

- As of the DCO of 22 March 2018, treatment with durvalumab demonstrated a statistically significant (HR: 0.68; 95% CI: 0.53, 0.87; p-value=0.00251) and clinically meaningful benefit in OS compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.
    - The risk of death was reduced by 32% on the durvalumab treatment compared with placebo
    - Median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group.
    - The treatment effects were observed early and sustained over time, as supported by the estimates of the OS rates at 12 months (83.1% in the durvalumab group and 75.3% in the placebo group) and 24 months (66.3% and 55.6%, respectively; p-value 0.005).
- The sensitivity analyses support the robustness of the primary OS analysis.
- Improvements OS favored durvalumab across all predefined subgroups analyzed, including ethnicity, age, gender, smoking history, and histology.
- Treatment with durvalumab prolonged the time to start of first subsequent therapy or death compared to placebo (HR: 0.58; 95% CI: 0.47, 0.72), with a median TFST of 21.0 months, compared to 10.4 months in the placebo group.
- A clinically meaningful 11.2-month delay in time from randomization to second progression or death was observed in patients on durvalumab when compared with those on placebo (HR: 0.58; 95% CI: 0.46,0.73; nominal p<0.0001), with a median

PFS2 of 28.3 months in the durvalumab group (95% CI: 25.1, 34.7), compared with 17.1 months (95% CI: 14.5, 20.7) in the placebo group.

- Treatment with durvalumab prolonged the TSST compared to placebo (HR: 0.63; 95% CI: 0.50, 0.79), with a median TSST of 29.3 months, compared to 18.6 months in the placebo group.
- A clinically meaningful incremental ORR was observed: 30.0% in the durvalumab group vs 17.8% in the placebo group (nominal p-value <0.001).
- The responses were durable with the median DoR not reached in the durvalumab group, compared to 18.4 months in the placebo group.
- TTDM was longer for the durvalumab group compared to the placebo group (HR: 0.53; 95% CI: 0.41, 0.68; nominal p-value < 0.0001). The median TTDM was 28.3 months in the durvalumab group, compared to 16.2 months in the placebo group.

8. SAFETY EVALUATION

The safety analyses at the 22 March 2018 DCO were conducted based on the safety analysis set, which includes 475 patients in the durvalumab group and 234 patients in the placebo group (Table 3).

Two patients PPD randomized to the placebo group inadvertently received a single infusion of durvalumab therapy at Week 8 and Week 28, respectively, and thus were included in the safety analysis set for durvalumab. These were captured as important protocol deviations; for a further description, see Section 6.2 and Section 6.3, PACIFIC Interim CSR, Module 5.3.5.1.

8.1 Extent of exposure

The number of patients exposed, and the totality of exposure and follow-up in the study, were adequate to characterize the safety profile of durvalumab in comparison with placebo.

All patients had been randomized into the study as of 22 April 2016: 476 patients to durvalumab and 237 patients to placebo. Of these, 473 (99.4%) patients in the durvalumab group and 236 (99.6%) patients in the placebo group received study treatment (see Section 6.1). At the time of the 13 February 2017 DCO, the majority of patients had been randomized more than 12 months previously and so had had the opportunity to complete the protocol-defined 12 months of study treatment. At that DCO, 42 patients were still receiving treatment: 30/473 (6.3%) patients in the durvalumab group and 12/236 (5.1%) patients in the placebo group who received study treatment. As of early May 2017, all patients had the opportunity to have completed the protocol-defined 12 months of initial treatment.

Between the 13 February 2017 DCO and the 22 March 2018 DCO, the total treatment duration increased by only 4.7 patient years overall: 3.5 patient-years (from 319.8 to 323.3) in the durvalumab group and 1.2 patient years (from 138.8 to 140.0) in the placebo group) (Table 11.3.1.1.OS and see Table 11.3.1.1, PACIFIC Interim CSR, Module 5.3.5.1). As a result, the amount of new exposure and safety data is limited.

As of the 22 March 2018 DCO, the median number of infusions was 20.0 for durvalumab and 14.0 for placebo. The median total duration of treatment was 48.0 weeks and 31.7 weeks, respectively (Table 12).

Cumulative exposure over time is summarized in Table 11.3.1.3.OS. A total of 318 (66.9%) of patients in the durvalumab group and 135 (57.7%) in the placebo group were treated for at least 6 months, with 174 (36.6%) and 65 (27.8%), respectively, treated for 12 months.

Table 12 Duration of exposure (safety analysis set)

Treatment duration	Durvalumab (N=475)	Placebo (N=234)	Total (N=709)
Number of infusions			
Mean (standard deviation)	16.7 (9.12)	14.9 (8.93)	16.1 (9.09)
Median	20.0	14.0	18.0
Minimum, maximum	1, 27	1, 26	1, 27
≥17 infusions (% of population)	269 (56.6)	108 (46.2)	377 (53.2)
≥20 infusions (% of population)	243 (51.2)	94 (40.2)	337 (47.5)
≥26 infusions (% of population)	101 (21.3)	43 (18.4)	144 (20.3)
Total treatment duration (weeks) [a]			
Mean (standard deviation)	35.5 (18.94)	31.2 (18.54)	34.1 (18.90)
Median	48.0	31.7	40.1
Minimum, maximum	1, 55	1, 54	1, 55
Total treatment duration (patient years)	323.3	140.0	463.3
Actual treatment duration (weeks) [b]			
Mean (standard deviation)	33.3 (18.27)	29.8 (17.91)	32.2 (18.21)
Median	40.1	28.0	36.1
Minimum, maximum	1, 54	1, 53	1, 54
Total treatment duration (patient years)	303.5	133.8	437.3

a Total treatment duration is defined as (last dose date + 13 days or death date or data cut off, whichever occurs earlier - first dose date + 1) / 7.
b Actual treatment duration = total treatment duration, excluding total duration of dose delays.
Source: Table 11.3.1.1.OS

8.1.1 Infusion interruptions and delays

At the 13 February 2017 DCO, 34 (7.2%) patients treated with durvalumab and 11 (4.7%) patients treated with placebo required infusion interruptions and 246 (51.8%) durvalumab and 82 (35.0%) placebo patients had dose delays (see Table 11.3.1.2, PACIFIC Interim CSR, Module 5.3.5.1). As of the 22 March 2018 DCO, there were no additional patients with dose interruptions in either treatment group and 1 additional patient in the placebo group with a dose delay.

The majority of patients (20 of 34 for durvalumab and 9 of 11 for placebo) required only 1 interruption. The most common reason for infusion interruptions in both treatment groups was technical issues (3.8% for durvalumab and 2.1% for placebo). Infusion interruptions due to an AE occurred in 1.5% and 1.3% of durvalumab and placebo patients, respectively.

A total of 246 (51.8%) patients who received durvalumab and 83 (35.5%) of patients who received placebo had dose delays, the majority of whom had only 1 delay: 134/246 (54.5%) durvalumab; 49/83 (59.0%) placebo. The most common reason for dose delays was AEs: 179 (37.7%) patients in the durvalumab group; 58 (24.8%) patients in the placebo group.

8.2 Adverse events

Adverse events are included in the summary tables of AEs if they started after the first dose of study treatment (or for pre-existing AEs the severity worsened after the first dose) up to 90 days after the last dose of study treatment received or up to the start date of any subsequent systemic anticancer therapy, whichever occurred first.

8.2.1 Overview of adverse events

A summary of all AEs by category is presented in Table 13. As expected in this patient population, the majority of patients (96.8% and 94.9% of patients receiving durvalumab and placebo, respectively) experienced an AE (regardless of causality). Overall, the incidence and severity of AEs were comparable for patients receiving durvalumab and the patients receiving placebo. The majority of AEs were CTCAE Grade 1 or 2, with CTCAE Grade 3 or 4 AEs reported in 32.6% and 28.2% of patients, respectively.

Sections 8.2 and 8.3 discuss the AEs reported during patients' initial 12-month treatment period. The safety of the 18 durvalumab and 8 placebo patients who had received re-treatment at the time of the 22 March 2018 DCO is discussed in Section 8.4.

Overall, the small numerical differences (<1 percentage point [pp] increase in frequency in either treatment group) in AE categories from those at the 13 February 2017 DCO are attributable to the slightly longer exposure and follow-up at the 22 March 2018 DCO.

Table 13 Adverse events in any category (safety analysis set)

Adverse event category	Number (%) of patients[a]	
	Durvalumab (N=475)	Placebo (N=234)
Any AE	460 (96.8)	222 (94.9)
Any AE causally related to treatment [b]	322 (67.8)	125 (53.4)
Any AE of CTCAE Grade 3 or 4	155 (32.6)	66 (28.2)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	59 (12.4)	11 (4.7)
Any SAE (including events with outcome of death)	138 (29.1)	54 (23.1)
Any SAE (including events with outcome of death), causally related to treatment [b]	41 (8.6)	9 (3.8)
Any AE leading to discontinuation of study treatment	73 (15.4)	23 (9.8)
Any AE leading to discontinuation of study treatment, causally related to treatment [b]	47 (9.9)	8 (3.4)
Any AE with outcome of death	21 (4.4)	15 (6.4) [c]
Any AE with outcome of death, causally related to treatment [b]	7 (1.5)	4 (1.7)
Any AE leading to dose delay [d]	203 (42.7)	72 (30.8)
Any AESI	317 (66.7)	115 (49.1)

AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events version 4; SAE = serious adverse event.
a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b As assessed by the Investigator. Missing responses are counted as related.
c Includes 1 patient who had a fatal AE initially reported to be CTCAE grade 3 .
d AEs on the AE CRF form with Action taken = Drug interrupted, excluding those AEs on the dosing CRF forms only leading to infusion interruptions.
Includes AEs with an onset date on or after the date of first dose or pretreatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Source: Table 11.3.2.1.OS, Table 11.3.5.1.4.OS

8.2.2 Common adverse events

8.2.2.1 All adverse events

As noted above, at the time of the 22 March 2018 DCO, AEs were reported by 96.8% patients who received durvalumab and 94.9% of patients reported AEs regardless of causality (Table 14). Only cough was reported at an incidence >20% in either treatment group and occurred at an incidence >5 pp higher in patients receiving durvalumab (35.2%) than patients receiving placebo (25.2%). Other AEs that occurred at an incidence >5 pp higher in the

durvalumab group than the placebo group were pyrexia (15.2% vs 9.4%), pneumonia (13.3% vs 7.7%), pruritus (12.4% vs 5.1%), hypothyroidism (11.6% vs 1.7%), and hyperthyroidism (7.4% vs 1.7%).

There was no increase in frequency >1 percentage point in any AE between the 13 February 2017 and 22 March 2018 DCOs in either treatment group.

Table 14 Adverse events reported in at least 20% of patients in either treatment group and/or with a difference of at least 5 percentage points higher in patients receiving durvalumab versus placebo (Safety analysis set)

	Number (%) of patients[a]	
MedDRA preferred term	**Durvalumab (N=475)**	**Placebo (N=234)**
Patients with any AE	**460 (96.8)**	**222 (94.9)**
Cough	167 (35.2)	59 (25.2)
Fatigue	114 (24.0)	48 (20.5)
Dyspnoea	106 (22.3)	56 (23.9)
Radiation pneumonitis	96 (20.2)	37 (15.8)
Pyrexia	72 (15.2)	22 (9.4)
Pneumonia	63 (13.3)	18 (7.7)
Pruritus	59 (12.4)	12 (5.1)
Hypothyroidism	55 (11.6)	4 (1.7)
Hyperthyroidism	35 (7.4)	4 (1.7)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities, version 19.1.
a Number (%) of patients with AEs, sorted in decreasing frequency of preferred term.
Patients with multiple AEs are counted once for each preferred term.
Includes AEs with an onset date on or after the date of first dose or pretreatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication.
Source: Table 11.3.2.4.OS

8.2.3 Adverse events by severity

At the time of the 22 March 2018 DCO, the majority of AEs were CTCAE Grade 1 or 2. AEs of CTCAE Grade 3 or 4 were reported for 155 (32.6%) patients in the durvalumab group and 66 (28.2%) patients in the placebo group, which includes 3 additional patients in the durvalumab group and 1 patient in the placebo group who had a CTCAE Grade 3 or 4 AE between the 13 February 2017 and 22 March 2018 DCOs.

8.2.4 Adverse events of special interest (AESIs) and immune-mediated adverse events (imAEs)

At the time of the 22 March 2018 DCO, a higher proportion of patients who received durvalumab than those who received placebo experienced an AESI during the study (66.7% and 49.1%, respectively; Table 11.3.5.1.4.OS), which is consistent with the 65.5% and 48.7%, respectively, reported at the 13 February 2017 DCO (Table 11.3.5.1.OS and see Section 8.2.4, PACIFIC Interim CSR, Module 5.3.5.1).

The majority of AESIs were CTCAE Grade 1 or 2, with CTCAE Grade 3 or 4 AESIs reported in 9.1% and 3.4% of patients, respectively. No AESI of CTCAE Grade3 or 4 occurred at a more than 2-percentage-point difference between the 2 treatment groups.

The most frequently reported AESIs were dermatitis or rash (33.1% vs 18.4%), diarrhea (18.5% vs 20.1%), pneumonitis (13.7% vs 9.4%), and hypothyroidism (13.3% vs 3.0%) for patients receiving durvalumab and placebo, respectively (Table 11.3.5.1.4.OS, Table 11.3.5.2.2.OS, Table 11.3.5.2.3.OS). There was no increase in frequency >1 percentage point in any AESI between the 13 February 2017 and 22 March 2018 DCOs in either treatment group.

At the time of the 22 March 2018 DCO, pneumonitis or radiation pneumonitis was reported in 161 (33.9%) of patients who received durvalumab and 58 (24.8%) of patients who received placebo (Table 11.3.8.10.OS and Table 11.3.8.11.OS), which is unchanged from the 13 February 2017 DCO. A change in severity for 2 patients resulted in an increase in the number of patients in the durvalumab group with a CTCAE Grade 3 event (from 16 to 17 patients), and an increase in the number of patients in the placebo group with a CTCAE Grade 5 event (from 4 to 5 patients):

- CTCAE Grade 3 pneumonitis or radiation pneumonitis occurred in 3.6% of durvalumab patients and 3.0% of placebo patients
- No Grade 4 events of pneumonitis or radiation pneumonitis were reported in either treatment group
- Fatal events of pneumonitis or radiation pneumonitis occurred in 1.1% of durvalumab patients and 2.1% of placebo patients.

For narratives for patients with AESIs, see Section 11.4.4, PACIFIC Interim CSR, Module 5.3.5.1.

A total of 116 (24.4%) patients receiving durvalumab and 19 (8.1%) patients receiving placebo had an AESI that was adjudicated as an imAE. With the exception of 1 patient in the durvalumab group with an event of hypothyroidism that required endocrine therapy, there were no additional patients between the 13 February 2017 DCO and the 22 March 2018 DCO

who had AESIs that were adjudicated to be imAEs. One patient in the durvalumab group had a second imAE of radiation pneumonitis reported between the 2 DCOs.

8.3 Deaths, serious adverse events, discontinuation of study treatment due to adverse events, and other significant adverse events

8.3.1 Deaths

At the time of the 22 March 2018 DCO, 183 (38.4%) patients in the durvalumab group and 116 (48.9%) patients in the placebo group had died. The majority of deaths were related to disease under investigation only (147/183 [80.3%] and 86/116 [74.1%], respectively.

In 21 (4.4%) patients treated with durvalumab and 15 (6.4%) patients treated with placebo, the death was due to an AE or due to both the disease under investigation and an AE (Table 11.3.3.1.6.OS), which is consistent with the results from the 13 February 2017 DCO. An additional 2 patients in the placebo arm died due to an AE that started within the 90-day follow-up period after the last dose of study drug, but the start date of the AE was after the start of subsequent therapy.

Between the 13 February 2017 and 22 March 2018 DCOs, the only death during treatment or within 90 days of last dose was 1 patient in the placebo group who died due to disease under investigation only (Table 11.3.3.1.7.OS and see Table 11.3.3.1.2, PACIFIC Interim CSR, Module 5.3.5.1). For narratives, see Section 11.4.1, PACIFIC Interim CSR, Module 5.3.5.1. A by-patient listing of all deaths is included in Table 11.3.3.1.8.OS.

8.3.2 Serious adverse events

A total of 138 (29.1%) patients in the durvalumab group and 54 (23.1%) patients in the placebo group reported SAEs regardless of causality, which is consistent with the 136 (28.6%) and 53 (22.6%), respectively, reported from the 13 February 2017 DCO (see Section 8.3.2.1, PACIFIC Interim CSR, Module 5.3.5.1).

The most frequently reported SAEs were pneumonia (5.7% vs 5.1% for durvalumab and placebo groups, respectively), pneumonitis (3.6% vs. 3.0%), and radiation pneumonitis (3.6% vs. 1.7%) (Table 11.3.4.1.1.OS). For no SAE was there a difference of >1 percentage point between the results at the 13 February 2017 and the 22 March 2018 DCOs.

For a listing of all patients who had an SAE, including those with outcome of death, see Table 11.3.7.3.2.OS, PACIFIC Interim CSR, Module 5.3.5.1. For narratives for patients with SAEs other than death, see Section 11.4.2, PACIFIC Interim CSR, Module 5.3.5.1.

8.3.3 Adverse events leading to discontinuation of study medication

At the 13 February 2017 DCO, 73 (15.4%) patients treated with durvalumab and 23 (9.8%) patients treated with placebo had AEs leading to discontinuation of study medication

(Table 11.3.4.2.1.OS). There were no additional discontinuations due to AEs as of the 22 March 2018 DCO.

For a listing of key information for all patients who had an AE that led to discontinuation of study treatment, see Table 11.3.4.2.3.OS, PACIFIC Interim CSR, Module 5.3.5.1. For narratives for these patients, see Section 11.4.3, PACIFIC Interim CSR, Module 5.3.5.1.

8.4 Patients who were re-treated

Patients who completed 12 months of therapy and had SD, PR, or CR at completion continued to be followed up for RECIST 1.1 progression. Per the protocol, patients had the option to re-start study treatment (the treatment they were originally randomized to for the first 12 months) upon evidence of disease progression if they were eligible to do so, and it was considered the best treatment option for the patient. Amendment 5, which was implemented after the study was unblinded for PFS, specified that only patients whose disease progressed after completing 12 months of durvalumab treatment could be re-treated.

CCI

8.5 ADA-related adverse events

Between the 13 February 2017 and the 22 March 2018 DCOs, there was 1 patient PPD whose ADA status was reclassified from non-evaluable to transient positive. Review of AEs of this patient identified no infusion-related reaction or other safety concern. There was no new case of positive nAb.

Overall, the incidence of treatment-emergent positive ADA remains low: 1.9% in durvalumab group and 2.5% in the placebo group. No observable pattern was noted in the types of events seen and the timing of the event in association with the incident ADA. The incidence and severity of AEs reported in the ADA-positive patients were similar to those reported in patients who were ADA-negative. There was no clear evidence of any impact of positive ADA or nAb on durvalumab safety (Table 11.3.10.8.3.OS and Table 11.3.10.8.5.OS).

8.6 Clinical laboratory evaluation

8.6.1 Hematology

Hematology parameters were a maximum of CTCAE Grade 0, 1, or 2 for the majority of patients in both treatment groups while on study treatment (Table 15). In both treatment groups, the highest proportion of patients experiencing a change to CTCAE 3 or Grade 4 was in lymphocytes: 17.2% of patients in the durvalumab group and 18.8% of patients in the

placebo group, compared to 16.7% and 18.1%, respectively, at the 13 February 2017 DCO (see Table 11.3.10.4.1.OS, PACIFIC Interim CSR, Module 5.3.5.1).

For no hematology parameter was there a difference of >1 percentage point between the results at the 13 February 2017 and the 22 March 2018 DCOs.

Table 15 Clinically important changes in haematology parameters (Safety analysis set)

	n/N (%) of patients							
	Durvalumab (N=475)				Placebo (N=234)			
Haematology parameter	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4
Hemoglobin	471	74 (15.7)	6 (1.3)	9 (1.9)	229	37 (16.2)	5 (2.2)	9 (3.9)
Leukocytes	471	88 (18.7)	6 (1.3)	1 (0.2)	229	46 (20.1)	5 (2.2)	0
Lymphocytes	470	203 (43.2)	57 (12.1)	81 (17.2)	229	93 (40.6)	33 (14.4)	43 (18.8)
Neutrophils	470	38 (8.1)	17 (3.6)	4 0.9)	229	15 (6.6)	5 (2.2)	1 (0.4)
Platelets	471	53 11.3)	5 (1.1)	2 0.4)	229	30 (13.1)	0	0

CTCAE = Common Terminology Criteria for Adverse Events (version 4).
Derived from lab assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first).
Patient's worst changes from baseline are used.
Haematology parameters are all low unless stated otherwise.
Source: Table 11.3.10.4.1.OS

8.6.2 Clinical chemistry

Changes in clinical chemistry parameters were a maximum of CTCAE Grade 0, 1, or 2 for the majority of patients in both treatment groups (Table 16).

Apart from hyperglycemia (8.5% for durvalumab vs 7.5% for placebo, which represents 1 additional durvalumab patient after the 13 February 2017 DCO), shifts to CTCAE Grade 3 or 4 laboratory results were reported in less than 5% of patients across both treatment groups (Table 16).

For most clinical chemistry parameters, there were no clinically meaningful differences in the percentage of patients experiencing a change to a maximum CTCAE Grade 3 or 4 laboratory result between the 2 treatment groups. There was a difference of more than 1 percentage point between the treatment groups in patients with a shift to CTCAE Grade 3 or 4 in ALT (2.6% vs 0.4%, respectively), AST (3.0% vs 0.4%, respectively), and albumin (0.4% vs 2.2%, respectively).

For no clinical chemistry parameter was there a difference of >1 percentage point between the results at the 13 February 2017 and the 22 March 2018 DCOs.

Table 16 Clinically important changes in clinical chemistry parameters (safety analysis set)

	n/N (%) of patients							
	Durvalumab (N=475)				Placebo (N=234)			
Haematology parameter	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4
ALT	470	183 (38.9)	24 (5.1)	12 (2.6)	228	49 (21.5)	2 (0.9)	1 (0.4)
Albumin	469	82 (17.5)	34 (7.2)	2 (0.4)	228	46 (20.2)	28 (12.3)	5 (2.2)
Alkaline Phosphatase	471	90 (19.1)	7 (1.5)	5 (1.1)	228	32 (14.0)	1 (0.4)	1 (0.4)
AST	469	169 (36.0)	18 (3.8)	14 (3.0)	228	51 (22.4)	4 (1.8)	1 (0.4)
Bicarbonate	332	52 (15.7)	4 (1.2)	1 (0.3)	159	20 (12.6)	3 (1.9)	0
Corrected calcium	468	228 (48.7)	8 (1.7)	2 (0.4)	226	96 (42.5)	1 (0.4)	1 (0.4)
Low	468	220 (47.0)	4 (0.9)	1 (0.2)	226	93 (41.2)	0	0
High	468	9 (1.9)	4 (0.9)	1 (0.2)	226	3 (1.3)	1 (0.4)	1 (0.4)
Creatinine	465	76 (16.3)	5 (1.1)	0	226	24 (10.6)	1 (0.4)	0
GGT	203	42 (20.7)	7 (3.4)	6 (3.0)	75	14 (18.7)	1 (1.3)	2 (2.7)
Glucose	461	248 (53.8)	91 (19.7)	39 (8.5)	227	118 (52.0)	36 (15.9)	18 (7.9)
Low	461	15 (3.3)	4 (0.9)	0	227	3 (1.3)	2 (0.9)	1 (0.4)
High	461	240 (52.1)	89 (19.3)	39 (8.5)	227	116 (51.1)	35 (15.4)	17 (7.5)
Magnesium	442	44 (10.0)	3 (0.7)	5 (1.1)	218	11 (5.0)	0	0
Low	442	30 (6.8)	0	2 (0.5)	218	9 (4.1)	0	0
High	442	15 (3.4)	3 (0.7)	3 (0.7)	218	2 (0.9)	0	0

Table 16 Clinically important changes in clinical chemistry parameters (safety analysis set)

	n/N (%) of patients							
	Durvalumab (N=475)				Placebo (N=234)			
Haematology parameter	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4	N	At least 1 CTCAE grade change	At least 2 CTCAE grade changes	CTCAE grade changes to Grade 3 or 4
Potassium	470	209 (44.5)	35 (7.4)	12 (2.6)	228	89 (39.0)	16 (7.0)	8 (3.5)
Low	470	66 (14.0)	7 (1.5)	7 (1.5)	228	24 (10.5)	4 (1.8)	4 (1.8)
High	470	152 (32.3)	28 (6.0)	5 (1.1)	228	66 (28.9)	12 (5.3)	4 (1.8)
Sodium	470	210 (44.7)	19 (4.0)	18 (3.8)	228	90 (39.5)	7 (3.1)	7 (3.1)
Low	470	157 (33.4)	17 (3.6)	17 (3.6)	228	72 (31.6)	7 (3.1)	7 (3.1)
High	470	56 (11.9)	2 (0.4)	1 (0.2)	228	19 (8.3)	0	0
Total Bilirubin	469	31 (6.6)	5 (1.1)	0	229	14 (6.1)	1 (0.4)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events (version 4); GGT = gamma glutamyl transferase

Derived from lab assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first).

Patient's worst changes from baseline are used.

Clinical chemistry parameters are all high unless stated otherwise.

Source: Table 11.3.10.4.2.OS

8.6.2.1 Elevations in ALT, AST, or total bilirubin

A summary of the percentage of patients experiencing increases in liver enzymes ALT, AST, and bilirubin based on multiples of the ULN are presented in Table 17.

None of the patients in either treatment group had ALT at least 3 × ULN or AST at least 3 × ULN and total bilirubin at least 2 × ULN at any time point. A plot of ALT vs total bilirubin and of AST vs total bilirubin (expressed as multiples of ULN) is presented in Figure 11.3.10.5.2.2.OS and Figure 11.3.10.5.2.3.OS, respectively.

As of the 22 March 2018 DCO, 17 (3.6%) patients receiving durvalumab and 1 (0.4%) patient receiving placebo had a Grade 3 ALT or AST value >5 × ULN. Five (1.1%) patients receiving durvalumab had an ALT or AST value >10 × ULN. With the addition of 1 patient described below, these results are consistent with those seen at the 13 February 2017 DCO. No patients met the biochemical criteria for a potential Hy's Law case. Two patients receiving durvalumab discontinued due to increases in Grade 3 transaminases (Table 11.3.4.2.1.OS and see Section 8.5.2.4, PACIFIC Interim CSR, Module 5.3.5.1). For additional information on these 4 patients who had an ALT or AST value greater than 10 x ULN, see Section 8.5.2.1, PACIFIC Interim CSR, Module 5.3.5.1.

There was 1 new patient with ALT/AST >10 × ULN:

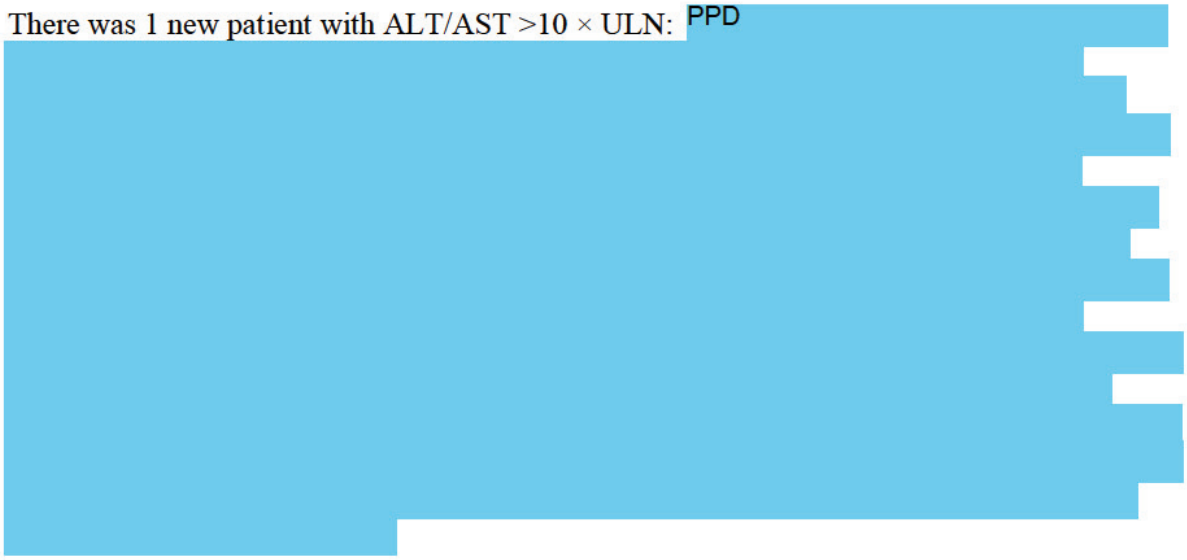


Table 17 Liver function abnormalities on treatment (safety analysis set)

Parameter	Number (%) of patients	
	Durvalumab (N=475)	Placebo (N=234)
ALT		
≥3 x - ≤5 x ULN	16 (3.4)	3 (1.3)
>5 x - ≤8 x ULN	7 (1.5)	1 (0.4)

Table 17 Liver function abnormalities on treatment (safety analysis set)

Parameter	Number (%) of patients	
	Durvalumab (N=475)	Placebo (N=234)
>8 x - ≤10 x ULN	0	0
>10 x - ≤20 x ULN	5 (1.1)	0
>20 x ULN	0	0
AST		
≥3 x - ≤5 x ULN	5 (1.1)	4 (1.7)
>5 x - ≤8 x ULN	10 (2.1)	0
>8 x - ≤10 x ULN	2 (0.4)	1 (0.4)
>10 x - ≤20 x ULN	1 (0.2)	0
>20 x ULN	1 (0.2)	0
Total bilirubin		
≥2 x - ≤3 x ULN	0	2 (0.9)
>3 x - ≤5 x ULN	0	0
>5 x ULN	0	0
ALT or AST		
≥3 x - ≤5 x ULN	16 (3.4)	6 (2.6)
>5 x - ≤8 x ULN	10 (2.1)	0
>8 x - ≤10 x ULN	2 (0.4)	1 (0.4)
>10 x - ≤20 x ULN	4 (0.8))	0
>20 x ULN	1 (0.2)	0
Potential Hy's law [a]		
ALT or AST ≥3 x ULN) and total bilirubin ≥2 x ULN	0	0

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.
a The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin evaluation.
Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first).
Source: Table 11.3.10.5.1.OS

8.6.2.2 Creatinine clearance

Patients were allowed into the study with creatinine clearance of 40 mL/min or greater, as determined by Cockcroft-Gault formula.

There were no differences in creatinine clearance results between the 13 February 2017 and the 22 March 2018 DCOs (Table 11.3.10.3.2.OS and see Section 8.5.2.4, PACIFIC Interim CSR, Module 5.3.5.1).

No patients developed kidney failure (defined as glomerular filtration rate [GFR] of < 15 mL/min) during the study. Three (0.7%) patients in the durvalumab group had severe impairment (defined as GFR at least 15 to < 30 mL/min), during the study. All 3 of these patients entered the study with moderate renal impairment (defined as GFR ≥ 30 to < 60 mL/min).

8.7 Vital signs, electrocardiograms, physical findings, and other observations related to safety

8.7.1 Changes in vital signs and ECG over time

See Section 8.6.1, PACIFIC Interim CSR, Module 5.3.5.1.

8.7.2 Clinically important abnormalities in vital signs and electrocardiogram

See Section 8.6.2, PACIFIC Interim CSR, Module 5.3.5.1.

8.7.3 Physical findings and other observations related to safety

See Section 8.6.3, PACIFIC Interim CSR, Module 5.3.5.1.

8.7.4 Pregnancy and overdose

No pregnancy was reported during the study. PPD

8.8 Safety evaluation conclusions

- Overall, durvalumab was well-tolerated and had a manageable safety profile relative to the standard of care for the population under study. The type, incidence, and severity of AEs were generally comparable between the treatment groups. Where not comparable, the type, incidence, and severity of events were consistent with the established durvalumab safety profile to date, with the exception of the events of pneumonitis/radiation pneumonitis.

- In general, as expected in this population of patients who had received platinum-based cCRT, there was a high background incidence of radiation pneumonitis and pneumonitis. Pneumonitis or radiation pneumonitis was reported in 161 (33.9%) of patients who received durvalumab and 58 (24.8%) of patients who received placebo. CTCAE Grade 3 events occurred in 3.6% and 3.0%, respectively, and fatal events occurred in 1.1% and 2.1%, respectively. No CTCAE Grade 4 events were reported.

- No clinically important changes from baseline or trends in hematology or clinical chemistry values over time were observed in either treatment group. No patient in either treatment group met the biochemical criteria for a potential Hy's Law case or had post-baseline changes in creatinine values greater than CTCAE Grade 2.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

In patients with locally advanced, unresectable, NSCLC, chemoradiation provides only a small chance of cure (Eberhardt et al (ESMO) 2015). There are no approved consolidation therapies after definitive chemoradiation (Saijo et al 2010). Patients whose disease does not progress after chemoradiation are carefully monitored, and are followed-up without treatment until their disease progresses. In most patients, the relapse is systemic, making the disease incurable, with a poor prognosis and a 5-year survival rate of approximately 15% (Aupérin et al 2010). Patients who relapse may be eligible for subsequent therapies; however, the clinical reality remains that nearly half of these patients never receive subsequent therapies due to poor performance status, limited treatment options, and co-morbidities associated with disease recurrence. If therapy is possible, options are limited because platinum-based chemotherapy has already been used as part of chemoradiation. In addition, most patients experience local and/or distant metastasis and, thereby, present a clinical challenge for improving outcomes. At present, there are no treatments that can delay or prevent recurrence. These realities highlight the need for early intervention following initial treatment with chemoradiation to keep patients progression-free and maintain them in a potentially curative state.

PACIFIC is an ongoing, randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in patients with locally advanced, unresectable Stage III NSCLC who have not progressed following definitive, platinum-based cCRT.

A total of 713 patients were randomized in a 2:1 ratio to receive either durvalumab 10 mg/kg Q2W (476 patients) or placebo (237 patients). At the time of the data cut-off date of 22 March 2018 for this addendum, 49.0% patients in the durvalumab group and 82 (34.7%) patients in the placebo group had completed the protocol-defined 12 months of treatment.

The demographic and disease characteristics were representative of the intended patient population and were well-balanced between the 2 treatment groups.

The study's 2 primary efficacy endpoints were met and the results of the respective interim analyses were considered final. In the pre-planned interim analysis of PFS (13 February 2017 DCO), durvalumab treatment demonstrated a statistically significant and clinically meaningful benefit in PFS compared with placebo (HR: 0.52; 95%CI: 0.42, 0.65 p-value <0.0001).

In the pre-planned interim analysis of OS (DCO of 22 March 2018), durvalumab treatment demonstrated a statistically significant and clinically meaningful benefit in OS compared with placebo (HR: 0.68; 95%CI: 0.53, 0.87; p-value=0.00251). Durvalumab treatment resulted in a 32% reduction in the overall risk of death. Median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was observed early and was sustained over the treatment period, with a numerically higher OS rate for the durvalumab group vs the placebo group at both the OS12 (83.1% vs. 75.3%, respectively) and OS24 (66.3% vs. 55.6%, respectively)

landmarks. Results from a sensitivity analysis that used stratification factors as determined by the baseline CRF variables were consistent with the primary analysis of OS, and improvements in OS in favor of durvalumab over placebo were observed across all pre-specified subgroups.

Treatment with durvalumab was also associated with clinically meaningful improvements when compared to placebo in all of the secondary/supportive efficacy parameters: ORR, DoR, TTDM, TFST, PFS2, and TSST.

Patient-reported-outcome data showed a high level of compliance (>80%) for both groups for up to 48 weeks. Results across all sub-scales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.

There was no evidence that the ADA and/or nAb had any impact on PK or safety of durvalumab.

At the time of the 22 March 2018 DCO, the median total duration of treatment was 48 weeks on durvalumab and 32 weeks on placebo. Durvalumab treatment demonstrated a well-tolerated and manageable safety and tolerability profile, which was consistent with that reported at the DCO of 13 February 2017. No new safety signals had emerged.

9.2 Overall conclusion

Despite the recent advances in the treatment of NSCLC, the prognosis of patients with unresectable locally advance disease is still poor with survival rates still disappointing. A significant unmet medical need exists for the development of new treatment strategies that can prolong the favorable clinical state after patients achieve initial disease control with chemoradiation.

In the pre-planned interim analyses of the 2 primary endpoints of PFS (13 February 2017 DCO) and OS (22 March 2018 DCO), durvalumab treatment demonstrated a statistically significant and clinically meaningful benefit compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.

Consistent PFS and OS benefits were also noted across all key secondary efficacy endpoints, as well as in prespecified subgroups.

Durvalumab treatment continued to demonstrate a well-tolerated and manageable safety profile that was generally consistent with the established safety profile to date.

Taken together, the overall benefit:risk of durvalumab treatment is highly favorable in this population. And, thus, treatment with durvalumab should be considered a new standard of care for patients with locally advanced, unresectable NSCLC whose disease had not progressed after platinum-based cCRT.

10. REFERENCE LIST

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11. SUMMARY TABLES AND FIGURES AND LISTINGS

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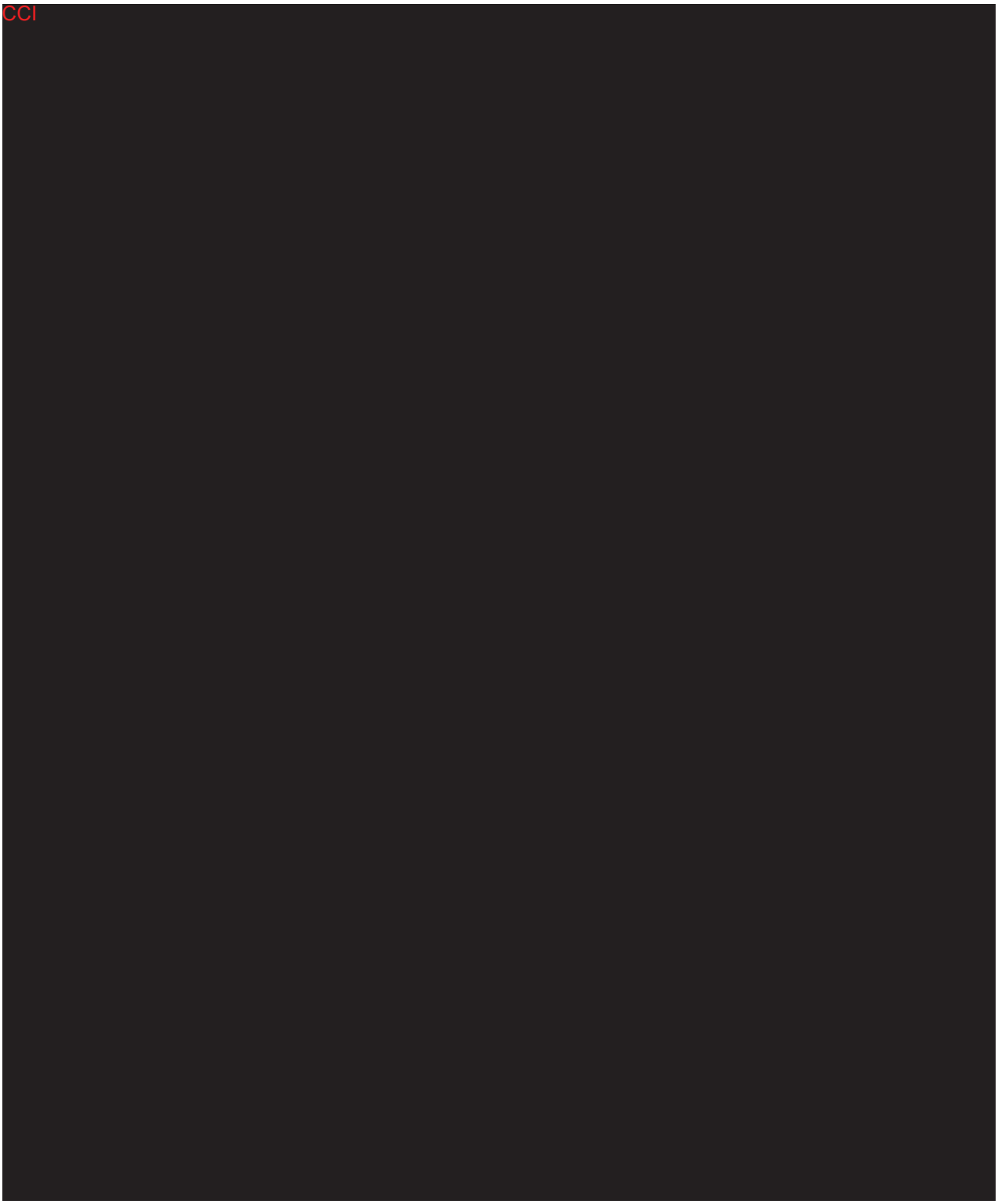

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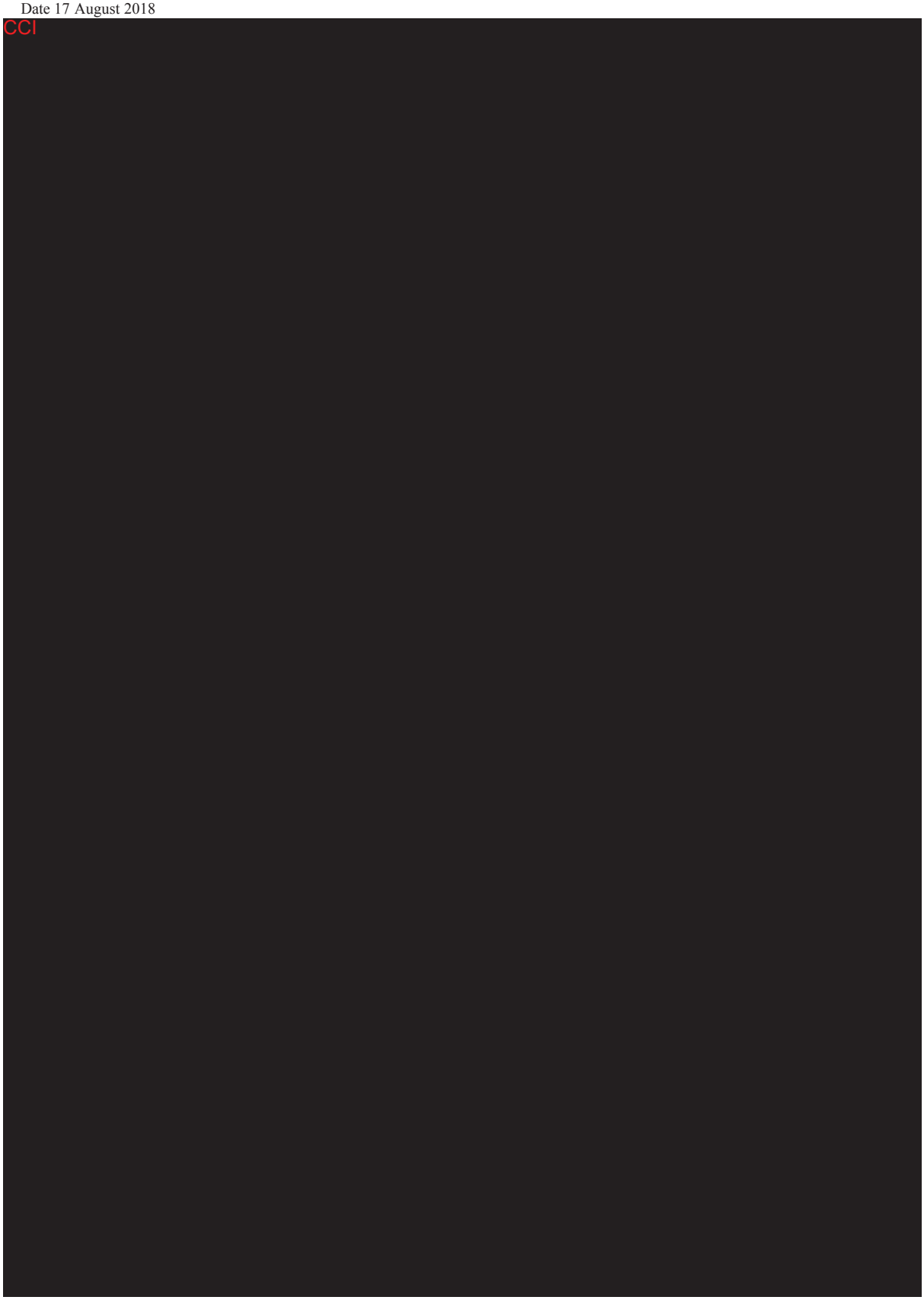

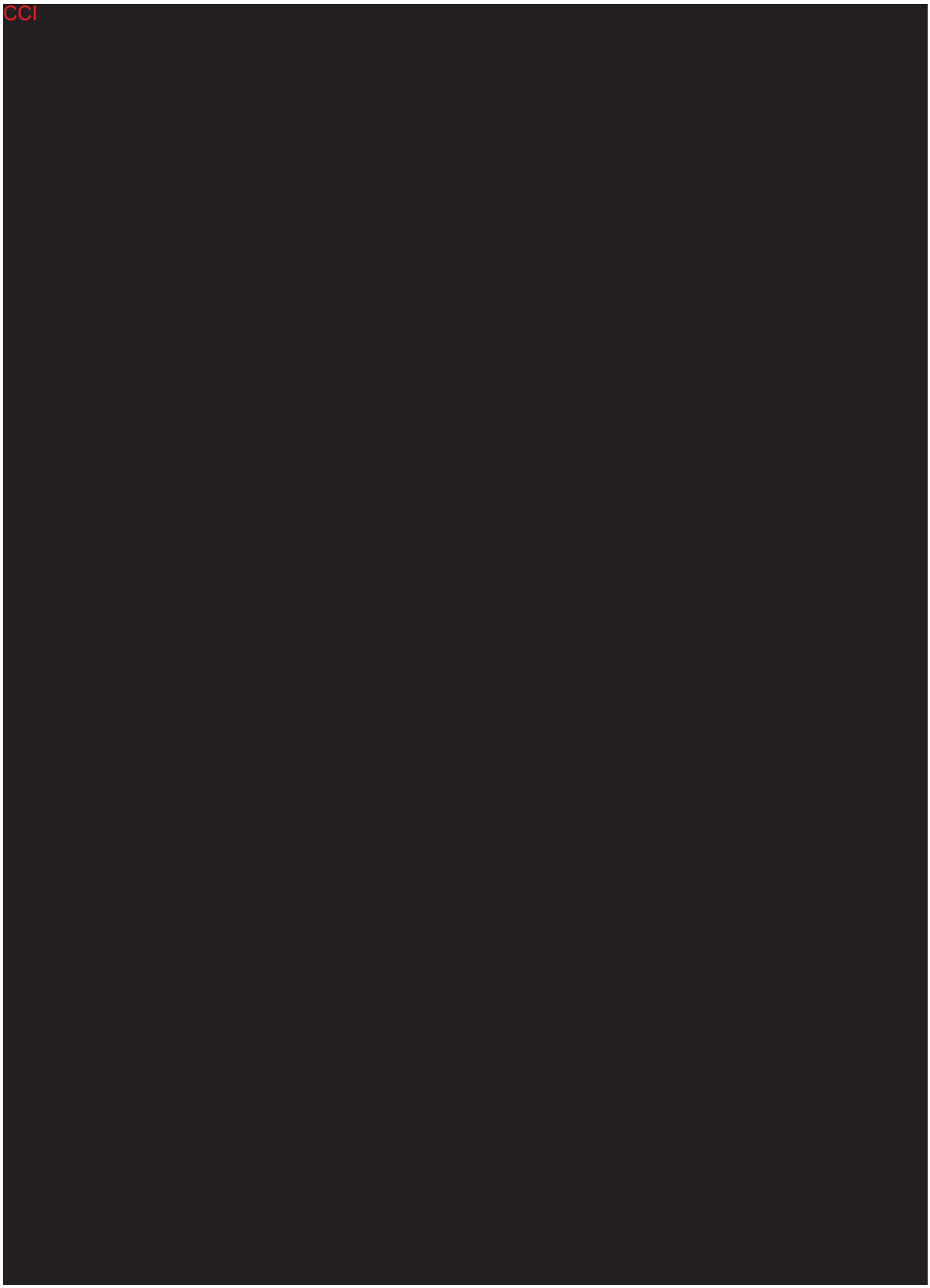
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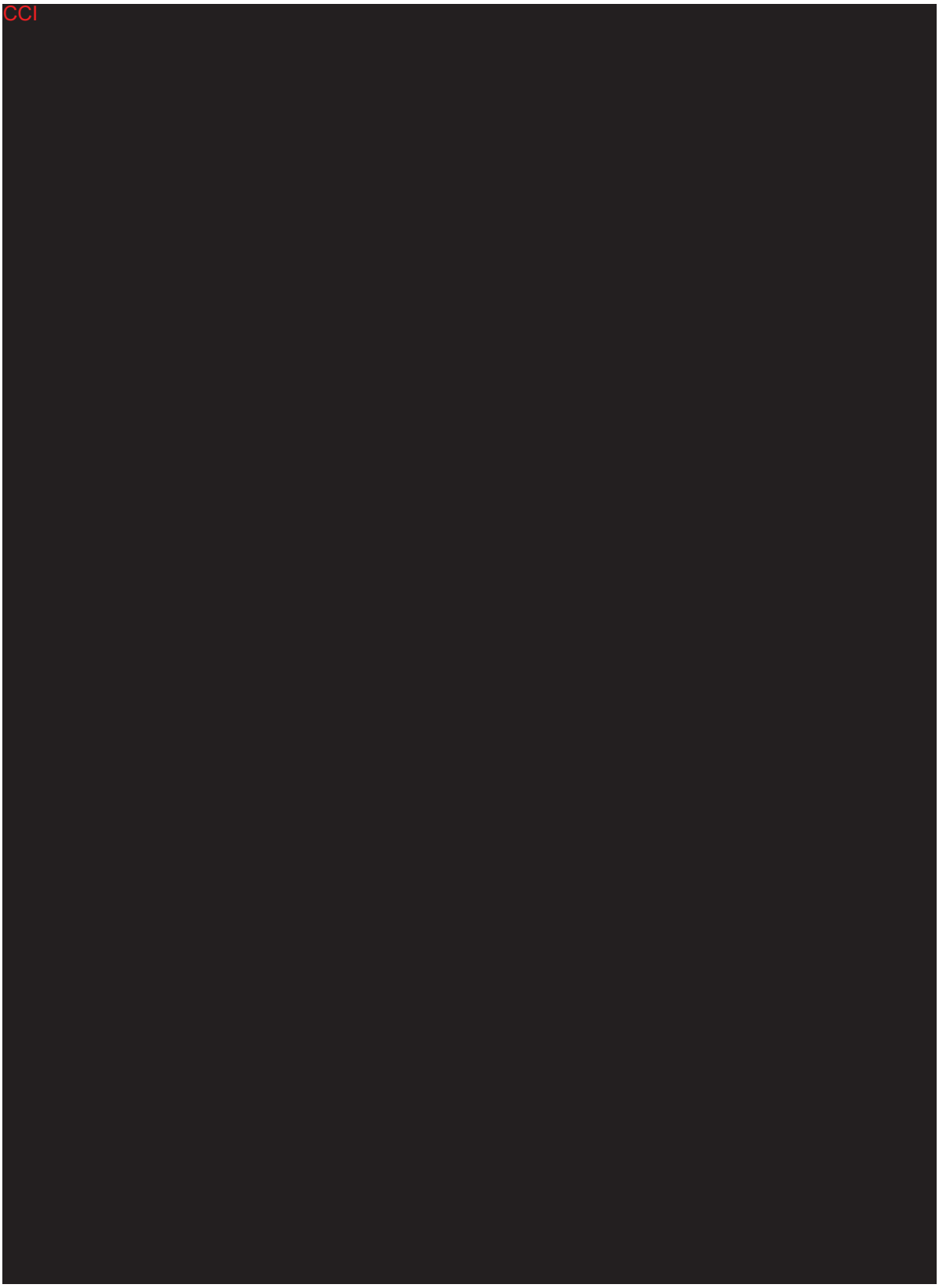

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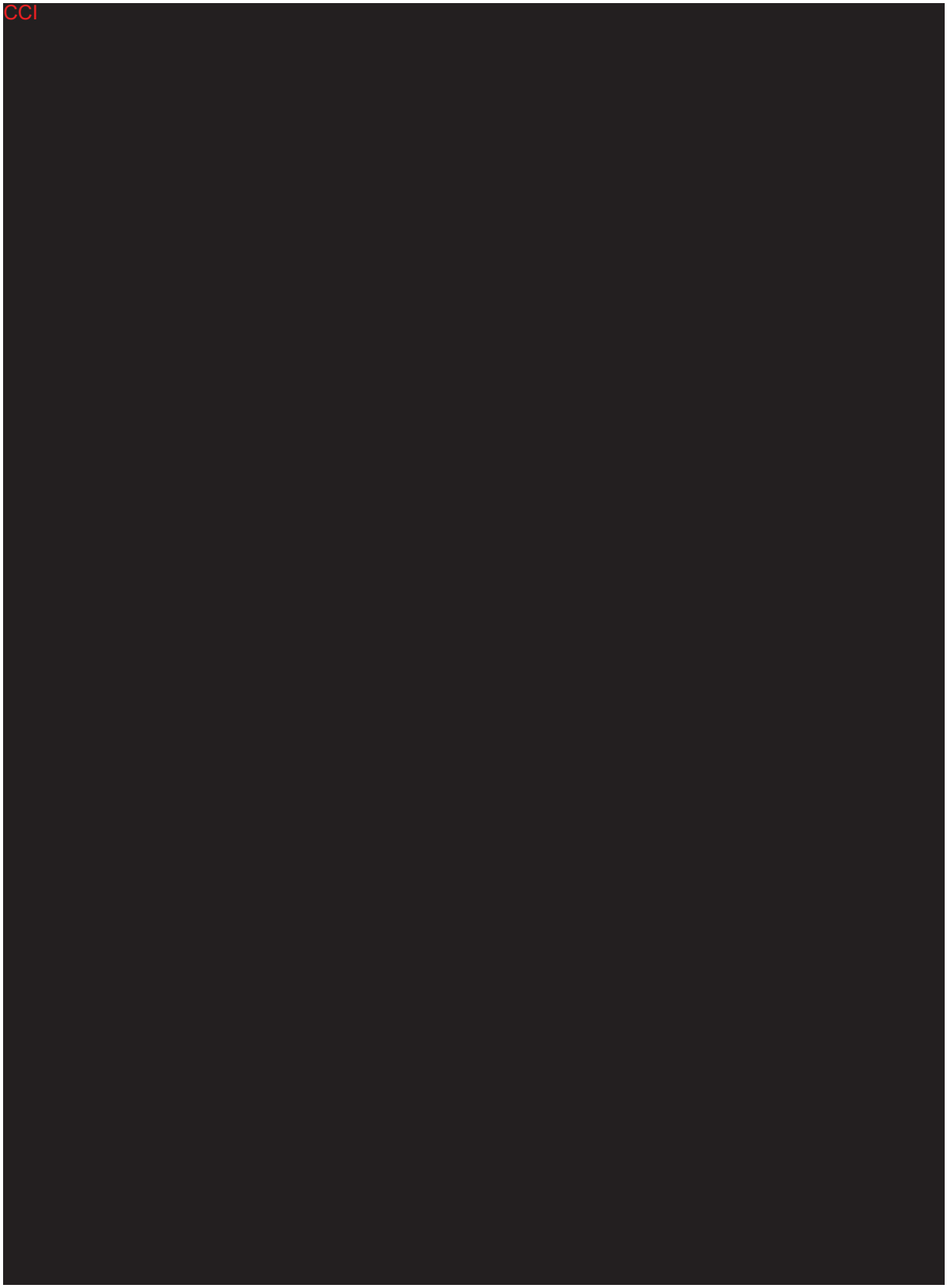

Clinical Study Report Addendum2

Drug Substance	Durvalumab
Study Code	D4191C00001
Edition Number	01
Date	08 May 2019
EudraCT Number	2014-000336-42

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of DURVALUMAB as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Study dates: First patient randomized: 09 May 2014
Last patient randomized: 22 April 2016
Data cut-off date: 31 January 2019 (study ongoing)

Phase of development: III

Sponsor's Responsible Medical Officer:

PPD
AstraZeneca LP
PPD
Gaithersburg, MD 20878

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
AE	adverse event
BICR	blinded independent central review
CI	confidence interval
CR	complete response
CSR	clinical study report
DCO	data cut-off
DoR	duration of response
eCRF	electronic case report form
HR	hazard ratio
LSI	last subject in
NR	not reached
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-L1	programmed death ligand 1
PFS	progression-free survival
PFS2	time to second progression or death
PR	partial response
PRO	patient-reported outcome
SAE	serious adverse event
SD	stable disease or standard deviation
TFST	time to first subsequent therapy or death
TSST	time to second subsequent therapy or death
TTDM	time to death or distant metastasis
WHO	World Health Organization

1. ETHICS

For information on ethics, please see Section 1, PACIFIC Interim clinical study report (CSR), Module 5.3.5.1.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

For information on study personnel and administrative structure, please see Section 2, PACIFIC Interim CSR, Module 5.3.5.1.

3. INTRODUCTION

PACIFIC (D4191C00001) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multi-centre, global clinical study designed to evaluate the efficacy and safety of durvalumab (IMFINZI™) compared with placebo in patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemoradiation. The primary objective is to assess the efficacy of durvalumab compared with placebo in terms of progression-free survival (PFS; based on blinded independent central review [BICR]) and overall survival (OS). Secondary efficacy endpoints included OS at 24 months, objective response rate (ORR), duration of response (DoR), time to death or distant metastases (TTDM), time to second progression or death (PFS2), and patient-reported outcome (PRO). Time to first subsequent therapy or death (TFST) was derived as a supportive summary to PFS and time to second subsequent therapy or death (TSST) was derived as a supportive summary to PFS2.

Four DCOs were originally planned for this study including 1 interim for PFS and 2 interims for OS as follows:

- The planned interim analysis of PFS was conducted after 371 events (80%) of the target 458 events were observed (data cut-off [DCO]: 13 February 2017).
    - The results of the interim PFS analysis were reviewed by the IDMC (20 April 2017). Since the study achieved pre-specified statistical significance (p-value <0.011035), the interim analysis of PFS was considered to be the final PFS analysis. Therefore, it will be referred to as “the primary PFS analysis” in this document.
    - Based on the review of that interim analysis, the Sponsor unblinded the study for PFS and safety.
    - A comprehensive analysis of PFS along with a detailed presentation of the safety and tolerability profile of the durvalumab treatment is outlined/presented in the PACIFIC interim CSR (see PACIFIC interim CSR, Module 5.3.5.1).

- The planned interim OS analysis was conducted after 299 (61%) of the target 491 death events were observed (DCO: 22 March 2018).
    - Results from the interim OS analysis were reviewed by the Independent Data Monitoring Committee on 21 May 2018.
    - Since the study achieved the statistical significance level of ≤0.00274 that met the predefined criterion for unblinding the OS data, the results of the first interim OS analysis (see CSR Addendum 1) was considered the final OS analysis. Therefore, it will be referred to as "the primary OS analysis" in this document.
    - The CSR addendum 1 reported the results from the 22 March 2018 DCO.
    - All tables, figures and listings that were generated based on the 22 March 2018 DCO are presented in Section 11 of the CSR Addendum 1, including new outputs for the OS results and secondary endpoints of OS24, PFS2, TSST; updated results for the secondary/supportive efficacy parameters of ORR, DoR, TFST, TDDM, and PRO; and updated results for the primary safety parameters (ie, adverse events [AEs], serious adverse events [SAEs], deaths).
    - Due to the small number of patients still ongoing study treatment at the time of the initial data cut-off (13 February 2017) (a total of 42 patients: 30 in the durvalumab group and 12 in the placebo group), the additional safety data for CSR addendum 1 were limited, thus other safety sections primarily referred to the full results in the Interim CSR.
    - At the time of the CSR addendum 1, all patients had completed the protocol-defined 12 months of study drug treatment or discontinued treatment prior to the defined 12 months of treatment.
        - Since May 2017, no patient has received study drug under the initial protocol defined 12-month treatment period.
- The OS follow-up was performed approximately 3 years after last subject in (LSI) (DCO: 31 January 2019).
    - This CSR addendum reports the results of a long-term overall survival follow-up and subsequent anti-cancer therapy usage, as of 31 January 2019 DCO.

This CSR addendum (PACIFIC Interim CSR Addendum 2) is related to the long-term survival follow up of PACIFIC (D4191C00001) study. There are no updates on PFS, pharmacokinetic, immunogenicity, or safety to be presented in this document. Therefore, the focus is on the long-term survival follow-up data providing updates on disposition, overall survival and subsequent anti-cancer usage

Patients will continue to be followed for long-term survival and follow-up analyses will be presented in future reports, as needed.

4. STUDY OBJECTIVES

The primary and secondary objectives are presented in the PACIFIC Interim CSR (see Section 4, PACIFIC Interim CSR, Module 5.3.5.1).

Appendix 12.1.14 in the CSR Addendum 1 presents results of efficacy analyses from exploratory *post hoc* biomarker (programmed death ligand 1 [PD-L1]) subgroup analyses (see Appendix 12.1.14, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

5. STUDY PLAN AND PROCEDURES

5.1 Overall study design and flow chart

This is an ongoing, randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable Stage III NSCLC, who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

For details on the study design, see Section 5.1, PACIFIC Interim CSR, Module 5.3.5.1.

5.2 Rationale for study design, doses, and control groups

See Section 5.2, PACIFIC Interim CSR, Module 5.3.5.1.

5.3 Selection of study population

See Section 5.3, PACIFIC Interim CSR, Module 5.3.5.1.

5.4 Treatments

See Section 5.4, PACIFIC Interim CSR, Module 5.3.5.1.

5.5 Measurements of study variables and definitions of outcome variables

See Section 5.5, PACIFIC Interim CSR, Module 5.3.5.1.

5.6 Data management and quality assurance

See Section 5.6, PACIFIC Interim CSR, Module 5.3.5.1.

5.7 Statistical methods and determination of sample size

See Section 5.7, PACIFIC Interim CSR, Module 5.3.5.1.

5.8 Clinical study protocol amendments and other changes in the conduct of the study or planned analyses

5.8.1 Changes in the conduct of the study

Important amendments to the original study protocol, including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct are presented in the Interim CSR (see Table 8, PACIFIC Interim CSR, Module 5.3.5.1) and Interim CSR Addendum 1 (Table 1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

There were no protocol amendments between the primary OS analysis (DCO: 22 March 2018) as reflected in the PACIFIC CSR Addendum 1 and the OS follow-up analysis (DCO: 31 January 2019) as reflected in this document (PACIFIC CSR Addendum 2).

5.8.2 Changes to planned analyses

No additional changes have been made to the planned analyses from those outlined in the PACIFIC Interim CSR (see Section 5.8.2, PACIFIC Interim CSR, Module 5.3.5.1).

6. STUDY PATIENTS

Summary tables and figures pertaining to this section are presented in Section 11.1.

6.1 Disposition

A total of 983 patients were enrolled in 235 study centers across 26 countries worldwide. Of these, 713 patients were randomized in 2:1 ratio to receive either durvalumab 10 mg/kg every 2 weeks (476 patients) or placebo (237 patients; full analysis set; Table 1).

Of the 713 patients, 709 (473 [99.4%] in the durvalumab group and 236 [99.6%] in the placebo group) received study treatment (Table 1). The other 4 patients (3 [0.6%] in the durvalumab group and 1 [0.4%] in the placebo group) were randomized but did not receive study treatment because of patient decision (2 patients), neutropenia (1 patient), and worsening chronic obstructive pulmonary disease (1 patient) (see Section 6.1, PACIFIC Interim CSR, Module 5.3.5.1). The first patient was randomized into the study on 09 May 2014, and the last patient was randomized on 22 April 2016.

At the time of the primary OS primary analysis (DCO: 22 March 2018) for the CSR Addendum 1, 314 patients had completed the protocol-defined 12 months of treatment: 232 (49.0%) patients in the durvalumab group and 82 (34.7%) patients in the placebo group. Treatment had been discontinued prior to the defined 12 months of treatment in the other 241 (51.0%) patients in the durvalumab group and 154 (65.3%) patients in the placebo group (see Table 2 in PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). For further details on the patient disposition at the time of OS interim analysis see Table 2 in PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the OS follow-up (approximately 3 years from LSI) analysis (DCO: 31 January 2019) for the CSR Addendum 2, the patient disposition was consistent with that of the OS primary analysis (DCO: 22 March 2018) except for the two following factors (Table 1):

- As anticipated with a longer follow-up, a lower number of patients remained on the study: 245 (51.5%) patients in the durvalumab group and 92 (38.8%) patients in the placebo group at the OS follow-up, as compared to 273 (57.4%) patients in the durvalumab group and 108 (45.6%) patients in the placebo group at the primary OS analysis.

- A total of 376 patients had terminated the study at the OS follow-up analysis, 231 (48.5%) patients in the durvalumab group and 145 (61.2%) patients in the placebo group, as compared to 203 (42.6%) patients in the durvalumab group and 129 (54.4%) patients in the placebo group at the primary OS analysis.

The reasons for study termination, included death (207 [43.5%] and 128 [54.0%] patients in the durvalumab and placebo groups, respectively), subject decision (23 [4.8%] and 16 [6.8%] patients in the durvalumab and placebo groups, respectively), subject lost to follow-up (1 [0.2%] and 0 [0%] patients in the durvalumab and placebo groups, respectively), and a missing reason for a patient who died (0 [0%] and 1 [0.4%] patients in the durvalumab and placebo groups, respectively) (Table 1). The detailed information on the number of new deaths from the primary OS analysis (DCO: 22 March 2018) in each arm is presented in Section 8.1.1 (deaths).

Table 1 Patient disposition (all patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Patients enrolled [a]			983
Patients randomized	476 (48.4)	237 (24.1)	713 (72.5)
Patients who were not randomized			270 (27.5)
Subject decision			35 (3.6)
Eligibility criteria not fulfilled			225 (22.9)
Death			6 (0.6)
Other			4 (0.4)
Full analysis set	476 (100.0)	237 (100.0)	713 (100.0)
Patients who received study treatment [b]	473 (99.4)	236 (99.6)	709 (99.4)
Patients who did not receive study treatment [b]	3 (0.6)	1 (0.4)	4 (0.6)
Patients who completed 12 months of treatment [c][d]	232 (49.0)	82 (34.7)	314 (44.3)
Patients who discontinued study treatment [c]	241 (51.0)	154 (65.3)	395 (55.7)
Subject decision	14 (3.0)	12 (5.1)	26 (3.7)
Adverse event	73 (15.4)	23 (9.7)	96 (13.5)
Severe non-compliance to protocol	1 (0.2)	1 (0.4)	2 (0.3)
Condition under investigation worsened	148 (31.3)	117 (49.6)	265 (37.4)
Development of study specific discontinuation criteria	1 (0.2)	1 (0.4)	2 (0.3)
Other	4 (0.8)	0	4 (0.6)
Patients ongoing study at data cut off [b]	245 (51.5)	92 (38.8)	337 (47.3)
Patients who terminated study [b]	231 (48.5)	145 (61.2)	376 (52.7)
Subject decision	23 (4.8)	16 (6.8)	39 (5.5)

Table 1 Patient disposition (all patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Death	207 (43.5)	128 (54.0)	335 (47.0)
Subject lost to follow-up	1 (0.2)	0	1 (0.1)
Missing	0	1 (0.4)	1 (0.1)

[a] Informed consent received.
[b] In this section, percentages are calculated from number of patients in the full analysis set.
[c] In this section, percentages are calculated from number of patients who received treatment.
[d] Patients who completed 12 months of treatment have reported maximum cycle of immunotherapy reached on the electronic case report form (eCRF).
Note: Eight patients who terminated study due to subject decision have died. One patient with missing termination reason has died.
Source: Table 11.1.1.OSUP1

Prior to the primary PFS analysis of the PACIFIC study, the option for re-treatment was conducted in a blinded manner and treatment allocation was not known. The PACIFIC study protocol was amended after the PFS primary endpoint was met since treatment options available to patients had changed since the study was first designed, including the availability of anti PD-1 and PD-L1 agents for advanced NSCLC. Sites remained blinded to treatment allocation prior to the primary analysis of overall survival (OS); however, any patient who was eligible for re-treatment and wished to receive further study drug at the time of progression was unblinded at the site by the investigator and only patients randomized to the durvalumab arm were then eligible for re-treatment. In addition re-treatment was no longer restricted to a 12- month treatment period as in the original study design, but was amended to a treatment duration for as long as the patient continues to benefit which was consistent with the re-treatment period for newer studies in the clinical development program for durvalumab.

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6.2 Protocol deviations

The important protocol deviations for the Interim PFS analysis (DCO: 13 February 2017) are reported in the Interim CSR (See Section 6.2, PACIFIC Interim CSR, Module 5.3.5.1).

No additional important protocol deviations were identified at the primary OS analysis or the OS follow-up analysis (DCO: 31 January 2019). PPD

6.3 Patients analyzed (analysis sets)

A full presentation of the analysis set used for each outcome variable is presented in the Interim CSR and CSR Addendum 1 (see Section 6.3, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.3, PACIFIC Interim CSR addendum 1, Module 5.3.5.1).

6.4 Demographic and other patient characteristics

A full presentation of the demographic and key baseline characteristics of study patients, including prior therapies, is presented in the Interim CSR and CSR addendum 1 (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.4, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). Demographics and baseline characteristics were representative of the intended patient population, and well balanced between the 2 treatment groups.

6.4.1 Concomitant medication after study entry

Concomitant medication was collected whilst patients received study drug and for 90 days after receiving the last dose of study drug. All patients had completed the 90 days follow-up following the last dose of the protocol defined 12-month treatment period in August 2018. As such there is no update for the concomitant medication after study entry at the OS follow-up analysis (DCO: 31 January 2019) as compared to the primary OS analysis (DCO: 22 March 2018).

A detailed description of concomitant medication after study entry was provided at the primary OS analysis (DCO: 22 March 2018) in the Interim CSR Addendum 1 (See Table 11.1.12.OS and Table 11.1.12, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

6.4.2 Post-discontinuation disease-related anti-cancer therapy

Post-discontinuation disease-related anti-cancer therapy analysis was presented in PACIFIC Interim CSR Addendum 1 at the primary OS analysis (DCO: 22 March 2018) (See Table 11.1.18.OS and Section 6.4.2, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of OS follow-up analysis (DCO: 31 January 2019), the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to OS primary analysis.

A total of 206 (43.3%, 11 more patients from the OS interim analysis DCO) patients in the durvalumab group and 137 (57.8%, 9 more patients from the OS interim analysis DCO) patients in the placebo group received post-discontinuation disease-related, anti-cancer therapy (Table 2). Most patients in both treatment groups received cytotoxic chemotherapy (eg, carboplatin and pemetrexed): 138 (29.0%) patients in the durvalumab group and 81 (34.2%) patients in the placebo group. Other systemic therapy (eg, targeted therapies) was administered in 50 (10.5%) of patients in the durvalumab group and 34 (14.3%) in the placebo group. Fewer patients in the durvalumab group than the placebo group received immunotherapy: 46 (9.7%) vs 63 (26.6%), respectively. A total of 89 (18.7%) patients in the durvalumab group and 60 (25.3%) patients in the placebo group received radiotherapy.

Table 2 Post-discontinuation disease-related anti-cancer therapy (Full analysis set)

		Number(%) of patients		
Anti-cancer therapy [a]	**Treatment**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Total (N=713)**
Number of patients with post-discontinuation disease-related anti-cancer therapy		206 (43.3)	137 (57.8)	343 (48.1)
Radiotherapy		89 (18.7)	60 (25.3)	149 (20.9)
Immunotherapy		46 (9.7)	63 (26.6)	109 (15.3)
	Atezolizumab	2 (0.4)	1 (0.4)	3 (0.4)
	Avelumab	0	1 (0.4)	1 (0.1)
	Bms 986205	1 (0.2)	0	1 (0.1)
	Durvalumab	1 (0.2)	2 (0.8)	3 (0.4)
	Ipilimumab	1 (0.2)	1 (0.4)	2 (0.3)
	Nivolumab	33 (6.9)	52 (21.9)	85 (11.9)
	Pembrolizumab	10 (2.1)	8 (3.4)	18 (2.5)
	Tremelimumab	1 (0.2)	0	1 (0.1)
	Uncoded	3 (0.6)	1 (0.4)	4 (0.6)
Cytotoxic Chemotherapy		138 (29.0)	81 (34.2)	219 (30.7)
	Amrubicin Hydrochloride	2 (0.4)	1 (0.4)	3 (0.4)
	Carboplatin	79 (16.6)	44 (18.6)	123 (17.3)
	Cisplatin	20 (4.2)	16 (6.8)	36 (5.0)
	Docetaxel	42 (8.8)	15 (6.3)	57 (8.0)
	Fluorouracil	0	1 (0.4)	1 (0.1)
	Gemcitabine	37 (7.8)	19 (8.0)	56 (7.9)
	Gemcitabine Hydrochloride	7 (1.5)	5 (2.1)	12 (1.7)
	Gimeracil;Oteracil Potassium;Tegafur	8 (1.7)	4 (1.7)	12 (1.7)
	Irinotecan	0	1 (0.4)	1 (0.1)
	Nedaplatin	1 (0.2)	0	1 (0.1)
	Oxaliplatin	0	1 (0.4)	1 (0.1)
	Paclitaxel	28 (5.9)	16 (6.8)	44 (6.2)
	Paclitaxel Albumin	11 (2.3)	6 (2.5)	17 (2.4)
	Pemetrexed	27 (5.7)	16 (6.8)	43 (6.0)
	Pemetrexed Disodium	20 (4.2)	15 (6.3)	35 (4.9)
	Pemetrexed disodium heptahydrate	1 (0.2)	0	1 (0.1)
	Topotecan	0	1 (0.4)	1 (0.1)
	Uncoded	1 (0.2)	1 (0.4)	2 (0.3)
	Vinorelbine	8 (1.7)	5 (2.1)	13 (1.8)
	Vinorelbine tartrate	8 (1.7)	3 (1.3)	11 (1.5)
Systemic Therapy (Targeted therapy)		50 (10.5)	34 (14.3)	84 (11.8)
	Afatinib	11 (2.3)	4 (1.7)	15 (2.1)
	Alectinib	1 (0.2)	1 (0.4)	2 (0.3)
	Alectinib hydrochloride	1 (0.2)	0	1 (0.1)
	Bevacizumab	7 (1.5)	3 (1.3)	10 (1.4)
	Carboplatin	1 (0.2)	1 (0.4)	2 (0.3)

Table 2 Post-discontinuation disease-related anti-cancer therapy (Full analysis set)

		Number(%) of patients		
Anti-cancer therapy [a]	Treatment	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
	Crizotinib	4 (0.8)	6 (2.5)	10 (1.4)
	Dasatinib	1 (0.2)	0	1 (0.1)
	Erlotinib	4 (0.8)	4 (1.7)	8 (1.1)
	Erlotinib hydrochloride	6 (1.3)	9 (3.8)	15 (2.1)
	Gefitinib	4 (0.8)	3 (1.3)	7 (1.0)
	Glesatinib	1 (0.2)	0	1 (0.1)
	Itacitinib	1 (0.2)	0	1 (0.1)
	Lenvatinib	0	1 (0.4)	1 (0.1)
	Lorlatinib	0	1 (0.4)	1 (0.1)
	Naquotinib	1 (0.2)	0	1 (0.1)
	Necitumumab	3 (0.6)	2 (0.8)	5 (0.7)
	Nintedanib	2 (0.4)	1 (0.4)	3 (0.4)
	Nintedanib esilate	1 (0.2)	0	1 (0.1)
	Osimertinib	3 (0.6)	2 (0.8)	5 (0.7)
	Pemetrexed	0	1 (0.4)	1 (0.1)
	Ramucirumab	9 (1.9)	2 (0.8)	11 (1.5)
	Sitravatinib	1 (0.2)	0	1 (0.1)
	Uncoded	2 (0.4)	0	2 (0.3)
	Vandetanib	1 (0.2)	0	1 (0.1)
	Vemurafenib	1 (0.2)	0	1 (0.1)
	Vinorelbine	1 (0.2)	0	1 (0.1)
Other		1 (0.2)	0	1 (0.1)
	Uncoded	1 (0.2)	0	1 (0.1)

[a] Therapies post discontinuation of study treatment.
Source: Table 11.1.18.OSUP1

6.5 Conclusions on study patients

Demographics and disease characteristics were representative of the intended patient population and were well balanced between the durvalumab and placebo groups (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1).

7. EFFICACY EVALUATION

7.1 Efficacy results

Summary tables and figures pertaining to efficacy results are presented in Section 11.2.

7.1.1 Primary efficacy variables

7.1.1.1 Progression-free survival

At the time of the primary PFS analysis based on the BICR assessments according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) (DCO: 13 February 2017), the study met the pre-defined criteria of the primary PFS analysis. Durvalumab demonstrated a statistically significant and clinically meaningful benefit in PFS over placebo (hazard ratio [HR]: 0.52; 98.9% confidence interval [CI]: 0.39, 0.70; p-value <0.0001). The Kaplan-Meier estimate of median PFS was 16.8 months in the durvalumab group (95% CI:

13.0, 18.1), as compared to 5.6 months (95% CI: 4.6, 7.8) in the placebo group. The separation in the Kaplan-Meier curves between the treatment groups was observed early, sustained over the treatment period, and supported by the estimates of the 12-month and 18-month PFS rates. For a detailed description of the primary PFS results, see Section 7.1.1, PACIFIC Interim CSR, Module 5.3.5.1.

7.1.1.2 Overall survival

At the time of the primary OS analysis (DCO: 22 March 2018), the study met the pre-defined criteria of the interim OS analysis (ie, statistical significance level of ≤0.00274). Durvalumab demonstrated a statistically significant and clinically meaningful benefit in OS over placebo, with a 32% reduction in the risk of death (HR: 0.68; 99.73% confidence interval [CI]: 0.469, 0.997; 95% CI: 0.53, 0.87; p-value=0.00251) (see Table 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). The Kaplan-Meier estimate of the median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was observed early and was sustained over the treatment period (see Figure 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at both the OS12 (83.1% vs. 75.3%, respectively) and OS24 (66.3% vs. 55.6%, respectively) landmarks. For a detailed description of the primary OS analysis results, see Section 7.1.1.2, PACIFIC CSR Addendum-1, Module5.3.5.1.

At the time of the OS follow-up analysis (DCO: 31 January 2019), a total of 45 new OS events were reported since the primary OS analysis (a total of 344 deaths [44.1% and 56.5% in the durvalumab and placebo groups, respectively]). The survival benefit of durvalumab over placebo was consistent with the OS primary analysis (DCO: 22 March 2018), with a 31% reduction in the risk of death as compared to placebo (HR: 0.69; 95% CI: 0.55, 0.86) (Table 3). The Kaplan Meier estimate of the median OS was 29.1 months in the placebo group, while it was not yet reached in the durvalumab group (Figure 1). The separation of OS curves between the durvalumab and placebo groups was sustained over the treatment period (Figure 1). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at the OS12 (83.1% vs. 74.6%, respectively), OS24 (66.3% vs. 55.3%, respectively) landmarks as well as the OS36 (57.0% vs. 43.5%, respectively) landmark (Table 3).

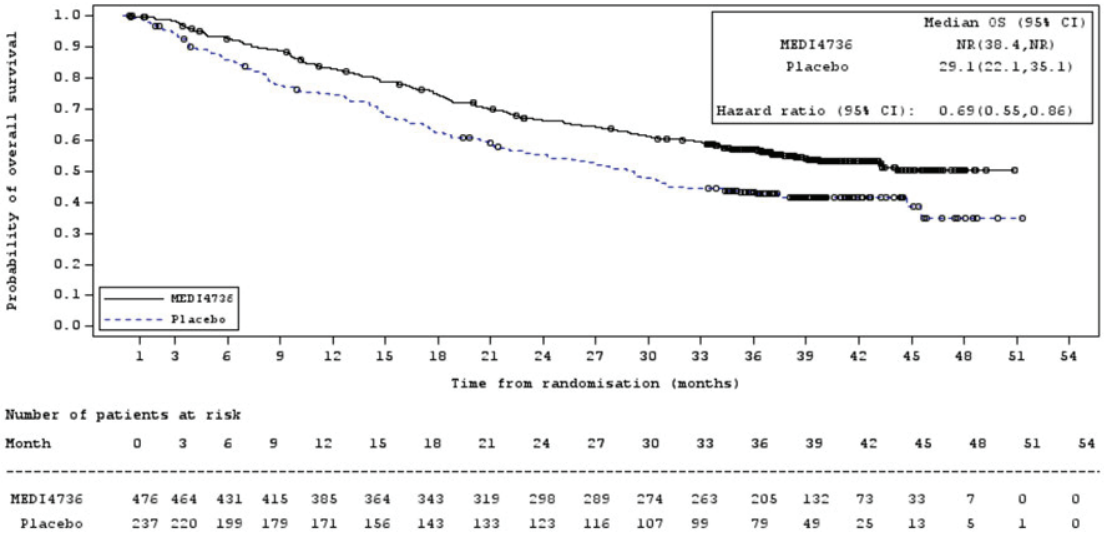
The OS results at the time of the OS follow-up analysis (DCO: 31 January 2019) and at the time of the primary OS primary analysis (DCO: 22 March 2018) are shown in Table 4.

Table 3 Overall survival (Full analysis set)

	OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Primary OS analysis (DCO: 22 March 2018)	
Survival status	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**
Death, n (%)	210 (44.1)	134 (56.5)	183 (38.4)	116 (48.9)
Median overall survival (months) [a]	NR	29.1	NR	28.7
95% CI for median overall survival [a]	38.4, NR	22.1, 35.1	34.7, NR	22.9, NR
Survival rate at 12 months (%) [a]	83.1	74.6	83.1	75.3
95% CI for survival rate at 12 months [a]	79.4, 86.2	68.5, 79.7	79.4, 86.2	69.2, 80.4
Survival rate at 24 months (%) [a]	66.3	55.3	66.3	55.6
95% CI for survival rate at 24 months [a]	61.8, 70.4	48.6, 61.4	61.7, 70.4	48.9, 61.8
Survival rate at 36 months (%) [a]	57.0	43.5	N/A	N/A
95% CI for survival rate at 36 months [a]	52.3, 61.4	37.0, 49.9	N/A	N/A
Hazard ratio, comparing Durvalumab vs. Placebo [b]	0.69		0.68	
95% CI for hazard ratio [b]	0.55, 0.86		0.53, 0.87	

CI= Confidence interval, NR = Not reached.
[a] Calculated using the Kaplan-Meier technique.
[b] The analysis was performed using stratified log-rank test adjusting for age at randomization (<65 vs ≥65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
Source: Table 11.2.1.1.OSUP1 and Table 11.2.1.1.OS, PACIFIC CSR Addendum-1, Module5.3.5.1

Figure 1 Kaplan-Meier plot of overall survival (Full analysis set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
MEDI4736	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

Circles indicate a censored observation
Source: Figure 11.2.1.1.OSUP1

As anticipated with a OS follow-up analysis (~3 years from LSI), the median duration of follow-up increased in both durvalumab and placebo groups. The median duration of follow-up in all patients was 33.9 months (range: 0.2 to 50.9) in the durvalumab group and 26.4 months (range: 0.3 to 51.3) in the placebo group (see Table 11.2.1.2.OSUP1).

A total of 369 patients (266 on durvalumab and 103 on placebo) were censored at the last date they were known to be alive. As anticipated with the OS follow-up analysis, the median duration of follow-up in censored patients also increased in both durvalumab and placebo groups, from 28.8 months (total) (see Table 11.2.1.2.OS, PACIFIC CSR Addendum-1, Module5.3.5.1) to 38.7 months (total) (see Table 11.2.1.2.OSUP1). The duration of follow-up for OS in the censored patients was balanced between the 2 treatment groups, with a median of 38.7 months (range: 0.4 to 50.9) in the durvalumab group and 38.7 (range: 0.5 to 51.3) in the placebo group. The majority (88.43%) of the patients who were censored at the time of the analysis had their latest follow-up for survival within 8 weeks of the DCO date. Therefore, the status of the majority of patients was known at the time of the analysis.

A KM plot of the time to censoring in which the censoring indicator of the primary OS analysis was reversed did not show any meaningful difference between the 2 treatment groups (see Figure 11.2.1.3.OSUP1).

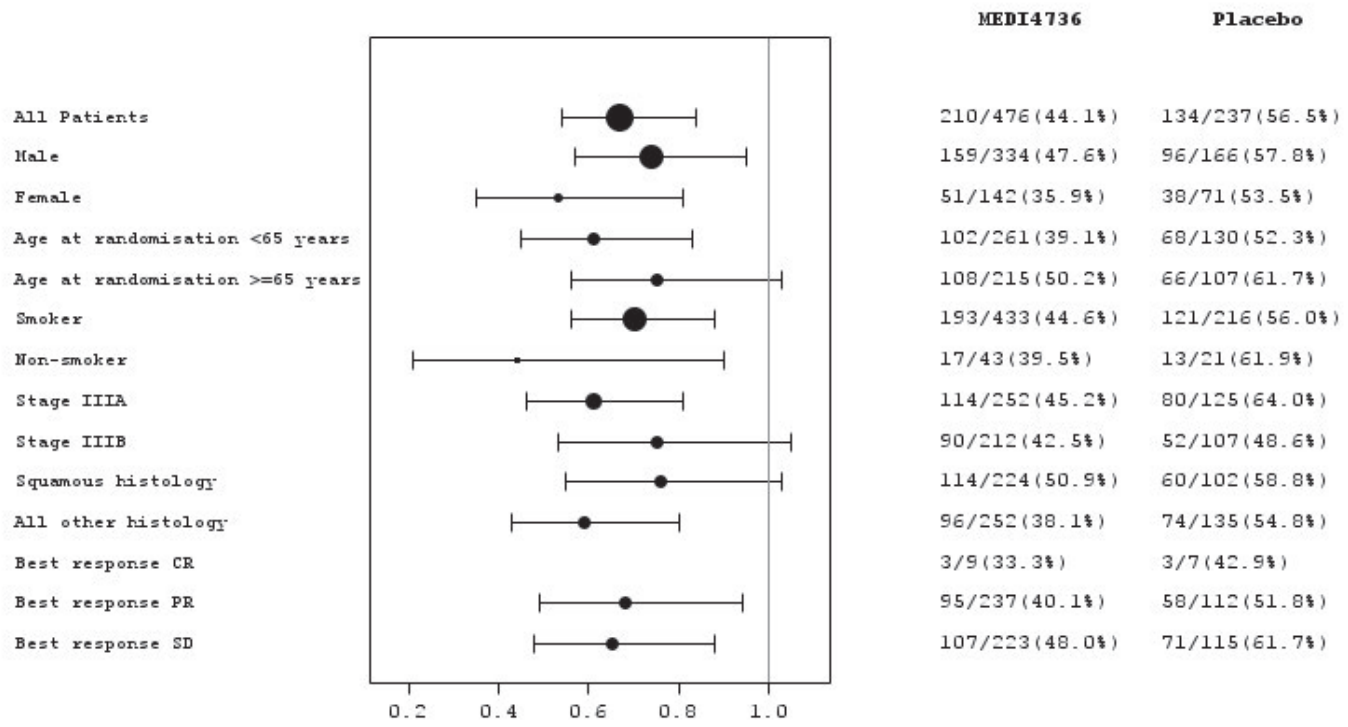
Subgroup analysis

Subgroup analysis for the data at the primary OS analysis (22 March 2018 DCO) is presented in the PACIFIC Interim CSR Addendum 1 (see Figure 3 and Table 11.2.1.3.OS in the PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Subgroup analysis for the data at the OS follow-up analysis (DCO: 31 January 2019) is presented in Figure 2and were generally consistent with that of the primary OS analysis (22 March 2018 DCO). Improvements in OS favoring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, and baseline disease characteristics (Figure 2) (see Table 11.2.1.3.OSUP1).

For further discussion on exploratory post-hoc subgroup biomarker analysis by PD-L1 status, see Appendix 12.1.14 in the PACIFIC Interim CSR Addendum 1. Further discussion on PD-L1 status based on the DCO of 31 January 2019 is presented in Appendix 12.1.14 of this document.

Figure 2 Overall survival Forest plot, by subgroup (Full analysis set)



CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy

Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.

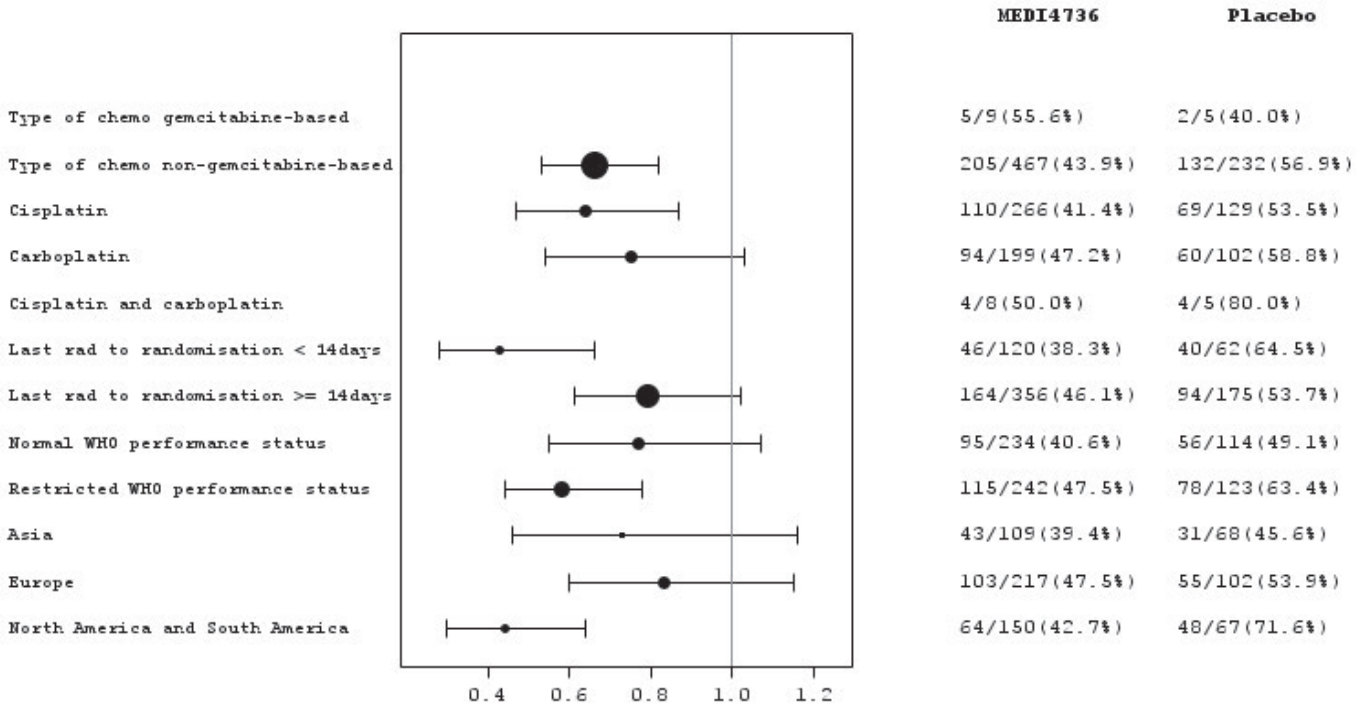
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.

Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.

Size of circle is proportional to the number of events.

Source: Figure 11.2.1.4.OSUP1

Figure 2 Overall survival Forest plot, by subgroup (Full analysis set)



CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy

Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.

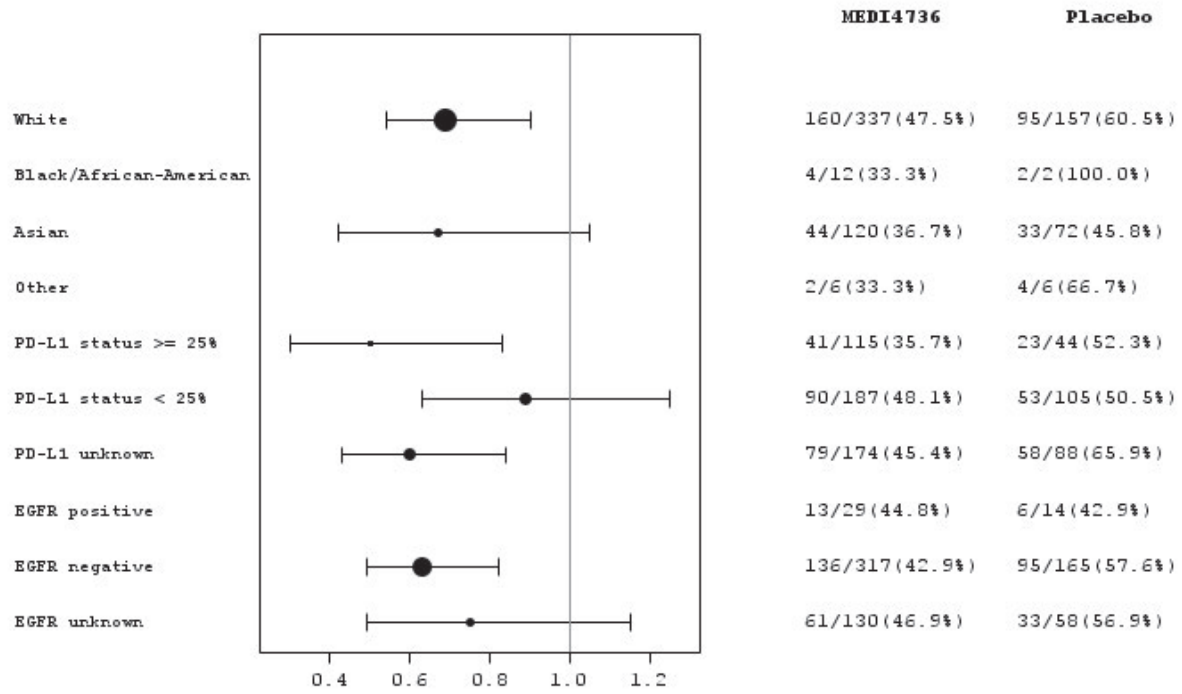
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.

Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.

Size of circle is proportional to the number of events.

Source: Figure 11.2.1.4.OSUP1

Figure 2 Overall survival Forest plot, by subgroup (Full analysis set)



CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy

Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.

The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.

Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.

Size of circle is proportional to the number of events.

Source: Figure 11.2.1.4.OSUP1

7.1.2 Secondary efficacy variables

7.1.2.1 Time to first subsequent therapy or death (TFST)

At the time of the OS follow-up analysis (DCO: 31 January 2019), treatment with durvalumab prolonged the TFST, as compared to placebo (HR: 0.58; 95% CI: 0.47, 0.71), consistent with the results at the time of the primary OS analysis. The median TFST was 21.2 months in the durvalumab group, as compared to 10.4 months in the placebo group.

The TFST results at the time of the OS follow-up analysis (DCO: 31 January 2019) and at the time of the OS primary analysis (22 March 2018 DCO) are shown in Table 4 and Figure 3.

Table 4 Time to first subsequent therapy or death, stratified log-rank test (Full analysis set)

	Number (%) of Patients			
	OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Primary OS analysis (22 March 2018 DCO)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	283 (59.5)	183 (77.2)	267 (56.1)	169 (71.3)
Subsequent therapy	207 (43.5)	138 (58.2)	196 (41.2)	130 (54.9)
Death	76 (16.0)	45 (19.0)	71 (14.9)	39 (16.5)
Median time to first subsequent therapy or death (months) [b]	21.2	10.4	21.0	10.4
95% CI for median time to first subsequent therapy or death [b]	17.1, 25.8	8.4, 12.5	16.6, 25.5	8.3, 12.5
Hazard ratio	0.58		0.58	
95% CI for hazard ratio	0.47, 0.71		0.47, 0.72	

CI= Confidence interval.

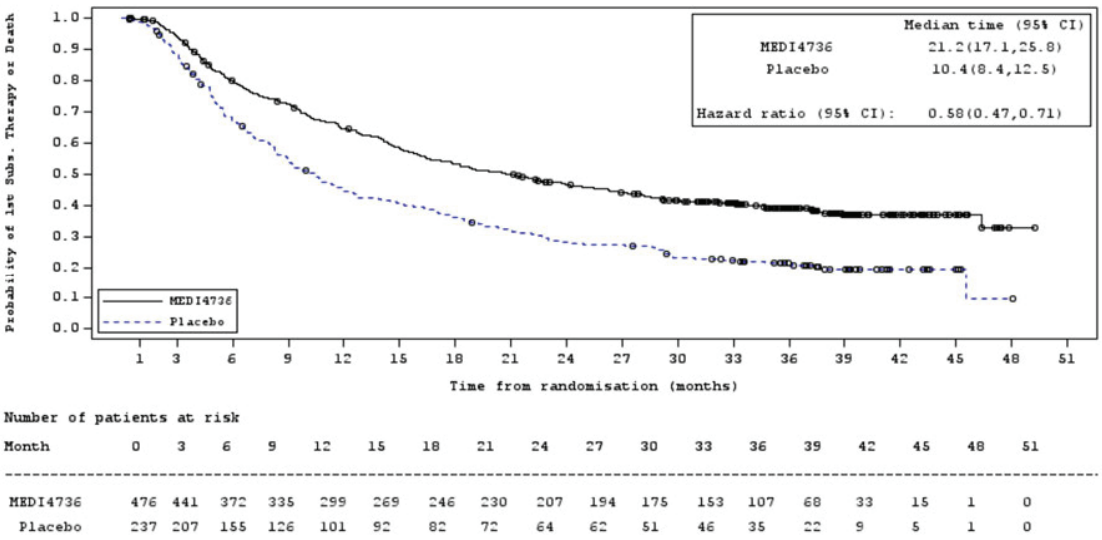
[a] Patients with first subsequent therapy or death (TFST). TFST is defined as the time from randomization to the start date of the first subsequent therapy after discontinuation of treatment, or death.

[b] Calculated using the Kaplan-Meier technique.

Note: The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Source: Table 11.2.5.1.OSUP1 and Table 11.2.5.1.OS, PACIFIC CSR Addendum 1, Module 5.3.5.1

Figure 3 **Kaplan-Meier plot of time to first subsequent therapy or death (Full analysis set)**



Circles indicate a censored observation.
Source: Figure 11.2.1.10.OSUP1

7.1.2.2 Time to second subsequent therapy or death (TSST)

At the time of the OS follow-up analysis (DCO: 31 January 2019), treatment with durvalumab prolonged the TSST, as compared to placebo (HR: 0.61; 95% CI: 0.49, 0.75; Table 5 and Figure 4), consistent with the results at the time of the primary OS analysis. The median TFST was 30.2 months in the durvalumab group, as compared to 17.8 months in the placebo group.

The TSST results at the time of the OS follow-up analysis (DCO: 31 January 2019), and at the time of the OS primary analysis (22 March 2018 DCO) are shown in Table 5.

Table 5 **Time to second subsequent therapy or death, stratified log-rank test (Full analysis set)**

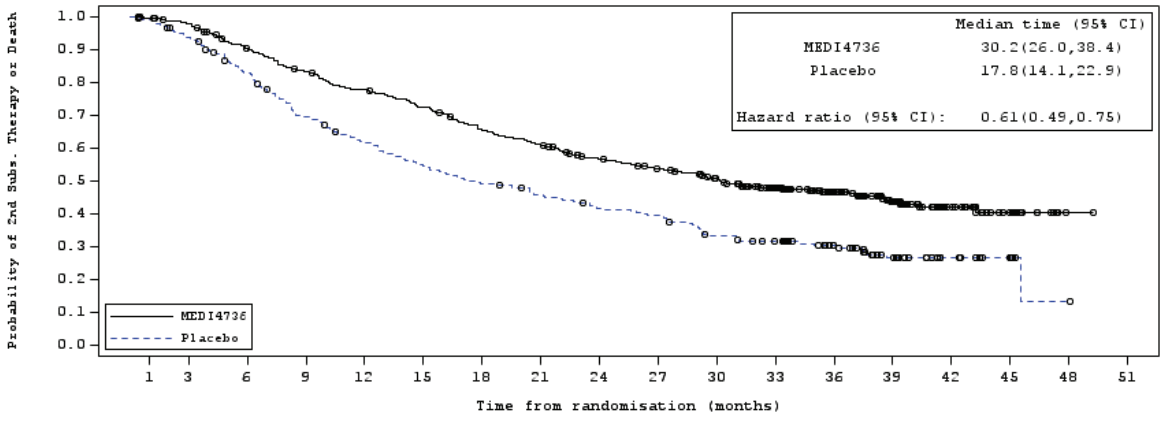
	Number (%) of patients			
	OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Primary OS analysis (22 March 2018 DCO)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	250 (52.5)	162 (68.4)	221 (46.4)	139 (58.6)
Subsequent therapy	109 (22.9)	79 (33.3)	83 (17.4)	61 (25.7)
Death	141 (29.6)	83 (35.0)	138 (29.0)	78 (32.9)

Table 5 **Time to second subsequent therapy or death, stratified log-rank test (Full analysis set)**

	Number (%) of patients			
	OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Primary OS analysis (22 March 2018 DCO)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Median time to second subsequent therapy or death (months) [b]	30.2	17.8	29.3	18.6
95% CI for median time to second subsequent therapy or death [b]	26.0, 38.4	14.1, 22.9	26.0, 34.9	14.8, 23.9
Hazard ratio	0.61		0.63	
95% CI for hazard ratio	0.49, 0.75		0.50, 0.79	

CI= Confidence interval.
[a] Patients with second subsequent therapy or death (TSST). TSST is defined as the time from randomization to the start date of the second subsequent therapy after discontinuation of treatment, or death.
[b] Calculated using the Kaplan-Meier technique.
Note: The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
Source: Table 11.2.9.1.OSUP1 and Table 11.2.9.1.OS, PACIFIC CSR Addendum 1, Module 5.3.5.1

Figure 4 **Kaplan-Meier plot of time to second subsequent therapy or death (Full analysis set)**



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
MEDI4736	476	461	419	386	359	334	301	278	250	233	211	180	126	80	36	17	1	0
Placebo	237	219	190	158	139	122	110	101	91	86	71	63	46	28	11	6	1	0

Circles indicate a censored observation.
Source: Figure 11.2.1.13.OSUP1

7.2 Efficacy evaluation conclusions

- At the time of the OS follow-up (approximately 3 years from LSI) analysis (DCO: 31 January 2019), the OS results were consistent with that reported at time of the primary OS analysis.
  - Durvalumab treatment resulted in a 31% reduction in the risk of death compared to placebo (HR: 0.69, 95%CI: 0.55, 0.86).
  - The Kaplan Meier estimate of the median OS was 29.1 months in the placebo group, while it was not reached in the durvalumab group.
  - The separation of OS curves between the durvalumab and placebo groups was sustained over the treatment period, supported by the numerically higher OS rates for the durvalumab group vs the placebo group at the OS12 (83.1% vs. 74.6%, respectively), OS24 (66.3% vs. 55.6%, respectively) landmarks as well as the OS36 (57.0% vs. 43.5%, respectively) landmark
- The TFST and TSST results were consistent with that reported at the time of the primary OS analysis.

8. SAFETY EVALUATION

The safety analyses at the 22 March 2018 DCO were conducted based on the safety analysis set, which included 475 patients in the durvalumab group and 234 patients in the placebo group (See Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.3).

By May 2017, all patients had completed their protocol-defined 12 months of study treatment or had discontinued prior to the defined 12 months of treatment. Therefore, a comprehensive safety presentation was provided in interim CSR and CSR addendum 1.

At the date of the OS follow-up (approximately 3 years from LSI) analysis (DCO: 31 January 2019), there was no safety updates to be provided (except for deaths), as compared to the primary OS analysis (DCO: 22 March 2018) (see Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.3). The listings of deaths on treatment are presented in Section 11 (see Table 11.3.3.1.8.OSUP1, Table 11.3.3.1.6..OSUP1, and Table 11.3.3.1.8.OSUP1).

8.1 Deaths, serious adverse events, discontinuation of study treatment due to adverse events, and other significant adverse events

8.1.1 Deaths

All deaths for the full analysis set is presented in Table 6 with death listings presented in Section 11.3 (see Table 11.3.3.1.8.OSUP1).

At the time of the OS follow-up analysis (DCO: 31 January 2019), a total of 344 deaths were observed, with 210 (44.1%) patients in the durvalumab group and 134 (56.5%) patients in the placebo group. The majority of deaths were solely related to disease under investigation (169/210 [80.5%] and 101/134 [75.4%], respectively.

In 21/476 (4.4%) patients treated with durvalumab and 17/237 (7.2%) patients treated with placebo, at the time of the primary OS analysis (DCO: 22 March 2018), the death was due to an AE or due to both the disease under investigation and an AE (Table 11.3.3.1.6.OS, PACIFIC CSR Addendum 1, Module 5.3.5.1). Since the 22 March 2018 DCO, there have been no new fatal adverse events.

Details of deaths at the time of the OS interim analysis (DCO: 22 March 2018) is presented in the interim CSR (Section 8.3.1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Table 6 All Deaths (Full analysis set)

	Number (%) of patients			
	OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Primary OS analysis (DCO: 22 March 2018)	
Category	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total number of deaths	210 (44.1)	134 (56.5)	183 (38.4)	116 (48.9)
Death related to disease under investigation only [a]	169 (35.5)	101 (42.6)	147 (30.9)	86 (36.3)
Death related to disease under investigation [a] and an AE with outcome of death	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)
AE onset prior to subsequent therapy [b]	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)
AE with outcome of death only	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)
AE onset prior to subsequent therapy [b]	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)
Death not due to either disease progression or an AE with a start date whilst on treatment or within the safety follow-up period	10 (2.1)	8 (3.4)	8 (1.7)	6 (2.5)
Unknown reason for death	10 (2.1)	7 (3.0)	7 (1.5)	6 (2.5)
Other deaths [d]	0	1 (0.4)	0	1 (0.4)

[a] Deaths related to disease under investigation as determined by the Investigator.
[b] Includes adverse events with an onset date (or pre-treatment AEs that increase in severity) on or after the date of first dose and up to and including 90 days following the last dose of study medication, or AE start date <= the date of initiation of the first subsequent therapy (whichever occurs first).
[c] AE start date >90 days following the last dose of study medication and AE start date > the date of initiation of the first subsequent therapy (whichever occurs first).
[d] Patients who died and are not captured in the earlier categories and patients who died due to AE with onset date in the re-treatment phase and up to and including 90 days following the last dose of study medication in the re-treatment phase.
Source: Table 11.3.3.1.6.OSUP1 and Table 11.3.3.1.6.OS, PACIFIC CSR Addendum 1, Module 5.3.5.1

8.2 Safety evaluation conclusions

At the time of the long-term OS analysis (DCO: 31 January 2019), there was no change in safety conclusions from those reported at the time of the primary OS analysis.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

A comprehensive discussion of the efficacy, safety, and pharmacokinetic results of the PACIFIC study, and the substantial clinical benefit of durvalumab treatment in patients with Stage III, locally advanced, unresectable, NSCLC is outlined in the PACIFIC Interim CSR and CSR addendum-1 (see Section 9.1, PACIFIC CSR Addendum 1, Module 5.3.5.1).

At the time of the OS follow-up analysis (DCO: 31 January 2019), durvalumab survival benefit over placebo was consistent with that reported at time of the primary OS analysis (DCO: 22 March 2018). Similarly TFST and TSST results were also consistent.

9.2 Overall conclusion

In the pre-planned interim analyses of the 2 primary endpoints of PFS (DCO: 13 February 2017) and OS (DCO: 22 March 2018), durvalumab treatment demonstrated a clinically meaningful benefit compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.

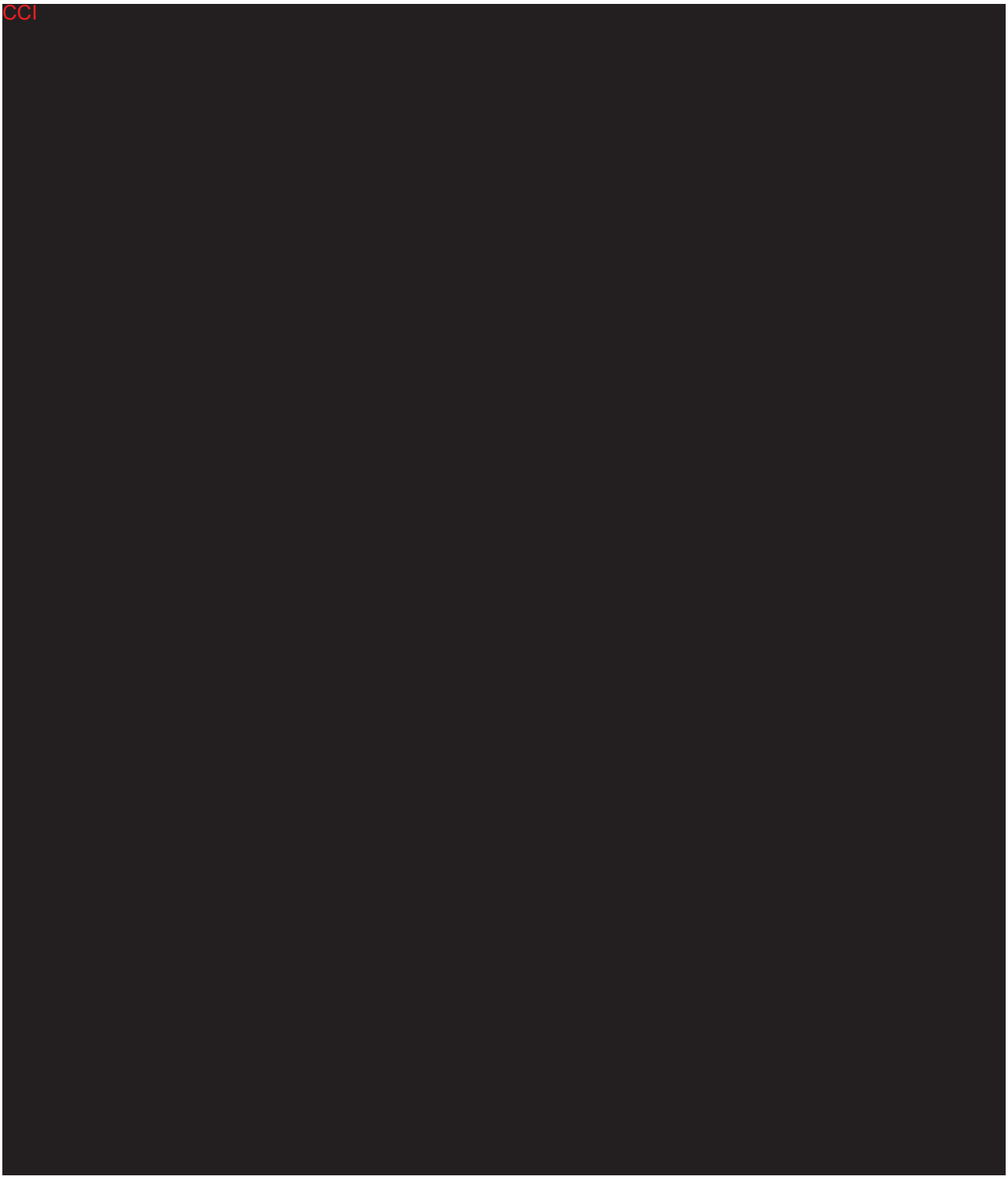
At the time of the OS follow-up (approximately 3 years from LSI) analysis (DCO: 31 January 2019), the efficacy results were consistent with those reported at the time of the OS primary analysis. Overall, durvalumab treatment demonstrated a well-tolerated and manageable safety profile that was generally consistent with the established safety profile to date.

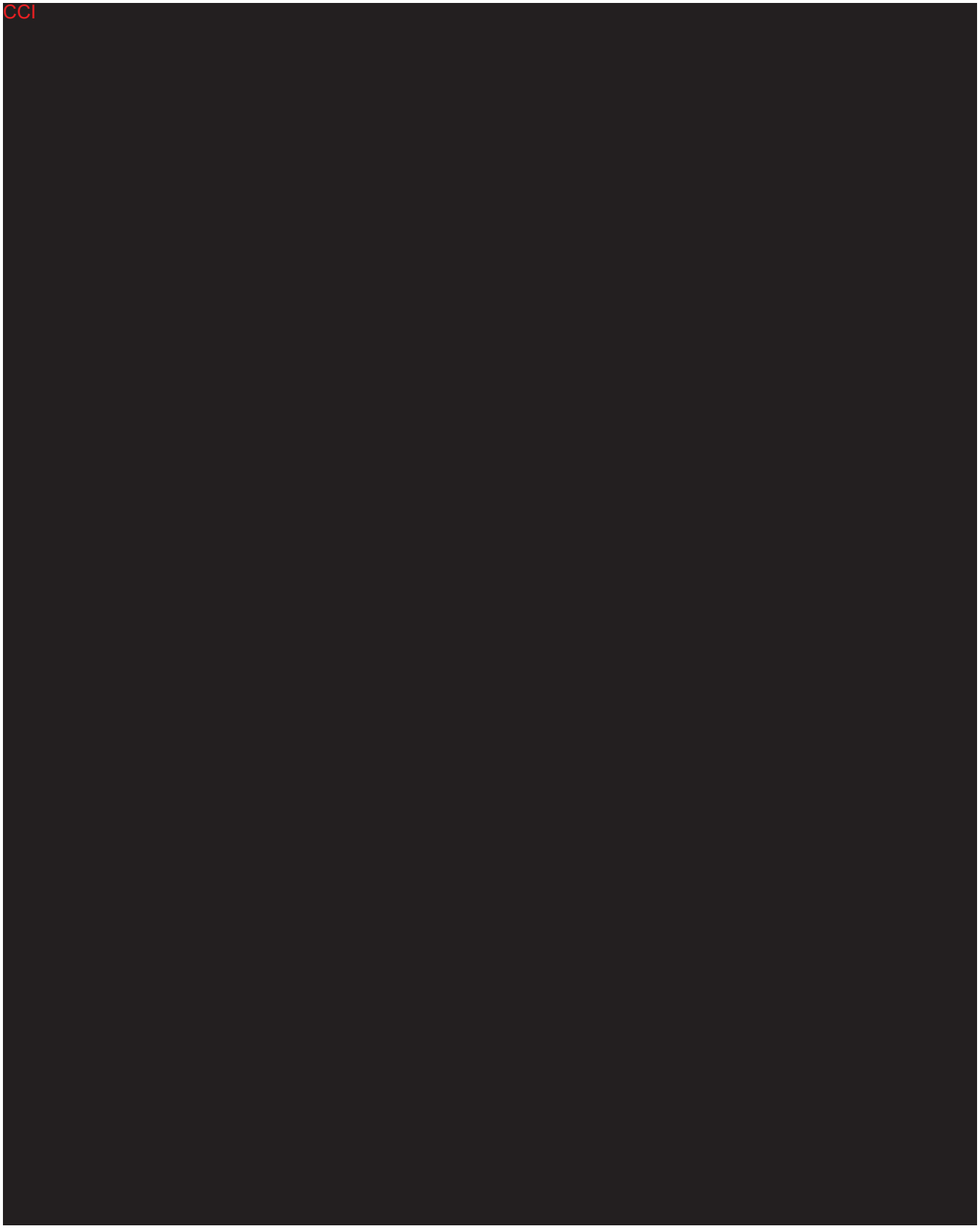
Taken together, the long-term survival follow up demonstrated that the overall benefit: risk of durvalumab treatment remains highly favourable and consistent with that previously reported in this patient population.

10. REFERENCE LIST

Not Applicable

11. SUMMARY TABLES AND FIGURES AND LISTINGS

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Clinical Study Report Addendum 3

Drug Substance	Durvalumab
Study Code	D4191C00001
Edition Number	01
Date	14 July 2020
EudraCT Number	2014-000336-42

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of durvalumab as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Study dates: First patient randomized: 09 May 2014
Last patient randomized: 22 April 2016
Data cut-off date: 20 March 2020 (study ongoing)

Phase of development: III

Sponsor's Responsible Medical Officer: PPD
AstraZeneca LP
PPD
Cambridge, UK

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
AE	adverse event
BICR	blinded independent central review
CI	confidence interval
CR	complete response
CSF	Cerebrospinal fluid
CSR	clinical study report
DCO	data cut-off
DoR	duration of response
eCRF	electronic case report form
EGFR	estimated glomerular filtration rate
HR	hazard ratio
IDMC	independent data monitoring committee
LSI	last subject in
MEDI4736	durvalumab
N/A	Not applicable
NR	not reached
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OS12	overall survival at 12 months
OS24	overall survival at 24 months
OS36	overall survival at 36 months
OS48	overall survival at 48 months
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PFS2	time to second progression or death
PR	partial response

Abbreviation or special term	Explanation
PRO	patient-reported outcome
QoLs	quality of life scale
RECIST	response evaluation criteria in solid tumours
SD	stable disease
TFST	time to first subsequent therapy or death
TMG	toxicity management guidelines
TSST	time to second subsequent therapy or death
TTDM	time to death or distant metastasis
WHO	World Health Organization

1. ETHICS

For information on ethics, please see Section 1, PACIFIC Interim clinical study report (CSR), Module 5.3.5.1.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

For information on study personnel and administrative structure, please see Section 2, PACIFIC Interim CSR, Module 5.3.5.1.

3. INTRODUCTION

PACIFIC (Study D4191C00001) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multi-centre, global clinical study designed to evaluate the efficacy and safety of durvalumab (IMFINZI™) compared with placebo in patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based concurrent chemoradiation. The primary objective is to assess the efficacy of durvalumab compared with placebo in terms of progression-free survival (PFS; based on blinded independent central review [BICR]) and overall survival (OS). Secondary efficacy endpoints include OS at 24 months, objective response rate (ORR), duration of response (DoR), time to death or distant metastases (TTDM), time to second progression or death (PFS2), and patient-reported outcome (PRO). Time to first subsequent therapy or death (TFST) was derived as a supportive summary to PFS and time to second subsequent therapy or death (TSST) was derived as a supportive summary to PFS2.

Four data cut-off s (DCO)s were originally planned for this study including 1 interim analysis for PFS and 2 interim analyses for OS as follows:

- The planned interim analysis of PFS was conducted after 371 events (80%) of the target 458 events were observed (DCO: 13 February 2017).
    - The results of the interim PFS analysis were reviewed by the Independent Data Monitoring Committee (IDMC) (20 April 2017). Since the study achieved pre-specified statistical significance (p-value <0.011035), the interim analysis of PFS was considered to be the final PFS analysis. Therefore, it will be referred to as “the primary PFS analysis” in this document.
    - Based on the review of that interim analysis, the Sponsor unblinded the study for PFS and safety.

    - A comprehensive analysis of PFS along with a detailed presentation of the safety and tolerability profile of the durvalumab treatment is outlined in the PACIFIC interim CSR (see PACIFIC Interim CSR, Module 5.3.5.1).

- The planned interim OS analysis was conducted after 299 (61%) of the target 491 death events were observed (DCO: 22 March 2018).
    - Results from the interim OS analysis were reviewed by the IDMC on 21 May 2018.
    - Since the study achieved the statistical significance level of ≤ 0.00274 that met the predefined criterion for unblinding the OS data, the results of the interim OS analysis (see PACIFIC Interim CSR Addendum 1, Module 5.3.5.1) was considered the final OS analysis. Therefore, it will be referred to as "the primary OS analysis" in this document.
    - The PACIFIC Interim CSR Addendum 1 reported the results from the 22 March 2018 DCO.
- The first OS follow-up was performed approximately 3 years after last subject in (LSI) (DCO: 31 January 2019).
    - The PACIFIC Interim CSR Addendum 2 reported the results of a long-term overall survival follow-up and subsequent anti-cancer therapy usage, as of 31 January 2019 DCO.
- The second OS follow-up was performed approximately 4 years after LSI (DCO: 20 March 2020).
    - This PACIFIC Interim CSR Addendum 3 reports the results of a long-term OS follow-up and subsequent anti-cancer therapy usage, as of 20 March 2020 DCO.

This PACIFIC Interim CSR Addendum (PACIFIC Interim CSR Addendum 3) is related to the long-term survival follow up of PACIFIC (Study D4191C00001) study. There are no updates on pharmacokinetic, immunogenicity, or safety data to be presented in this document. Therefore, the focus is on the long-term survival follow-up data providing updates on disposition, PFS, OS and subsequent anti-cancer therapy usage. Patients will continue to be followed for long-term survival and follow-up analyses will be presented in a future report.

4. STUDY OBJECTIVES

The primary and secondary objectives are presented in the PACIFIC Interim CSR (see Section 4, PACIFIC Interim CSR, Module 5.3.5.1).

Appendix 12.1.14 in the PACIFIC Interim CSR Addendum 1 presents results of efficacy analyses from exploratory *post hoc* biomarker (programmed death ligand 1 [PD-L1]) subgroup analyses (see Appendix 12.1.14, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

5. STUDY PLAN AND PROCEDURES

5.1 Overall study design and flow chart

This is an ongoing, randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable Stage III NSCLC, who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

For details on the study design, see Section 5.1, PACIFIC Interim CSR, Module 5.3.5.1.

5.2 Rationale for study design, doses, and control groups

See Section 5.2, PACIFIC Interim CSR, Module 5.3.5.1.

5.3 Selection of study population

See Section 5.3, PACIFIC Interim CSR, Module 5.3.5.1.

5.4 Treatments

See Section 5.4, PACIFIC Interim CSR, Module 5.3.5.1.

5.5 Measurements of study variables and definitions of outcome variables

See Section 5.5, PACIFIC Interim CSR, Module 5.3.5.1.

5.6 Data management and quality assurance

See Section 5.6, PACIFIC Interim CSR, Module 5.3.5.1.

5.7 Statistical methods and determination of sample size

See Section 5.7, PACIFIC Interim CSR, Module 5.3.5.1.

5.8 Clinical study protocol amendments and other changes in the conduct of the study or planned analyses

5.8.1 Changes in the conduct of the study

Important amendments to the original study protocol, including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct are presented in the Interim CSR (see Table 8, PACIFIC Interim CSR, Module 5.3.5.1) and PACIFIC Interim CSR Addendum 1 (Table 1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

There were no protocol amendments between the DCOs of the primary OS analysis (22 March 2018) and the first OS follow-up analysis (31 January 2019). However, there was one protocol amendment between the DCOs of the first OS follow-up analysis (31 January 2019) and the second OS follow-up analysis (20 March 2020). A summary of the major changes of that protocol amendment is presented here:

- Extension of the study for the purposes of long term follow up
    - Movement of estimated last patient completed from Q3 2019 to Q2 2021
- Clarification that both primary analyses have been performed and co-primary endpoints have both met statistical significance
- Reduction in table of assessments to be followed upon implementation of Protocol 7.1
    - Removal of quality of life scale (QoLs)
    - Removal of sampling – cerebrospinal fluid (CSF), mRNA etc
    - Reduction in frequency of scans
    - Limited data collection deemed as critical for analysis and required by payers /reimbursement agencies
        - Inclusive of reporting only a limited subset of concomitant medications
- Addition of mandatory biopsy for evidence of true progression when entering retreatment
- Clarification that following final DCO for the study, retreatment will not be available for new candidates under this protocol
- Clarification that survival follow up will be completed upon completion of this protocol
    - Those who have been progression free for approximately 5 years will be considered cured
    - Those who are on retreatment may continue to receive durvalumab on an alternate protocol or extension

- Removal of toxicity management guidelines (TMG)s as part of the body of the protocol
    - With the exception of Germany where TMGs are included in a concatenated version of the protocol
        - Note: this was not the purpose of the amendment; but was actioned at the same time

5.8.2 Changes to planned analyses

Exploratory efficacy analyses on PD-L1 subgroups were included. No additional changes have been made to the planned analyses from those outlined in the PACIFIC Interim CSR (see Section 5.8.2, PACIFIC Interim CSR, Module 5.3.5.1).

6. STUDY PATIENTS

Summary tables and figures pertaining to this section are presented in Section 11.1.

6.1 Disposition

A total of 983 patients were enrolled in 235 study centers across 26 countries worldwide. Of these, 713 patients were randomized in a 2:1 ratio to receive either durvalumab 10 mg/kg every 2 weeks (476 patients) or placebo (237 patients) (full analysis set; Table 1).

Of the 713 patients, 709 (473 [99.4%] in the durvalumab group and 236 [99.6%] in the placebo group) received study treatment (Table 1). The other 4 patients (3 [0.6%] in the durvalumab group and 1 [0.4%] in the placebo group) were randomized but did not receive study treatment because of patient decision (2 patients), neutropenia (1 patient), and worsening chronic obstructive pulmonary disease (1 patient) (see Section 6.1, PACIFIC Interim CSR, Module 5.3.5.1). The first patient was randomized into the study on 09 May 2014, and the last patient was randomized on 22 April 2016.

The disposition of patients at the time of the primary OS analysis and the first OS follow-up analysis is summarized in the PACIFIC Interim CSR Addendum 1 and PACIFIC Interim CSR Addendum 2, respectively.

At the second OS follow-up (approximately 4 years from LSI) analysis for the PACIFIC Interim CSR Addendum 3, the patient disposition was consistent with that of the first OS follow-up analysis except for the two following factors (Table 1):

As anticipated with a longer follow-up, a lower number of patients remained on the study: 205 (43.1%) patients in the durvalumab group and 77 (32.5%) patients in the placebo group, as compared to 245 (51.5%) patients in the durvalumab group and 92 (38.8%) patients in the placebo group at the first OS follow-up analysis, and 273 (57.4%) patients in the durvalumab group and 108 (45.6%) patients in the placebo group at the primary OS analysis.

A total of 430 patients had terminated the study at the second OS follow-up analysis, 270 (56.7%) patients in the durvalumab group and 160 (67.5%) patients in the placebo group, as compared to 231 (48.5%) patients in the durvalumab group, and 145 (61.2%) patients in the placebo group in the first OS follow-up analysis and 203 (42.6%) patients in the durvalumab group and 129 (54.4%) patients in the placebo group at the primary OS analysis.

The reasons for study termination, included death (243 [51.1%] and 143 [60.3%] patients in the durvalumab and placebo groups, respectively), subject decision (26 [5.5%] and 16 [6.8%] patients in the durvalumab and placebo groups, respectively), subject lost to follow-up (1 [0.2%] and 0 [0%] patients in the durvalumab and placebo groups, respectively), and a missing reason for a patient who died (0 [0%] and 1 [0.4%] patients in the durvalumab and placebo groups, respectively) (Table 1). The detailed information on the number of new deaths from the second OS follow-up analysis in each arm is presented in Section 8.1.1 (deaths).

Table 1 Patient Disposition (All Patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Patients enrolled [a]			983
Patients randomized	476 (48.4)	237 (24.1)	713 (72.5)
Patients who were not randomized			270 (27.5)
Subject decision			35 (3.6)
Eligibility criteria not fulfilled			225 (22.9)
Death			6 (0.6)
Other			4 (0.4)
Full analysis set	476 (100.0)	237 (100.0)	713 (100.0)
Patients who received study treatment [b]	473 (99.4)	236 (99.6)	709 (99.4)
Patients who did not receive study treatment [b]	3 (0.6)	1 (0.4)	4 (0.6)
Patients who completed 12 months of treatment [cd]	232 (49.0)	82 (34.7)	314 (44.3)
Patients who discontinued study treatment [c]	241 (51.0)	154 (65.3)	395 (55.7)
Subject decision	14 (3.0)	12 (5.1)	26 (3.7)
Adverse event	73 (15.4)	23 (9.7)	96 (13.5)
Severe non-compliance to protocol	1 (0.2)	1 (0.4)	2 (0.3)
Condition under investigation worsened	148 (31.3)	117 (49.6)	265 (37.4)
Development of study specific discontinuation criteria	1 (0.2)	1 (0.4)	2 (0.3)
Other	4 (0.8)	0	4 (0.6)
Patients ongoing study at data cut off [b]	205 (43.1)	77 (32.5)	282 (39.6)
Patients who completed study [b]	1 (0.2)	0	1 (0.1)
Patients who terminated study [b]	270 (56.7)	160 (67.5)	430 (60.3)
Subject decision	26 (5.5)	16 (6.8)	42 (5.9)

Table 1 Patient Disposition (All Patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Death	243 (51.1)	143 (60.3)	386 (54.1)
Subject lost to follow-up	1 (0.2)	0	1 (0.1)
Missing	0	1 (0.4)	1 (0.1)

a Informed consent received.
b In this section, percentages are calculated from number of patients in the full analysis set.
c In this section, percentages are calculated from number of patients who received treatment.
d Patients who completed 12 months of treatment have reported maximum cycle of immunotherapy reached on the electronic case report form (eCRF).
Nine patients who terminated study due to subject decision have died. One patient with missing termination reason has died.
Source: Table 11.1.1.OSUP2.

Prior to the primary PFS analysis of the PACIFIC study, the option for re-treatment was conducted in a blinded manner and treatment allocation was not known. The PACIFIC study protocol was amended after the PFS primary endpoint was met since treatment options available to patients had changed since the study was first designed, including the availability of anti-programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) agents for advanced NSCLC. Sites remained blinded to treatment allocation prior to the primary analysis of OS; however, any patient who was eligible for re-treatment and wished to receive further study drug at the time of progression was unblinded at the site by the investigator and only patients randomized to the durvalumab arm were then eligible for re-treatment. In addition re-treatment was no longer restricted to a 12-month treatment period as in the original study design, but was amended to a treatment duration for as long as the patient continues to benefit which was consistent with the re-treatment period for newer studies in the clinical development program for durvalumab.

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6.2 Protocol deviations

The important protocol deviations for the primary PFS analysis are reported in the PACIFIC Interim CSR (See Section 6.2, PACIFIC Interim CSR, Module 5.3.5.1).

6.3 Patients analyzed (analysis sets)

A full presentation of the analysis set used for each outcome variable is included in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 6.3, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.3, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

6.4 Demographic and other patient characteristics

A full presentation of the demographic and key baseline characteristics of study patients, including prior therapies, is presented in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.4, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). Demographics and baseline characteristics were representative of the intended patient population, and well balanced between the 2 treatment groups.

6.4.1 Concomitant medication after study entry

Concomitant medication was collected whilst patients received study drug and for 90 days after receiving the last dose of study drug. All patients had completed the 90 days follow-up following the last dose of the protocol defined 12-month treatment period in August 2018. As such there is no update for the concomitant medication after study entry at the first OS follow up analysis as compared to the primary OS analysis.

A detailed description of concomitant medication after study entry was provided at the primary OS analysis in the PACIFIC Interim CSR Addendum 1 (See Table 11.1.12.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

6.4.2 Post-discontinuation disease-related anti-cancer therapy

Post-discontinuation disease-related anti-cancer therapy analysis was presented in PACIFIC Interim CSR Addendum 1 at the primary OS analysis (See Table 11.1.18.OS and Section 6.4.2, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of the first OS follow-up analysis, the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to OS primary analysis (see Table 2 PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the second OS follow-up analysis, the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to OS primary analysis. A total of 225 (47.3%, 30 more patients from the OS interim analysis DCO and 19 more patients from the first OS follow-up analysis) patients in the durvalumab group and 138

(58.2%, 10 more patients from the OS interim analysis DCO, and one more patients from the first OS follow-up analysis) patients in the placebo group received post-discontinuation disease-related, anti-cancer therapy (Table 2). Most patients in both treatment groups received cytotoxic chemotherapy (eg, carboplatin and pemetrexed): 150 (31.5%) patients in the durvalumab group and 83 (35.0%) patients in the placebo group. Other systemic therapy (eg, targeted therapies) was administered in 54 (11.3%) patients in the durvalumab group and 35 (14.8%) patients in the placebo group. Fewer patients in the durvalumab group than the placebo group received immunotherapy: 55 (11.6%) vs 67 (28.3%), respectively. A total of 96 (20.2%) patients in the durvalumab group and 61 (25.7%) patients in the placebo group received radiotherapy.

Table 2 Post-Discontinuation Disease-Related Anti-Cancer Therapy at the Second OS Follow-Up Analysis (Full Analysis Set)

		Number(%) of patients		
Anti-cancer therapy [a]	**Treatment**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Total (N=713)**
Number of patients with post-discontinuation disease-related anti-cancer therapy		225 (47.3)	138 (58.2)	363 (50.9)
Radiotherapy		96 (20.2)	61 (25.7)	157 (22.0)
Immunotherapy		55 (11.6)	67 (28.3)	122 (17.1)
	Atezolizumab	4 (0.8)	3 (1.3)	7 (1.0)
	Avelumab	0	1 (0.4)	1 (0.1)
	BMS 986205	1 (0.2)	0	1 (0.1)
	Durvalumab	1 (0.2)	2 (0.8)	3 (0.4)
	Ipilimumab	1 (0.2)	1 (0.4)	2 (0.3)
	Nivolumab	37 (7.8)	53 (22.4)	90 (12.6)
	Pembrolizumab	13 (2.7)	10 (4.2)	23 (3.2)
	Tremelimumab	1 (0.2)	0	1 (0.1)
	Uncoded	3 (0.6)	1 (0.4)	4 (0.6)
Cytotoxic Chemotherapy		150 (31.5)	83 (35.0)	233 (32.7)
	Amrubicin Hydrochloride	2 (0.4)	1 (0.4)	3 (0.4)
	Carboplatin	86 (18.1)	45 (19.0)	131 (18.4)
	Cisplatin	22 (4.6)	17 (7.2)	39 (5.5)
	Docetaxel	43 (9.0)	20 (8.4)	63 (8.8)
	Etoposide	1 (0.2)	0	1 (0.1)
	Fluorouracil	1 (0.2)	1 (0.4)	2 (0.3)
	Gemcitabine	40 (8.4)	19 (8.0)	59 (8.3)
	Gemcitabine Hydrochloride	7 (1.5)	5 (2.1)	12 (1.7)
	Gimeracil;Oteracil Potassium;Tegafur	9 (1.9)	5 (2.1)	14 (2.0)
	Irinotecan	0	1 (0.4)	1 (0.1)
	Irinotecan Hydrochloride	0	1 (0.4)	1 (0.1)
	Nedaplatin	1 (0.2)	0	1 (0.1)
	Oxaliplatin	0	1 (0.4)	1 (0.1)
	Paclitaxel	30 (6.3)	16 (6.8)	46 (6.5)
	Paclitaxel Albumin	11 (2.3)	6 (2.5)	17 (2.4)
	Pemetrexed	33 (6.9)	17 (7.2)	50 (7.0)
	Pemetrexed Disodium	21 (4.4)	16 (6.8)	37 (5.2)
	Pemetrexed disodium heptahydrate	1 (0.2)	0	1 (0.1)
	Topotecan	0	1 (0.4)	1 (0.1)
	Uncoded	1 (0.2)	1 (0.4)	2 (0.3)
	Vinorelbine	8 (1.7)	5 (2.1)	13 (1.8)
	Vinorelbine tartrate	9 (1.9)	3 (1.3)	12 (1.7)
Systemic Therapy (Targeted therapy)		54 (11.3)	35 (14.8)	89 (12.5)
	Afatinib	12 (2.5)	5 (2.1)	17 (2.4)
	Afatinib Dimaleate	0	1 (0.4)	1 (0.1)
	Alectinib	2 (0.4)	2 (0.8)	4 (0.6)
	Alectinib hydrochloride	1 (0.2)	0	1 (0.1)

Table 2 Post-Discontinuation Disease-Related Anti-Cancer Therapy at the Second OS Follow-Up Analysis (Full Analysis Set)

		Number(%) of patients		
Anti-cancer therapy [a]	Treatment	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
	Bevacizumab	8 (1.7)	3 (1.3)	11 (1.5)
	Carboplatin	2 (0.4)	1 (0.4)	3 (0.4)
	Crizotinib	4 (0.8)	6 (2.5)	10 (1.4)
	Dasatinib	1 (0.2)	0	1 (0.1)
	Docetaxel	1 (0.2)	1 (0.4)	2 (0.3)
	Erlotinib	4 (0.8)	4 (1.7)	8 (1.1)
	Erlotinib hydrochloride	6 (1.3)	9 (3.8)	15 (2.1)
	Gefitinib	4 (0.8)	3 (1.3)	7 (1.0)
	Glesatinib	1 (0.2)	0	1 (0.1)
	Itacitinib	1 (0.2)	0	1 (0.1)
	Lenvatinib	0	1 (0.4)	1 (0.1)
	Lorlatinib	0	1 (0.4)	1 (0.1)
	Naquotinib	1 (0.2)	0	1 (0.1)
	Necitumumab	3 (0.6)	2 (0.8)	5 (0.7)
	Nintedanib	2 (0.4)	1 (0.4)	3 (0.4)
	Nintedanib esilate	1 (0.2)	0	1 (0.1)
	Osimertinib	4 (0.8)	2 (0.8)	6 (0.8)
	Osimertinib Mesilate	1 (0.2)	0	1 (0.1)
	Pemetrexed	0	1 (0.4)	1 (0.1)
	Ramucirumab	9 (1.9)	3 (1.3)	12 (1.7)
	Sitravatinib	1 (0.2)	0	1 (0.1)
	Uncoded	2 (0.4)	0	2 (0.3)
	Vandetanib	1 (0.2)	0	1 (0.1)
	Vemurafenib	1 (0.2)	0	1 (0.1)
	Vinorelbine	1 (0.2)	0	1 (0.1)
Other		2 (0.4)	0	2 (0.3)
	Uncoded	2 (0.4)	0	2 (0.3)

a Therapies post discontinuation of study treatment.
Source: Table 11.1.18.OSUP2.

6.5 Conclusions on study patients

Demographics and disease characteristics were representative of the intended patient population and were well balanced between the durvalumab and placebo groups (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1).

7. EFFICACY EVALUATION

7.1 Efficacy results

Summary tables and figures pertaining to efficacy results are presented in Section 11.2.

7.1.1 Primary efficacy variables

7.1.1.1 Progression-free survival

At the time of the primary PFS analysis (DCO: 13 February 2017) based on the BICR assessments according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), the study met the pre-defined criteria of the primary PFS analysis (Table 3). For a detailed description of the primary PFS results, see Section 7.1.1, PACIFIC Interim CSR, Module 5.3.5.1.

At the time of the 4-year follow-up analysis (DCO: 20 March 2020) based on the BICR assessments of PFS according to RECIST 1.1, the PFS benefit seen in the durvalumab group (hazard ratio [HR]: 0.55; 95% confidence interval (CI): 0.44, 0.67) was consistent with the PFS primary analysis (HR: 0.52; 95% CI: 0.42, 0.65). The Kaplan-Meier estimate of median PFS was 17.2 months in the durvalumab group (95% CI: 12.3, 23.8), as compared to 5.6 months in the placebo group (95% CI: 4.6, 7.7) (Table 3). Likewise, based on the investigator assessments of PFS according to RECIST 1.1, the PFS benefit of durvalumab (HR: 0.66; 95% CI: 0.55, 0.8) over placebo was demonstrated. (Figure 11.2.1.5.1.OSUP2).

At the 4-year analysis, the separation in the Kaplan-Meier curves (Figure 1), originally observed between the treatment groups at the PFS primary analysis, appeared sustained with the longer follow up. This is supported by the numerical improvement of the PFS rates for the durvalumab group vs the placebo group at the 24-month landmark (44.8% vs 24.8%, respectively), 36-month landmark (39.8% vs 20.5%, respectively), as well as the 48-month landmark (35.3% vs 19.5%, respectively) (Table 3).

Table 3 Progression-Free Survival (Based on BICR Assessments According to RECIST 1.1) At the 4-Year Update (Full Analysis Set)

	Primary PFS analysis (DCO: 13 February 2017)		PFS Analysis (4-year update) (DCO: 20 March 2020)	
Progression status	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	214 (45.0)	157 (66.2)	266 (55.9)	174 (73.4)
Median progression-free survival (months) [b]	16.8	5.6	17.2	5.6
95% CI for median progression-free survival [b]	13.0, 18.1	4.6, 7.8	12.3, 23.8	4.6, 7.7
Progression-free survival rate at 12 months (%) [b]	55.9	35.3	55.3	34.4
95% CI for progression-free survival rate at 12 months [b]	51.0, 60.4	29.0, 41.7	50.5, 59.8	28.2, 40.7
Progression-free survival rate at 18 months (%) [b]	44.2	27.0	49.2	27.3
95% CI for progression-free survival rate at 18 months [b]	37.7, 50.5	19.9, 34.5	44.3, 53.8	21.4, 33.5
Progression-free survival rate at 24 months (%) [b]	N/A	N/A	44.8	24.8
95% CI for progression-free survival rate at 24 months [b]	N/A	N/A	39.8, 49.6	19.1, 31.0
Progression-free survival rate at 36 months (%) [b]	N/A	N/A	39.8	20.5
95% CI for progression-free survival rate at 36 months [b]	N/A	N/A	34.8, 44.8	15.0, 26.6
Progression-free survival rate at 48 months (%) [b]	N/A	N/A	35.3	19.5
95% CI for progression-free survival rate at 48 months [b]	N/A	N/A	30.3, 40.4	14.1, 25.7
Hazard ratio [c]	0.52		0.55	
95% CI for hazard ratio [c]	0.42, 0.65		0.44, 0.67	

a Patients who did not progress or dye, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or day 1 if there were no non-missing visits. Patients who had no non-missing visits or did not have baseline data were censored at study day 1 unless they died within 2 visits of baseline.

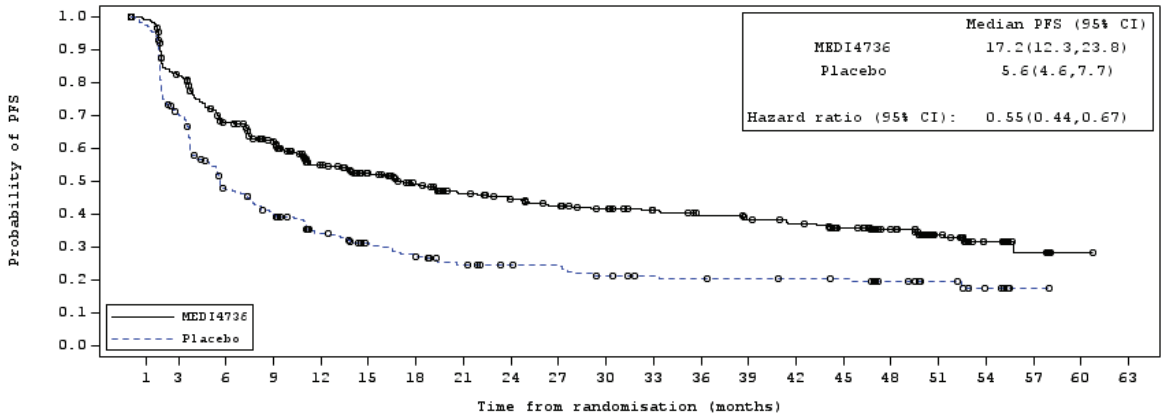
b Calculated using the Kaplan-Meier technique.

c The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
RECIST version 1.1.

BICR = blinded independent central review, CI= confidence interval, DCO= data cut-off, N/A= not applicable, PFS= progression-free survival, RECIST= response evaluation criteria in solid tumours.

Source: Table 11.2.2.1.OSUP2, and Table 11.2.2.1.

Figure 1 Progression-Free Survival (Based on BICR Assessments According to RECIST 1.1), Kaplan-Meier Plot at the 4-Year Update (Full Analysis Set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
MEDI4736	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

BICR= blinded independent central review. PFS= Progression-free survival, CI= confidence interval, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab.
Circles indicate a censored observation.
Source: Figure 11.2.1.5.OSUP2

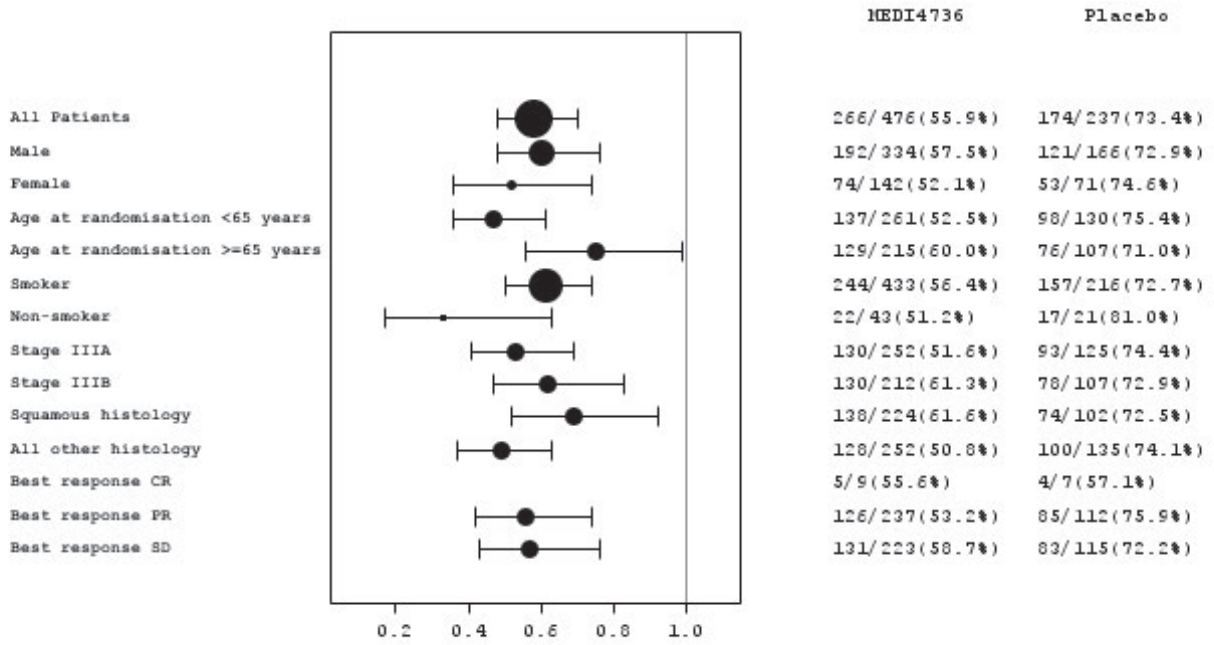
Subgroup analysis

Subgroup analysis for the data at the primary PFS analysis is presented in the PACIFIC Interim CSR (see Figure 7 and Table 11.2.2.10 in the PACIFIC Interim CSR, Module 5.3.5.1).

At the 3-year update, PFS analysis or subgroup analysis were not performed.

PFS subgroup analysis at the 4-year update is presented in detail in Figure 2. Improvements in PFS favouring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, baseline disease characteristics, and time from last dose of radiation to randomization. The results are generally consistent with that of the primary PFS analysis.

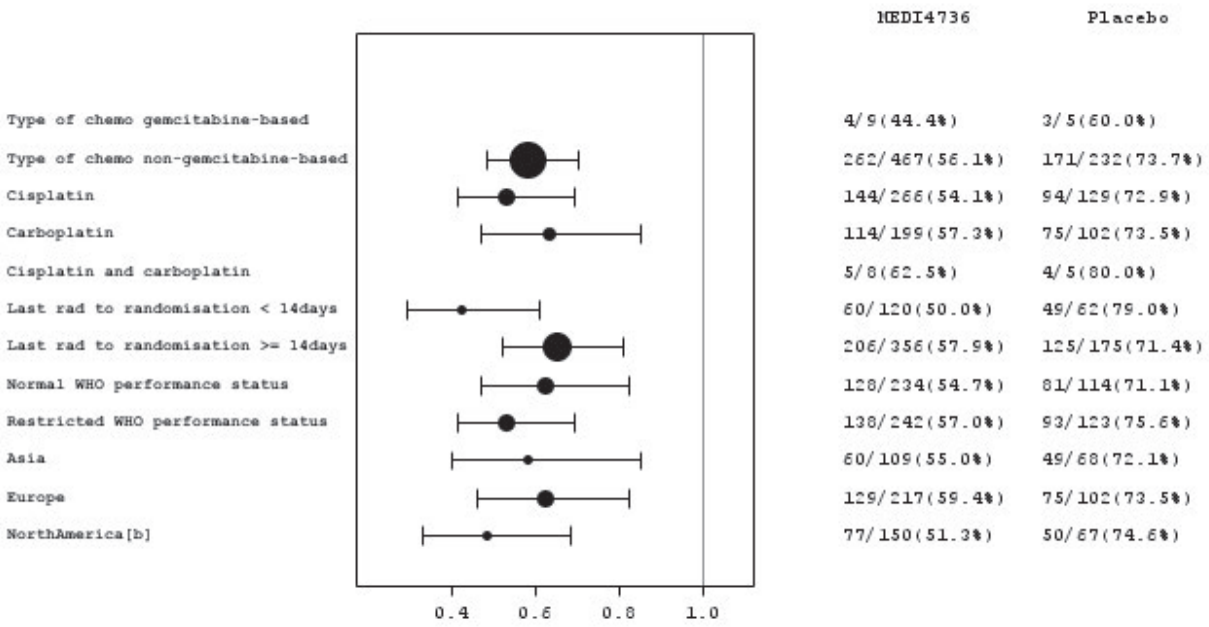
Figure 2 Progression free survival (based on BICR assessments according to RECIST 1.1), Forest plot, by subgroup (Full analysis set)



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or dye, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab. BICR= blinded independent central review, WHO= world Health Organization.

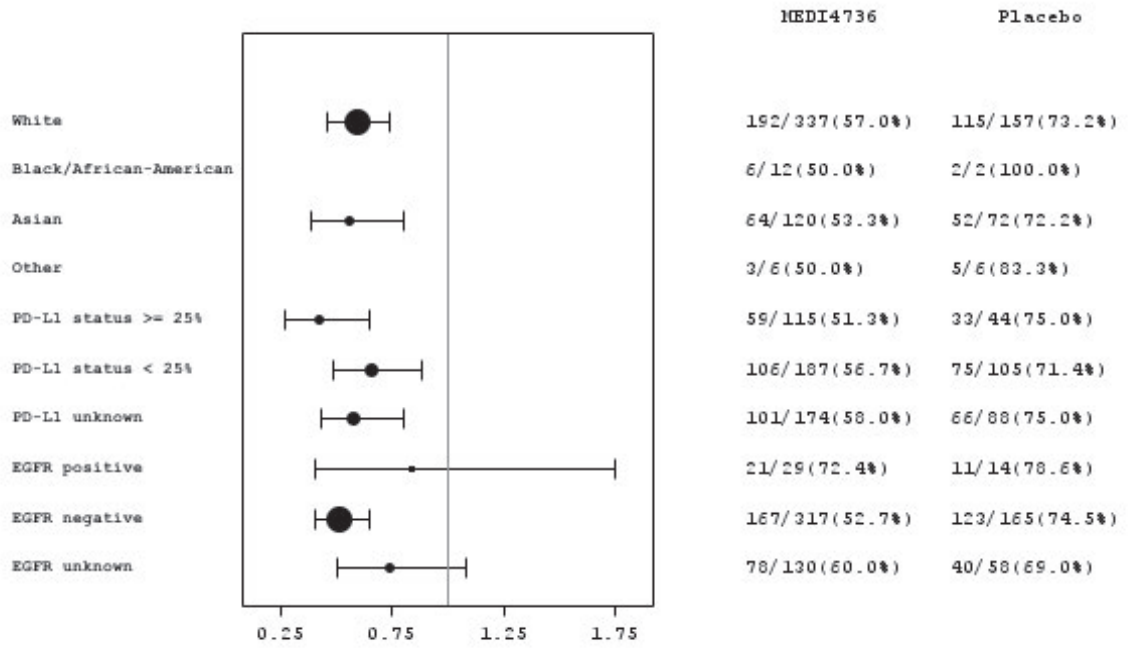
Source: Figure 11.2.1.9.OSUP2



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or dye, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab. BICR= blinded independent central review, WHO= world Health Organization.

Source: Figure 11.2.1.9.OSUP2



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or dye, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab. BICR= blinded independent central review, WHO= world Health Organization.

Source: Figure 11.2.1.9.OSUP2

7.1.1.2 Overall survival

At the time of the primary OS analysis, the study met the pre-defined criteria of the interim OS analysis (ie, statistical significance level of ≤ 0.00274). Durvalumab demonstrated a statistically significant and clinically meaningful benefit in OS over placebo, with a 32% reduction in the risk of death (HR: 0.68; 99.73% CI: 0.469, 0.997; 95% CI: 0.53, 0.87; p-value = 0.00251) (see Table 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). The Kaplan-Meier estimate of the median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was observed early and was sustained over the treatment period (see Figure 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at both the overall survival at 12 months (OS12) (83.1% vs 75.3%, respectively) and overall survival at 24 months (OS24) (66.3% vs 55.6%, respectively) landmarks. For a detailed description of the primary OS analysis results, see Section 7.1.1.2, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1.

At the time of the first OS follow-up analysis (3 years from LSI), a total of 45 new OS events were reported since the primary OS analysis (a total of 344 deaths [44.1% and 56.5% in the durvalumab and placebo groups, respectively]). For a detailed description of the first OS follow-up analysis results (Table 4 and Figure 3) (see Table 11.2.1.2.OSUP1, and Figure 11.2.1.3.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

The OS results at the time of the second OS follow-up are summarized in Table 4, where the OS results at the primary OS analysis, and at the time of the first OS follow-up analysis, are provided for the context.

At the time of the second OS follow-up analysis (approximately, 4 year from LSI), a total of 52 new OS events were reported since the first OS follow-up analysis (a total of 396 deaths [51.9% and 62.9% in the durvalumab and placebo groups, respectively]). The survival benefit of durvalumab over placebo was consistent with the OS primary analysis, with a 29% reduction in the risk of death as compared to placebo (HR: 0.71; 95% CI: 0.57, 0.88) (Table 4).

The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group (Figure 3). The separation of OS curves between the durvalumab and placebo groups was sustained (Figure 3). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at the overall survival at 36 months (OS36) landmark (56.7% vs 43.6%, respectively) as well as the overall survival at 48 months (OS48) landmark (49.6% vs. 36.3%, respectively) (Table 4).

As anticipated with the second OS follow-up analysis (~4 years from LSI), the median duration of follow-up increased in both durvalumab and placebo groups. The median duration of follow-up in all patients was 34.2 months (range: 0.2 to 64.9), 40.0 months (range: 0.2 to

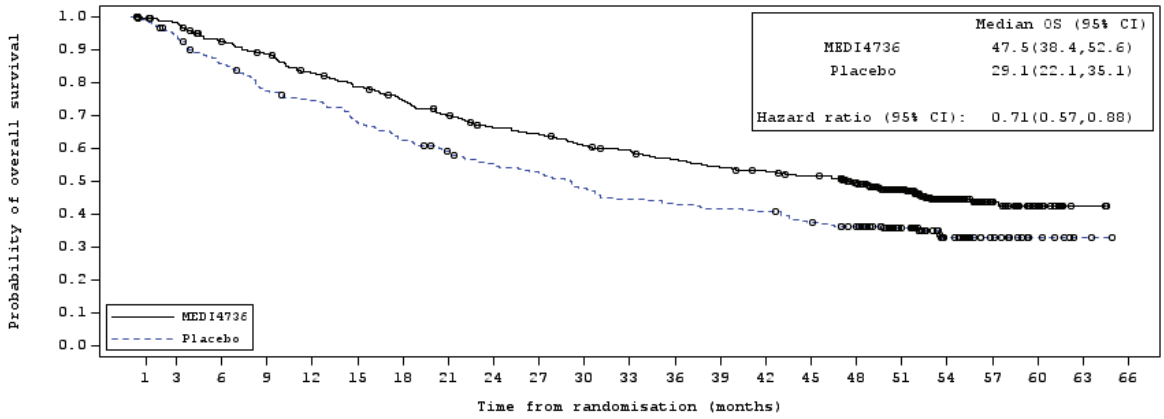
64.5) in the durvalumab group and 26.4 months (range: 0.3 to 64.9) in the placebo group (Table 11.2.1.2.OSUP2).

Table 4 Overall Survival at the Second OS Follow-Up Analysis (Full Analysis Set)

	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)	
Survival status	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**
Death, n (%)	183 (38.4)	116 (48.9)	210 (44.1)	134 (56.5)	247 (51.9)	149 (62.9)
Median overall survival (months) [a]	NR	28.7	NR	29.1	47.5	29.1
95% CI for median overall survival [a]	34.7, NR	22.9, NR	38.4, NR	22.1, 35.1	38.4, 52.6	22.1, 35.1
Survival rate at 12 months (%) [a]	83.1	75.3	83.1	74.6	83.1	74.6
95% CI for survival rate at 12 months [a]	79.4, 86.2	69.2, 80.4	79.4, 86.2	68.5, 79.7	79.4, 86.2	68.5, 79.7
Survival rate at 24 months (%) [a]	66.3	55.6	66.3	55.3	66.3	55.3
95% CI for survival rate at 24 months [a]	61.7, 70.4	48.9, 61.8	61.8, 70.4	48.6, 61.4	61.8, 70.4	48.6, 61.4
Survival rate at 36 months (%) [a]	N/A	N/A	57.0	43.5	56.7	43.6
95% CI for survival rate at 36 months [a]	N/A	N/A	52.3, 61.4	37.0, 49.9	52.1, 61.1	37.1, 49.9
Survival rate at 48 months (%) [a]	N/A	N/A	N/A	N/A	49.6	36.3
95% CI for survival rate at 48 months [a]	N/A	N/A	N/A	N/A	44.9, 54.1	30.1, 42.6
Hazard ratio, comparing Durvalumab vs. Placebo [b]	0.68		0.69		0.71	
95% CI for hazard ratio [b]	0.53, 0.87		0.55, 0.86		0.57, 0.88	

a Calculated using the Kaplan-Meier technique.
b The analysis was performed using stratified log-rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
CI = Confidence interval, NR = Not reached, DCO = data cut-off, LSI = last subject in, N/A = not applicable, OS = overall survival.
Source: Table 11.2.1.1.OSUP2, Table 11.2.1.1.OSUP1(PACIFIC Interim CSR Addendum-2, Module 5.3.5.1), and Table 11.2.1.1.OS (PACIFIC Interim CSR Addendum-1, Module 5.3.5.1).

Figure 3 **Kaplan-Meier Plot of Overall Survival at the Second OS Follow-Up Analysis (Full Analysis Set)**



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
MEDI4736	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

Circles indicate a censored observation.
CI = confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.1.OSUP2.

Subgroup analysis

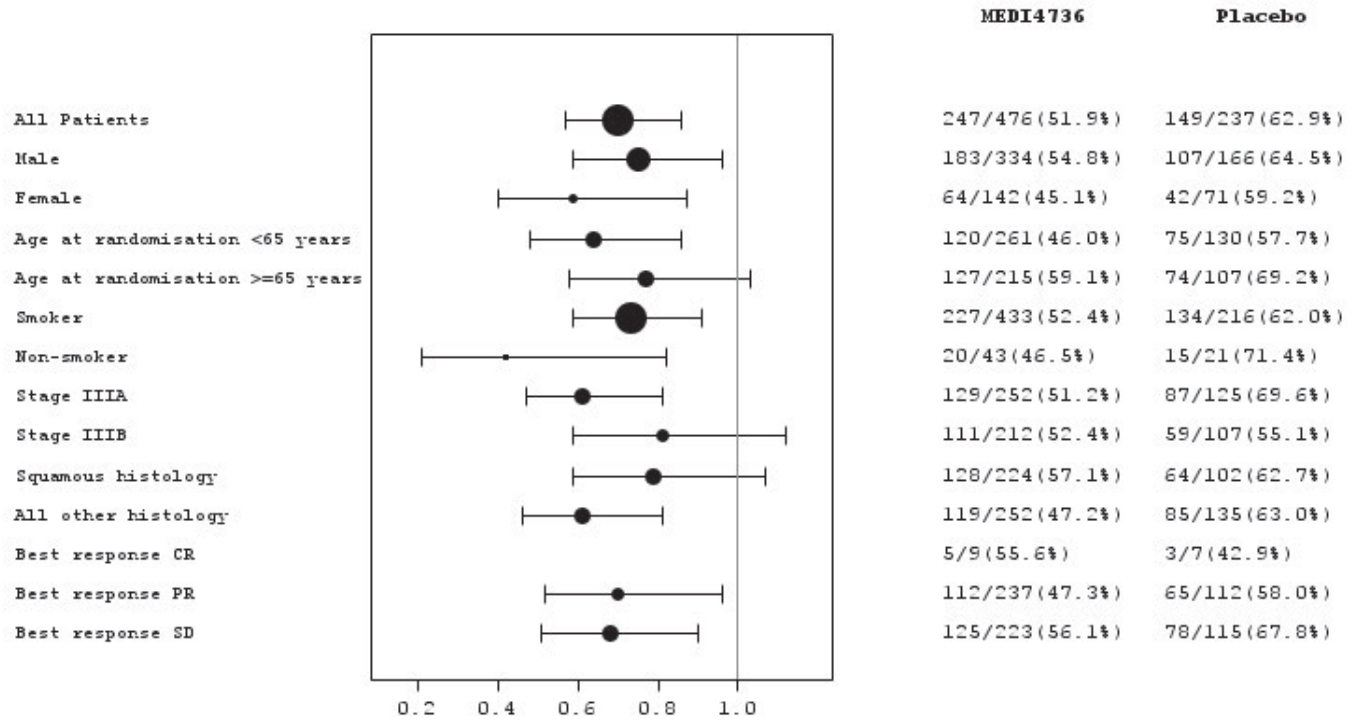
Subgroup analysis for the data at the primary OS analysis is presented in the PACIFIC Interim CSR Addendum 1 (see Figure 3 and Table 11.2.1.3.OS in the PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Subgroup analysis for the data at the first OS follow-up analysis is presented in detail in the PACIFIC Interim CSR Addendum 2 (See Figure 2, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1) and was generally consistent with that of the primary OS analysis. (see Figure 2 and Table 11.2.1.3.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

Subgroup analysis for the data at the second OS follow-up analysis is presented in detail in Figure 4 and was generally consistent with that of the primary OS analysis and the first OS follow-up analysis. Improvements in OS favouring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, and baseline disease characteristics (Figure 4, Table 11.2.1.3.OSUP2).

For further discussion on exploratory post-hoc subgroup biomarker analysis by PD-L1 status at the second OS follow-up analysis, see Appendix 12.1.14 in the PACIFIC Interim CSR Addendum 3.

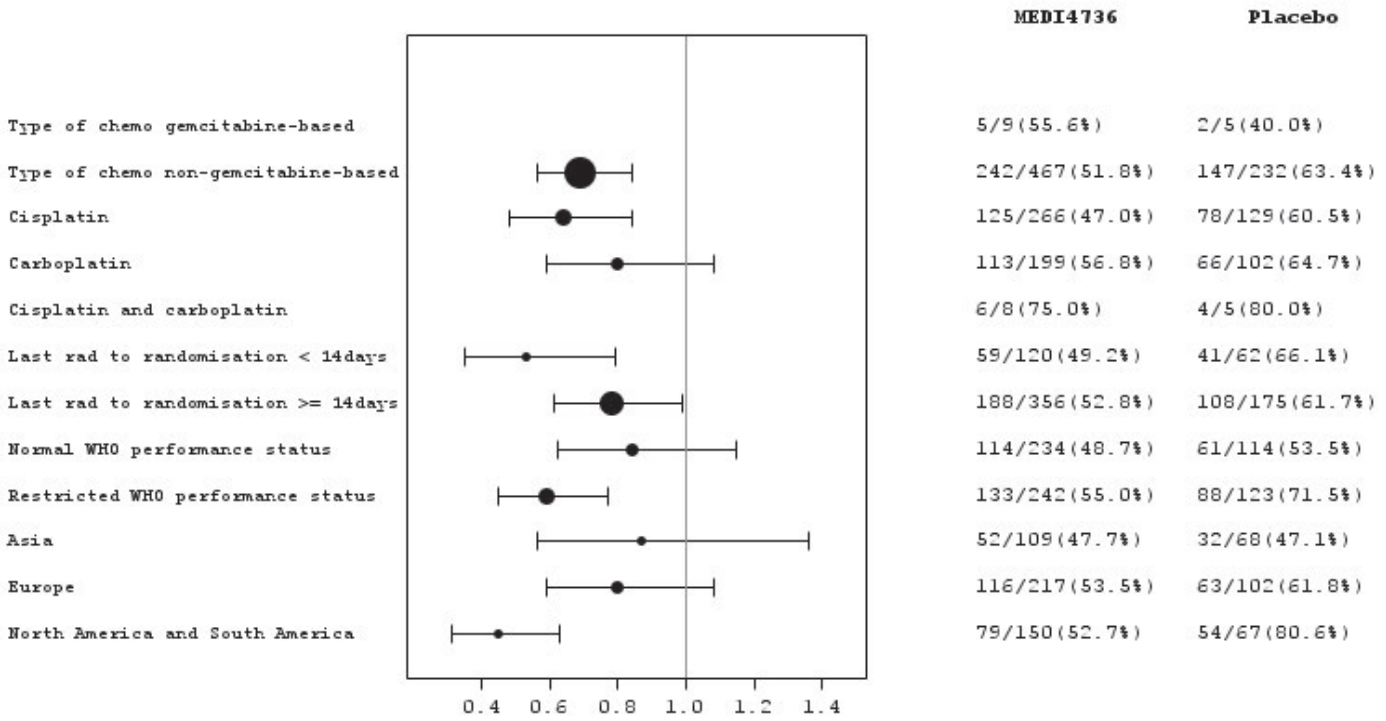
Figure 4 Overall Survival Forest Plot, by Subgroup at the Second OS Follow-Up Analysis (Full Analysis Set)



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

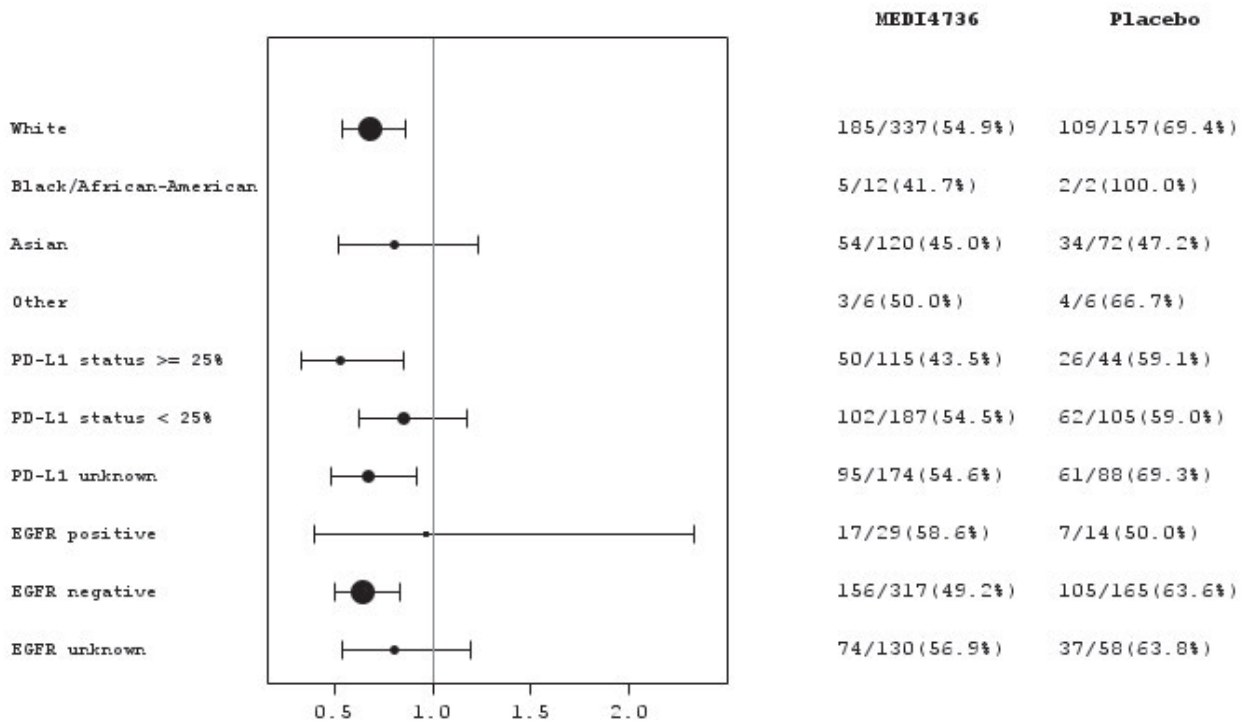
Source: Figure 11.2.1.4.OSUP2.



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

Source: Figure 11.2.1.4.OSUP2.



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
The change in scale appears to have arisen due to the wider confidence interval in one of the subgroups.

CI= Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

Source: Figure 11.2.1.4.OSUP2.

7.1.2 Secondary efficacy variables

7.1.2.1 Time to first subsequent therapy or death (TFST)

The TFST results at the time of the first OS follow-up analysis and at the time of the OS primary analysis are presented in the PACIFIC Interim CSR Addendum 2 (See Table 4 and Figure 3, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the 4-year update, treatment with durvalumab prolonged the TFST, as compared to placebo (HR: 0.62; 95% CI: 0.51, 0.76), consistent with the results at the time of the primary analysis and the 3-year update. The median TFST was 21.2 months in the durvalumab group, as compared to 10.4 months in the placebo group.

The TFST results at the time of the 4-year and 3-year updates as well as at the time of the primary analysis are presented in Table 5 and Figure 5).

Table 5 Time to First Subsequent Therapy or Death, Stratified Log-Rank Test at the 4-Year Update (Full Analysis Set)

	Number (%) of Patients					
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	267 (56.1)	169 (71.3)	283 (59.5)	183 (77.2)	310 (65.1)	186 (78.5)
Subsequent therapy	196 (41.2)	130 (54.9)	207 (43.5)	138 (58.2)	226 (47.5)	139 (58.6)
Death	71 (14.9)	39 (16.5)	76 (16.0)	45 (19.0)	84 (17.6)	47 (19.8)
Median time to first subsequent therapy or death (months) [b]	21.0	10.4	21.2	10.4	21.2	10.4
95% CI for median time to first subsequent therapy or death [b]	16.6, 25.5	8.3, 12.5	17.1, 25.8	8.4, 12.5	17.1, 25.8	8.4, 12.5
Hazard ratio	0.58		0.58		0.62	
95% CI for hazard ratio	0.47, 0.72		0.47, 0.71		0.51, 0.76	

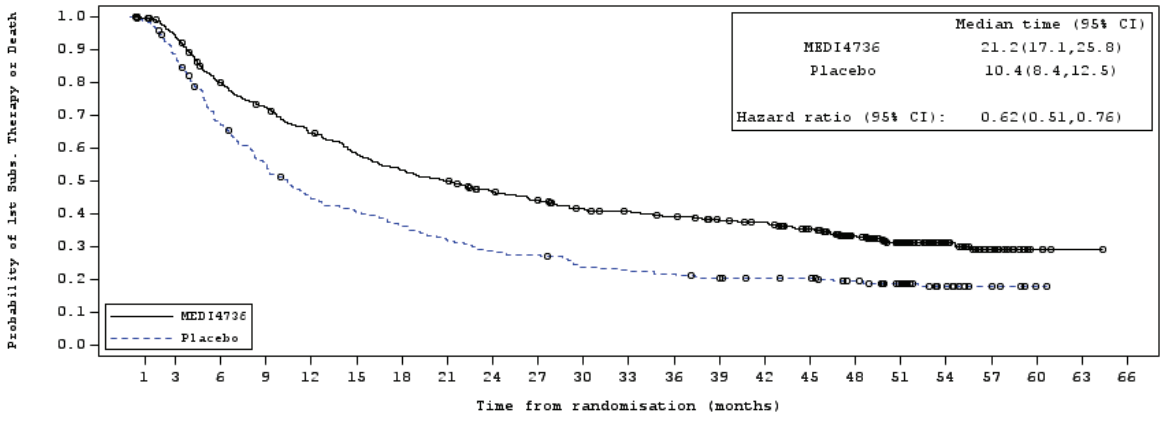
a Patients with first subsequent therapy or death (TFST). TFST is defined as the time from randomization to the start date of the first subsequent therapy after discontinuation of treatment, or death.

b Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

CI = Confidence interval, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.2.5.1.OSUP2, Table 11.2.5.1.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.2.5.1.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Figure 5 Kaplan-Meier Plot of Time to First Subsequent Therapy or Death at the Second OS Follow-Up Analysis (Full Analysis Set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
MEDI4736	476	441	372	335	299	269	246	230	209	195	180	173	166	156	150	133	104	68	36	17	4	1	0
Placebo	237	207	155	126	101	92	82	73	65	63	53	51	49	45	42	41	33	25	14	6	1	0	0

Circles indicate a censored observation.
CI = confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.10.OSUP2.

7.1.2.2 Time to second subsequent therapy or death (TSST)

The TSST results at the time of the first and second OS follow-up analyses , and at the time of the OS primary analysis are shown in Table 6.

At the time of the second OS follow-up analysis , treatment with durvalumab prolonged the TSST, as compared to placebo (HR: 0.62; 95% CI: 0.51, 0.77; Table 6 and Figure 6), consistent with the results at the time of the primary OS analysis and the first OS follow-up analysis. The median TSST was 30.2 months in the durvalumab group, as compared to 17.8 months in the placebo group.

Table 6 Time to Second Subsequent Therapy or Death, Stratified Log-Rank Test at the Second OS Follow-Up Analysis (Full Analysis Set)

	Number (%) of patients					
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	221 (46.4)	139 (58.6)	250 (52.5)	162 (68.4)	275 (57.8)	170 (71.7)
Subsequent therapy	83 (17.4)	61 (25.7)	109 (22.9)	79 (33.3)	117 (24.6)	82 (34.6)
Death	138 (29.0)	78 (32.9)	141 (29.6)	83 (35.0)	158 (33.2)	88 (37.1)
Median time to second subsequent therapy or death (months) [b]	29.3	18.6	30.2	17.8	30.2	17.8
95% CI for median time to second subsequent therapy or death [b]	26.0, 34.9	14.8, 23.9	26.0, 38.4	14.1, 22.9	26.0, 38.9	14.1, 22.9
Hazard ratio	0.63		0.61		0.62	
95% CI for hazard ratio	0.50, 0.79		0.49, 0.75		0.51, 0.77	

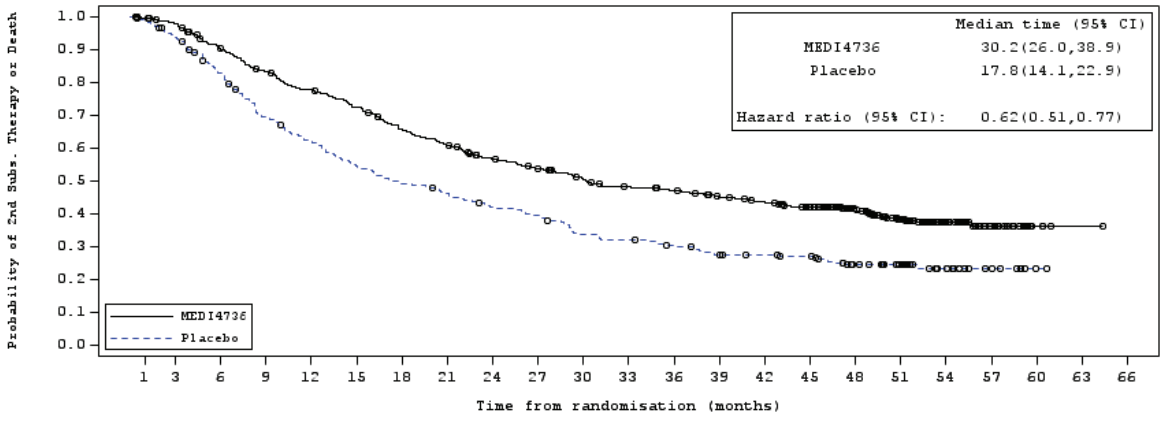
a Patients with second subsequent therapy or death (TSST). TSST is defined as the time from randomization to the start date of the second subsequent therapy after discontinuation of treatment, or death.

b Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

CI = Confidence interval, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.2.9.1.OSUP2, Table 11.2.9.1.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.2.9.1.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Figure 6 **Kaplan-Meier Plot of Time to Second Subsequent Therapy or Death at the Second OS Follow-Up Analysis (Full Analysis Set)**



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
MEDI4736	476	461	419	386	359	334	301	278	252	236	219	206	199	186	177	160	128	82	41	20	4	1	0
Placebo	237	219	190	158	140	123	111	103	93	88	74	70	65	58	55	52	39	30	17	7	1	0	0

Circles indicate a censored observation.
CI = confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.13.OSUP2.

7.2 Efficacy evaluation conclusions

At the time of the 4-year update (approximately 4 years from LSI), the PFS analysis results were consistent with that reported at the time of the primary PFS analysis:

- The PFS benefit of durvalumab over placebo (4-year update) was consistent with the PFS primary analysis (HR: 0.55; 95%; CI: 0.44, 0.67).
- The Kaplan-Meier estimate of median PFS was 17.2 months in the durvalumab group (95% CI: 12.3, 23.8), as compared to 5.6 months (95% CI: 4.6, 7.7) in the placebo group.
- The separation in the Kaplan-Meier curves between the treatment groups was observed early, and was sustained. This was supported by the numerical improvement of the median PFS rates for the durvalumab group vs the placebo group at the 24-month landmark (44.8% vs 24.8%, respectively), 36-month landmark (39.8% vs 20.5%, respectively), as well as the 48-month landmark (35.3% vs. 19.5%, respectively).

At the time of the 4-year update (approximately 4 years from LSI), the survival benefit of durvalumab over placebo was consistent with the OS primary analysis, with a 29% reduction in the risk of death as compared to placebo (HR: 0.71; 95% CI: 0.57, 0.88).

- The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group.
- The separation of OS curves between the durvalumab and placebo groups was sustained. This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at the OS36 landmark (57.0% vs 43.5%, respectively) as well as the OS48 landmark (49.6% vs 36.3%, respectively).

8. SAFETY EVALUATION

The safety analyses at the 22 March 2018 DCO were conducted based on the safety analysis set, which included 475 patients in the durvalumab group and 234 patients in the placebo group (See Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

By May 2017, all patients had completed their protocol-defined 12 months of study treatment or had discontinued prior to the defined 12 months of treatment. Therefore, a comprehensive safety presentation was provided in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1.

At the date of the first OS follow-up (approximately 3 years from LSI) analysis, there were no safety updates to be provided (except for deaths), as compared to the primary OS analysis (see Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). The listings of deaths on treatment are presented in Section 11 (see Table 11.3.3.1.6.OSUP1, and Table 11.3.3.1.8.OSUP1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the date of the second OS follow-up (approximately 4 years from LSI) analysis, there were no safety updates to be provided (except for deaths), as compared to the first OS analysis (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

8.1 Deaths, serious adverse events, discontinuation of study treatment due to adverse events, and other significant adverse events

8.1.1 Deaths

At the time of the second OS follow-up analysis, a total of 396 deaths were observed, with 247 (51.9%) patients in the durvalumab group and 149 (62.9%) patients in the placebo group. This was an addition of 52 deaths compared to the previous analysis. The majority of deaths

were solely related to disease under investigation (196/247 [79.4%] in durvalumab group and 114/149 [76.5%] in the placebo group, respectively. Since the 22 March 2018 DCO, there have been no new fatal adverse events.

All deaths for the full analysis set is presented in Table 7 with death listings presented in Section 11.3 (see Table 11.3.3.1.8.OSUP2). Details of deaths at the time of the primary OS analysis is presented in the PACIFIC Interim CSR Addendum 1 (Section 8.3.1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). Details of deaths at the time of the first OS follow-up analysis is presented in the PACIFIC Interim CSR Addendum 2 (Section 8.3.1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

Table 7 All Deaths at the Second OS Follow-Up Analysis (Full Analysis Set)

Category	Number (%) of patients					
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total number of deaths	183 (38.4)	116 (48.9)	210 (44.1)	134 (56.5)	247 (51.9)	149 (62.9)
Death related to disease under investigation only [a]	147 (30.9)	86 (36.3)	169 (35.5)	101 (42.6)	196 (41.2)	114 (48.1)
Death related to disease under investigation [a] and an AE with outcome of death	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)
AE onset prior to subsequent therapy [b]	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
AE with outcome of death only	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)
AE onset prior to subsequent therapy [b]	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Death not due to either disease progression or an AE with a start date whilst on treatment or within the safety follow-up period	8 (1.7)	6 (2.5)	10 (2.1)	8 (3.4)	16 (3.4)	9 (3.8)
Unknown reason for death	7 (1.5)	6 (2.5)	10 (2.1)	7 (3.0)	12 (2.5)	8 (3.4)
Other deaths [d]	0	1 (0.4)	0	1 (0.4)	2 (0.4)	1 (0.4)

a Deaths related to disease under investigation as determined by the Investigator.

b Includes adverse events with an onset date (or pre-treatment AEs that increase in severity) on or after the date of first dose and up to and including 90 days following the last dose of study medication, or AE start date <= the date of initiation of the first subsequent therapy (whichever occurs first).

c AE start date >90 days following the last dose of study medication and AE start date > the date of initiation of the first subsequent therapy (whichever occurs first).

d Patients who died and are not captured in the earlier categories and patients who died due to AE with onset date in the re-treatment phase and up to and including 90 days following the last dose of study medication in the re-treatment phase.

AE = adverse event, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.3.3.1.6.OSUP2, Table 11.3.3.1.6.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.3.3.1.6.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

8.2 Safety evaluation conclusions

At the time of the second OS follow-up analysis (DCO: 20 March 2020), there was no change in safety conclusions from those reported at the time of the primary OS analysis.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

A comprehensive discussion of the efficacy, safety, and pharmacokinetic results of the PACIFIC study, and the substantial clinical benefit of durvalumab treatment in patients with Stage III, locally advanced, unresectable, NSCLC is outlined in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 9.1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of the 4-year update, the PFS benefit of durvalumab over placebo was consistent with the PFS primary analysis and sustained with the longer duration of follow up (48 month PFS rate for durvalumab of 35.3% vs 19.5% for placebo). The durvalumab survival benefit over placebo was consistent with that reported at time of the primary OS analysis as well as the first OS follow-up analysis. Similarly TFST and TSST results were consistent with the previous analyses performed on an annual basis.

The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was sustained, which was supported by the higher OS rates for the durvalumab group vs the placebo group at the OS12 (83.1% vs 74.6%, respectively), OS24 (66.3% vs 55.3%, respectively), OS36 landmark (56.7% vs 43.6%, respectively) as well as the OS48 landmark (49.6% vs 36.3%, respectively).

9.2 Overall conclusion

In the pre-planned interim analyses of the 2 primary endpoints of PFS (DCO: 13 February 2017) and OS (DCO: 22 March 2018), durvalumab treatment demonstrated a clinically meaningful benefit compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.

The results of the second OS follow-up (approximately 4 years from LSI) analysis (DCO: 20 March 2020) were consistent with those reported at the time of the OS primary analysis and first OS follow-up analysis. Overall, durvalumab treatment demonstrated a well-tolerated and manageable safety profile that was generally consistent with the established safety profile to date.

Taken together, the long-term survival follow up demonstrated that the overall benefit: risk of durvalumab treatment remains highly favourable and consistent with that previously reported in this patient population.

10. REFERENCE LIST

Not Applicable

11. SUMMARY TABLES AND FIGURES AND LISTINGS

CCI


CCI

Clinical Study Report Addendum 4

Drug Substance	Durvalumab
Study Code	D4191C00001
Edition Number	01
Date	13 April 2021
EudraCT Number	2014-000336-42

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of durvalumab as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Study dates: First patient randomized: 09 May 2014
Last patient randomized: 22 April 2016
Data cut-off date: 11 January 2021 (study complete)

Phase of development: III

Sponsor's Responsible Medical Officer: PPD
AstraZeneca LP
PPD
Cambridge, UK

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
AE	adverse event
BICR	blinded independent central review
CI	confidence interval
CR	complete response
CSF	Cerebrospinal fluid
CSR	clinical study report
DCO	data cut-off
DoR	duration of response
eCRF	electronic case report form
EGFR	estimated glomerular filtration rate
HR	hazard ratio
IDMC	independent data monitoring committee
LSI	last subject in (enrolled)
MEDI4736	durvalumab
N/A	Not applicable
NR	not reached
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OS12	overall survival at 12 months
OS24	overall survival at 24 months
OS36	overall survival at 36 months
OS48	overall survival at 48 months
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PFS2	time to second progression or death
PR	partial response

Abbreviation or special term	Explanation
PRO	patient-reported outcome
QoLs	quality of life scale
RECIST	response evaluation criteria in solid tumours
SD	stable disease
TFST	time to first subsequent therapy or death
TMG	toxicity management guidelines
TSST	time to second subsequent therapy or death
TTDM	time to death or distant metastasis
WHO	World Health Organization

1. ETHICS

For information on ethics, please see Section 1, PACIFIC Interim clinical study report (CSR), Module 5.3.5.1.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

For information on study personnel and administrative structure, please see Section 2, PACIFIC Interim CSR, Module 5.3.5.1.

3. INTRODUCTION

PACIFIC (Study D4191C00001) is a Phase 3, randomized, double-blind, placebo-controlled, multi-centre, global clinical study designed to evaluate the efficacy and safety of durvalumab (IMFINZI™) compared with placebo in patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based concurrent chemoradiation. The primary objective was to assess the efficacy of durvalumab compared with placebo in terms of progression-free survival (PFS; based on blinded independent central review [BICR]) and overall survival (OS). Secondary efficacy endpoints included OS at 24 months, objective response rate (ORR), duration of response (DoR), time to death or distant metastases (TTDM), time to second progression or death (PFS2), and patient-reported outcome (PRO). Time to first subsequent therapy or death (TFST) was derived as a supportive summary to PFS and time to second subsequent therapy or death (TSST) was derived as a supportive summary to PFS2.

Four data cut-off s (DCO)s were originally planned for this study including 1 interim analysis for PFS and 2 interim analyses for OS as follows:

- The planned interim analysis of PFS was conducted after 371 events (80%) of the target 458 events were observed (DCO: 13 February 2017).
    - The results of the interim PFS analysis were reviewed by the Independent Data Monitoring Committee (IDMC) (20 April 2017). Since the study achieved pre-specified statistical significance (p-value <0.011035), the interim analysis of PFS was considered to be the final PFS analysis. Therefore, it will be referred to as “the primary PFS analysis” in this document.
    - Based on the review of that interim analysis, the Sponsor unblinded the study for PFS and safety.

  - A comprehensive analysis of PFS along with a detailed presentation of the safety and tolerability profile of the durvalumab treatment is outlined in the PACIFIC interim CSR (see PACIFIC Interim CSR, Module 5.3.5.1).

- The planned interim OS analysis was conducted after 299 (61%) of the target 491 death events were observed (DCO: 22 March 2018).
  - Results from the interim OS analysis were reviewed by the IDMC on 21 May 2018.
  - Since the study achieved the statistical significance level of ≤ 0.00274 that met the predefined criterion for unblinding the OS data, the results of the interim OS analysis (see PACIFIC Interim CSR Addendum 1, Module 5.3.5.1) was considered the final OS analysis. Therefore, it will be referred to as "the primary OS analysis" in this document.
  - The PACIFIC Interim CSR Addendum 1 reported the results from the 22 March 2018 DCO.
- The first OS follow-up was performed approximately 3 years after last subject in (LSI) (DCO: 31 January 2019).
  - The PACIFIC Interim CSR Addendum 2 reported the results of a long-term overall survival follow-up and subsequent anti-cancer therapy usage, as of 31 January 2019 DCO.
- The second OS follow-up was performed approximately 4 years after LSI (DCO: 20 March 2020).
  - The PACIFIC Interim CSR Addendum 3 reported the results of a long-term OS follow-up and subsequent anti-cancer therapy usage, as of 20 March 2020 DCO.
- The 5-year PFS and OS follow-up, performed approximately 5 years after LSI (DCO: 11 January 2021), is the final study report (CSR, Addendum 4) at the completion of this study.

There are no updates on pharmacokinetic, immunogenicity, or safety data presented in this document. Therefore, the focus is on the long-term survival follow-up data providing updates on disposition, PFS, OS and subsequent anti-cancer therapy usage.

4. STUDY OBJECTIVES

The primary and secondary objectives are presented in the PACIFIC Interim CSR (see Section 4, PACIFIC Interim CSR, Module 5.3.5.1).

Appendix 12.1.14 in the PACIFIC Interim CSR Addendum 1 presents results of efficacy analyses from exploratory *post hoc* biomarker (programmed death ligand 1 [PD-L1]) subgroup analyses (see Appendix 12.1.14, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

5. STUDY PLAN AND PROCEDURES

5.1 Overall study design and flow chart

This is a randomized, double-blind, placebo-controlled, multi-center, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable Stage III NSCLC, who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

For details on the study design, see Section 5.1, PACIFIC Interim CSR, Module 5.3.5.1.

5.2 Rationale for study design, doses, and control groups

See Section 5.2, PACIFIC Interim CSR, Module 5.3.5.1.

5.3 Selection of study population

See Section 5.3, PACIFIC Interim CSR, Module 5.3.5.1.

5.4 Treatments

See Section 5.4, PACIFIC Interim CSR, Module 5.3.5.1.

5.5 Measurements of study variables and definitions of outcome variables

See Section 5.5, PACIFIC Interim CSR, Module 5.3.5.1.

5.6 Data management and quality assurance

See Section 5.6, PACIFIC Interim CSR, Module 5.3.5.1.

5.7 Statistical methods and determination of sample size

See Section 5.7, PACIFIC Interim CSR, Module 5.3.5.1.

5.8 Clinical study protocol amendments and other changes in the conduct of the study or planned analyses

5.8.1 Changes in the conduct of the study

Important amendments to the original study protocol, including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct are presented in the Interim CSR (see Table 8, PACIFIC Interim CSR, Module 5.3.5.1) and PACIFIC Interim CSR Addendum 1 (Table 1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

There were no protocol amendments between the DCOs of the primary OS analysis (22 March 2018) and the first OS follow-up analysis (31 January 2019). However, there was one protocol amendment between the DCOs of the first OS follow-up analysis (31 January 2019) and the second OS follow-up analysis (20 March 2020). A summary of the major changes of that protocol amendment is presented in the PACIFIC Interim CSR Addendum 3 (Section 5.8.1, PACIFIC Interim CSR Addendum 3, Module 5.3.5.1).

There was one protocol amendment between the DCOs of the 4-year OS update (20 March 2020) and the 5-year OS update (11 January 2021). A summary of the major changes of that protocol amendment is presented below:

- Extension of the study for the purposes of long-term follow-up.
    - Movement of estimated last patient completed from Q3 2019 to Q2 2021.
- Clarification that both primary analyses have been performed and co-primary endpoints have both been met.
- Reduction in table of assessments to be followed upon implementation of protocol 7.1:
    - Removal of QoLs.
    - Removal of sampling – CSF and mRNA.
    - Reduction in frequency of Scans.
    - Limited data collection deemed as critical for analysis and required by Payers:
        - Inclusive of reporting only a limited subset of concomitant medications.
- Addition of mandatory biopsy for evidence of true progression when entering re-treatment.
- Clarification that following final DCO for the study, retreatment will <u>not</u> be available for new candidates under this protocol.
- Clarification that survival follow-up will be the final data reported upon completion of this protocol:
    - Those who have been progression free for <u>approximately</u> 5 years will be considered cured.
    - Those who are on re-treatment may continue to receive durvalumab on an alternate protocol or extension.
- Removal of TMGs as part of the body of the protocol:
    - With the exception of Germany where TMGs are included in a concatenated version of the protocol.

- Note: this was not the purpose of the amendment; but was actioned at the same time.

5.8.2 Changes to planned analyses

Exploratory efficacy analyses on PD-L1 subgroups were included. No additional changes have been made to the planned analyses from those outlined in the PACIFIC Interim CSR (see Section 5.8.2, PACIFIC Interim CSR, Module 5.3.5.1).

6. STUDY PATIENTS

Summary tables and figures pertaining to this section are presented in Section 11.1.

6.1 Disposition

A total of 983 patients were enrolled in 235 study centers across 26 countries worldwide. Of these, 713 patients were randomized in a 2:1 ratio to receive either durvalumab 10 mg/kg every 2 weeks (476 patients) or placebo (237 patients) (full analysis set; Table 1).

Of the 713 patients, 709 (473 [99.4%] in the durvalumab group and 236 [99.6%] in the placebo group) received study treatment (Table 1). The other 4 patients (3 [0.6%] in the durvalumab group and 1 [0.4%] in the placebo group) were randomized but did not receive study treatment because of patient decision (2 patients), neutropenia (1 patient), and worsening chronic obstructive pulmonary disease (1 patient) (see Section 6.1, PACIFIC Interim CSR, Module 5.3.5.1). The first patient was randomized into the study on 09 May 2014, and the last patient was randomized on 22 April 2016.

The disposition of patients at the time of the primary OS analysis and the first OS follow-up analysis is summarized in the PACIFIC Interim CSR Addendum 1 and PACIFIC Interim CSR Addendum 2, respectively.

At the second OS follow-up analysis (approximately 4 years from LSI), the patient disposition was consistent with that of the first OS follow-up analysis, and is summarized in the PACIFIC Interim CSR Addendum 3. As anticipated with a longer follow-up, a lower number of patients remained on the study.

Table 1 Patient Disposition (All Patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Patients enrolled [a]			983
Patients randomized	476 (48.4)	237 (24.1)	713 (72.5)
Patients who were not randomized			270 (27.5)
Subject decision			35 (3.6)

Table 1 Patient Disposition (All Patients)

	Number (%) of patients		
	Durvalumab	**Placebo**	**Total**
Eligibility criteria not fulfilled			225 (22.9)
Death			6 (0.6)
Other			4 (0.4)
Full analysis set	476 (100.0)	237 (100.0)	713 (100.0)
Patients who received study treatment [b]	473 (99.4)	236 (99.6)	709 (99.4)
Patients who did not receive study treatment [b]	3 (0.6)	1 (0.4)	4 (0.6)
Patients who completed 12 months of treatment [cd]	232 (49.0)	82 (34.7)	314 (44.3)
Patients who discontinued study treatment [c]	241 (51.0)	154 (65.3)	395 (55.7)
Subject decision	14 (3.0)	12 (5.1)	26 (3.7)
Adverse event	73 (15.4)	23 (9.7)	96 (13.5)
Severe non-compliance to protocol	1 (0.2)	1 (0.4)	2 (0.3)
Condition under investigation worsened	148 (31.3)	117 (49.6)	265 (37.4)
Development of study specific discontinuation criteria	1 (0.2)	1 (0.4)	2 (0.3)
Other	4 (0.8)	0	4 (0.6)
Patients ongoing study at data cut off [b]	178 (37.4)	68 (28.7)	246 (34.5)
Patients who terminated study [b]	298 (62.6)	169 (71.3)	467 (65.5)
Subject decision	30 (6.3)	16 (6.8)	46 (6.5)
Death	260 (54.6)	149 (62.9)	409 (57.4)
Subject lost to follow-up	8 (1.7)	3 (1.3)	11 (1.5)
Missing	0	1 (0.4)	1 (0.1)

a Informed consent received.
b In this section, percentages are calculated from number of patients in the full analysis set.
c In this section, percentages are calculated from number of patients who received treatment.
d Patients who completed 12 months of treatment have reported maximum cycle of immunotherapy reached on the electronic case report form (eCRF).
Nine patients who terminated study due to subject decision have died. One patient with missing termination reason has died.
Source: Table 11.1.1.OSUP3.

At the time of primary OS analysis, 26 patients were receiving re-treatment. Additional details on patient disposition with ongoing re-treatment are presented in the PACIFIC Interim CSR Addendum 1 (see Table 11.1.1.1.A.OSUP, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of the first OS follow-up, 9 additional patients had received re-treatment; a total of 35 patients (27 [5.7%] patients in the durvalumab group and 8 [3.4%] patients in the placebo group, respectively). Additional details on patient disposition with ongoing re-treatment are presented in the PACIFIC Interim CSR Addendum 2 (see Table 11.1.1.1.A.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the second OS follow-up, a further 7 patients had received re-treatment, resulting in a revised total of 42 patients, with 34 (7.1%) patients in the durvalumab group and 8 (3.4%) patients in the placebo group, respectively. Additional details on patient disposition with ongoing re-treatment are presented in the PACIFIC Interim CSR Addendum 3 (see Table 11.1.1.1.A.OSUP2, PACIFIC Interim CSR Addendum 3, Module 5.3.5.1).

At the time of the 5-year follow-up (final analysis), no further patients had received re-treatment, resulting in the same total of 42 patients, with 34 (7.1%) patients in the durvalumab group and 8 (3.4%) patients in the placebo group, respectively. Of those, 4 patients (11.8%) in the durvalumab group (none in the placebo group) completed the protocol specified 12 months of re-treatment, and 31 (73.8%) patients discontinued the re-treatment in the durvalumab (23 [67.6%]) and placebo (8 [100%]) groups, respectively. A total of 7 (16.7%) patients were ongoing on re-treatment at the time of the second OS follow-up analysis with all of them being in the durvalumab (7 [20.6%]) group. Additional details on patient disposition with ongoing re-treatment are presented in Table 11.1.1.1.A.OSUP3.

6.2 Protocol deviations

The important protocol deviations for the primary PFS analysis are reported in the PACIFIC Interim CSR (See Section 6.2, PACIFIC Interim CSR, Module 5.3.5.1). Important protocol deviations were not formally assessed for the DCO of 20 January 2021; however, a listing of study issues identified relating to the COVID-19 pandemic is provided in Appendix 12.2.7.11.OSUP3.

6.3 Patients analyzed (analysis sets)

A full presentation of the analysis set used for each outcome variable is included in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 6.3, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.3, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

6.4 Demographic and other patient characteristics

A full presentation of the demographic and key baseline characteristics of study patients, including prior therapies, is presented in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1 and Section 6.4, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). Demographics and baseline characteristics were representative of the intended patient population, and well balanced between the 2 treatment groups.

6.4.1 Concomitant medication after study entry

Concomitant medication was collected whilst patients received study drug and for 90 days after receiving the last dose of study drug. All patients had completed the 90 days follow-up following the last dose of the protocol defined 12-month treatment period in August 2018. As

such there is no update for the concomitant medication after study entry at the first OS follow up analysis as compared to the primary OS analysis.

A detailed description of concomitant medication after study entry was provided at the primary OS analysis in the PACIFIC Interim CSR Addendum 1 (See Table 11.1.12.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

6.4.2 Post-discontinuation disease-related anti-cancer therapy

Post-discontinuation disease-related anti-cancer therapy analysis was presented in PACIFIC Interim CSR Addendum 1 at the primary OS analysis (See Table 11.1.18.OS and Section 6.4.2, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of the first OS follow-up analysis, the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to OS primary analysis (see Table 2 PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the second OS follow-up analysis, the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to OS primary analysis. A total of 225 (47.3%, 30 more patients from the OS interim analysis DCO and 19 more patients from the first OS follow-up analysis) patients in the durvalumab group and 138 (58.2%, 10 more patients from the OS interim analysis DCO, and one more patients from the first OS follow-up analysis) patients in the placebo group received post-discontinuation disease-related, anti-cancer therapy (see Table 2 PACIFIC Interim CSR Addendum 3, Module 5.3.5.1).

At the time of the 5-year follow-up PFS and OS update, the use of post-discontinuation disease-related anticancer therapy indicated a modest increase relative to the OS primary analysis. A total of 231 (48.5%) patients (same number of patients as in the second OS follow-up analysis) in the durvalumab group and 139 (58.6%) patients (same number of patients as in the second OS follow-up analysis) in the placebo group received post-discontinuation disease-related anti-cancer therapy (Table 2). Most patients in both treatment groups received cytotoxic chemotherapy (eg, carboplatin and pemetrexed), which included 157 (33.0%) patients in the durvalumab group and 85 (35.9%) patients in the placebo group. Systemic therapy (eg, targeted therapies) was administered in 53 (11.1%) patients in the durvalumab group and 35 (14.8%) patients in the placebo group. Fewer patients in the durvalumab group than the placebo group received immunotherapy: 60 (12.6%) vs 69 (29.1%), respectively. A total of 97 (20.4%) patients in the durvalumab group and 61 (25.7%) patients in the placebo group received radiotherapy.

Table 2 Post-Discontinuation Disease-Related Anti-Cancer Therapy at the 5-Year Update (Full Analysis Set)

		Number(%) of patients		
Anti-cancer therapy [a]	**Treatment**	**MEDI4736 (N=476)**	**Placebo (N=237)**	**Total (N=713)**
Number of patients with post-discontinuation disease-related anti-cancer therapy		231 (48.5)	139 (58.6)	370 (51.9)
Radiotherapy		97 (20.4)	61 (25.7)	158 (22.2)
Immunotherapy		60 (12.6)	69 (29.1)	129 (18.1)
	Atezolizumab	7 (1.5)	5 (2.1)	12 (1.7)
	Avelumab	0	1 (0.4)	1 (0.1)
	Bms 986205	1 (0.2)	0	1 (0.1)
	Durvalumab	1 (0.2)	2 (0.8)	3 (0.4)
	Ipilimumab	1 (0.2)	1 (0.4)	2 (0.3)
	Nivolumab	37 (7.8)	53 (22.4)	90 (12.6)
	Pembrolizumab	16 (3.4)	10 (4.2)	26 (3.6)
	Tremelimumab	1 (0.2)	0	1 (0.1)
	Uncoded	3 (0.6)	1 (0.4)	4 (0.6)
Cytotoxic Chemotherapy		157 (33.0)	85 (35.9)	242 (33.9)
	Amrubicin Hydrochloride	2 (0.4)	1 (0.4)	3 (0.4)
	Carboplatin	90 (18.9)	47 (19.8)	137 (19.2)
	Cisplatin	24 (5.0)	17 (7.2)	41 (5.8)
	Docetaxel	47 (9.9)	20 (8.4)	67 (9.4)
	Etoposide	2 (0.4)	1 (0.4)	3 (0.4)
	Fluorouracil	1 (0.2)	1 (0.4)	2 (0.3)
	Gemcitabine	40 (8.4)	19 (8.0)	59 (8.3)
	Gemcitabine Hydrochloride	7 (1.5)	5 (2.1)	12 (1.7)
	Gimeracil;Oteracil	9 (1.9)	5 (2.1)	14 (2.0)
	Irinotecan	0	1 (0.4)	1 (0.1)
	Irinotecan Hydrochloride	0	1 (0.4)	1 (0.1)
	Nedaplatin	1 (0.2)	0	1 (0.1)
	Osimertinib Mesilate	1 (0.2)	0	1 (0.1)
	Oxaliplatin	0	1 (0.4)	1 (0.1)
	Paclitaxel	32 (6.7)	18 (7.6)	50 (7.0)
	Paclitaxel Albumin	11 (2.3)	6 (2.5)	17 (2.4)
	Pemetrexed	36 (7.6)	17 (7.2)	53 (7.4)
	Pemetrexed Disodium	21 (4.4)	16 (6.8)	37 (5.2)

		Number(%) of patients		
Anti-cancer therapy [a]	**Treatment**	**MEDI4736 (N=476)**	**Placebo (N=237)**	**Total (N=713)**
	Pemetrexed Disodium Heptahydrate	1 (0.2)	0	1 (0.1)
	Topotecan	0	1 (0.4)	1 (0.1)
	Uncoded	1 (0.2)	1 (0.4)	2 (0.3)
	Vinorelbine	8 (1.7)	5 (2.1)	13 (1.8)
	Vinorelbine Tartrate	9 (1.9)	3 (1.3)	12 (1.7)
Systemic Therapy		53 (11.1)	35 (14.8)	88 (12.3)
	Afatinib	11 (2.3)	4 (1.7)	15 (2.1)
	Afatinib Dimaleate	1 (0.2)	2 (0.8)	3 (0.4)
	Alectinib	2 (0.4)	2 (0.8)	4 (0.6)
	Alectinib Hydrochloride	1 (0.2)	0	1 (0.1)
	Bevacizumab	8 (1.7)	4 (1.7)	12 (1.7)
	Carboplatin	1 (0.2)	1 (0.4)	2 (0.3)
	Crizotinib	4 (0.8)	6 (2.5)	10 (1.4)
	Dasatinib	1 (0.2)	0	1 (0.1)
	Docetaxel	0	1 (0.4)	1 (0.1)
	Erlotinib	4 (0.8)	4 (1.7)	8 (1.1)
	Erlotinib Hydrochloride	6 (1.3)	9 (3.8)	15 (2.1)
	Gefitinib	4 (0.8)	3 (1.3)	7 (1.0)
	Glesatinib	1 (0.2)	0	1 (0.1)
	Itacitinib	1 (0.2)	0	1 (0.1)
	Lenvatinib	0	1 (0.4)	1 (0.1)
	Lorlatinib	0	1 (0.4)	1 (0.1)
	Naquotinib	1 (0.2)	0	1 (0.1)
	Necitumumab	3 (0.6)	2 (0.8)	5 (0.7)
	Nintedanib	2 (0.4)	1 (0.4)	3 (0.4)
	Nintedanib Esilate	1 (0.2)	0	1 (0.1)
	Osimertinib	4 (0.8)	2 (0.8)	6 (0.8)
	Osimertinib Mesilate	1 (0.2)	0	1 (0.1)
	Pemetrexed	0	1 (0.4)	1 (0.1)
	Ramucirumab	9 (1.9)	3 (1.3)	12 (1.7)
	Sitravatinib	1 (0.2)	0	1 (0.1)
	Uncoded	2 (0.4)	1 (0.4)	3 (0.4)
	Vandetanib	1 (0.2)	0	1 (0.1)
	Vemurafenib	1 (0.2)	0	1 (0.1)
	Vinorelbine	1 (0.2)	0	1 (0.1)
Other		2 (0.4)	0	2 (0.3)

		Number(%) of patients		
Anti-cancer therapy [a]	**Treatment**	**MEDI4736 (N=476)**	**Placebo (N=237)**	**Total (N=713)**
	Uncoded	2 (0.4)	0	2 (0.3)

a Therapies post discontinuation of study treatment.
Source: Table 11.1.18.OSUP3.

6.5 Conclusions on study patients

Demographics and disease characteristics were representative of the intended patient population and were well balanced between the durvalumab and placebo groups (see Section 6.4, PACIFIC Interim CSR, Module 5.3.5.1).

7. EFFICACY EVALUATION

7.1 Efficacy results

Summary tables and figures pertaining to efficacy results are presented in Section 11.2.

7.1.1 Primary efficacy variables

7.1.1.1 Progression-free survival

At the time of the primary PFS analysis (DCO: 13 February 2017) based on the BICR assessments according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), the study met the pre-defined criteria of the primary PFS analysis (Table 3). For a detailed description of the primary PFS results, see Section 7.1.1, PACIFIC Interim CSR, Module 5.3.5.1.

At the time of the 5-year follow-up analysis (DCO: 11 January 2021) based on the BICR assessments of PFS according to RECIST 1.1, the PFS benefit seen in the durvalumab group (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.45, 0.68) was consistent with the PFS primary analysis (HR: 0.52; 95% CI: 0.42, 0.65). The Kaplan-Meier estimate of median PFS was 16.9 months in the durvalumab group (95% CI: 13.0, 23.9), as compared to 5.6 months in the placebo group (95% CI: 4.8, 7.7) (Table 3). Likewise, based on the investigator assessments of PFS according to RECIST 1.1, the PFS benefit of durvalumab (HR: 0.67; 95% CI: 0.56, 0.81) over placebo was demonstrated (Figure 11.2.1.5.1.OSUP3).

At the 5-year analysis, the separation in the Kaplan-Meier curves (Figure 1), originally observed between the treatment groups at the PFS primary analysis (by BICR), appeared sustained with the longer follow-up. This is supported by the numerical improvement of the PFS rates for the durvalumab group vs the placebo group at the 24-month landmark (45.0% vs 25.1%, respectively), 36-month landmark (39.7% vs 20.8%, respectively), and the 48-month landmark (35.0% vs 19.9%, respectively). At the 5-year analysis, the estimated PFS rates for

the durvalumab group vs the placebo group were 33.1% vs 19.0%, respectively (the 60-month landmark).

Following a protocol amendment implemented to reduce the frequency of tumour scans during the long-term follow-up phase of the study, an additional sensitivity analysis of PFS by BICR was carried out to assess the impact of possible attrition bias. In the sensitivity analysis, patients were censored at the last evaluable assessment (prior to any subsequent therapy) whereas the primary assessment of PFS by BICR censored patients at last evaluable assessment prior to progression, if this occurred following at least 2 missed visits. The result of the sensitivity analysis was highly consistent with that presented above.

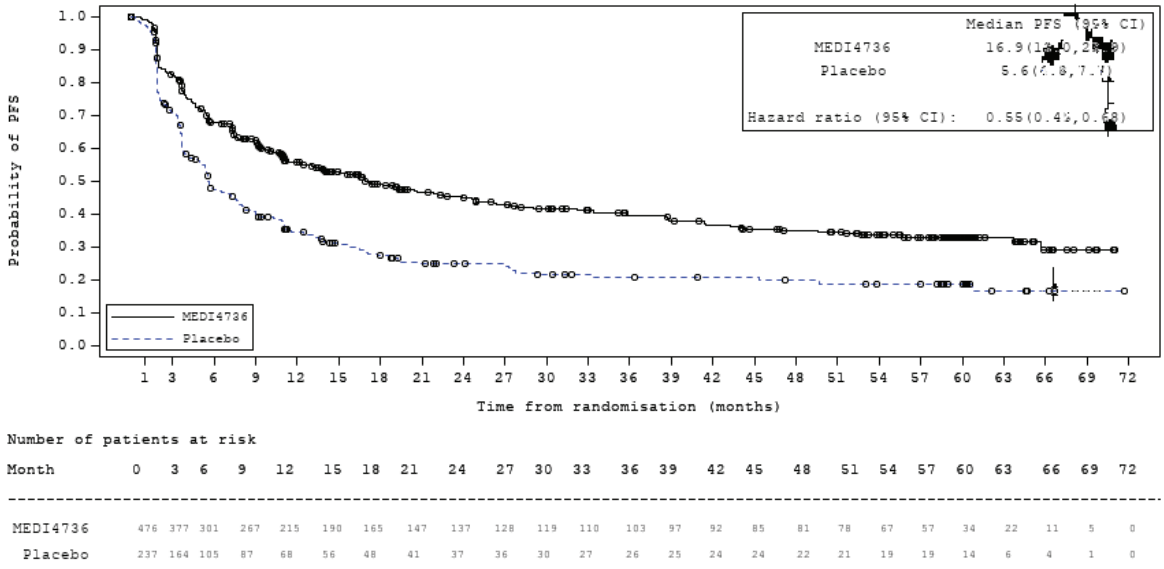
Table 3 Progression-Free Survival (Based on BICR Assessments According to RECIST 1.1) At the 5-Year Update (Full Analysis Set)

	Primary PFS analysis (DCO: 13 February 2017)		PFS Analysis (4-year update) (DCO: 20 March 2020)		PFS Analysis (5-year update) (DCO: 11 January 2021)	
Progression status	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	214 (45.0)	157 (66.2)	266 (55.9)	174 (73.4)	268 (56.3)	175 (73.8)
Median progression-free survival (months) [b]	16.8	5.6	17.2	5.6	16.9	5.6
95% CI for median progression-free survival [b]	13.0, 18.1	4.6, 7.8	12.3, 23.8	4.6, 7.7	13.0, 23.9	4.8, 7.7
Progression-free survival rate at 12 months (%) [b]	55.9	35.3	55.3	34.4	55.7	34.5
95% CI for progression-free survival rate at 12 months [b]	51.0, 60.4	29.0, 41.7	50.5, 59.8	28.2, 40.7	51.0, 60.2	28.3, 40.8
Progression-free survival rate at 18 months (%) [b]	44.2	27.0	49.2	27.3	49.1	27.5
95% CI for progression-free survival rate at 18 months [b]	37.7, 50.5	19.9, 34.5	44.3, 53.8	21.4, 33.5	44.2, 53.8	21.6, 33.6
Progression-free survival rate at 24 months (%) [b]	N/A	N/A	44.8	24.8	45.0	25.1
95% CI for progression-free survival rate at 24 months [b]	N/A	N/A	39.8, 49.6	19.1, 31.0	40.1, 49.8	19.3, 31.2
Progression-free survival rate at 36 months (%) [b]	N/A	N/A	39.8	20.5	39.7	20.8
95% CI for progression-free survival rate at 36 months [b]	N/A	N/A	34.8, 44.8	15.0, 26.6	34.7, 44.7	15.3, 26.9
Progression-free survival rate at 48 months (%) [b]	N/A	N/A	35.3	19.5	35.0	19.9
95% CI for progression-free survival rate at 48 months [b]	N/A	N/A	30.3, 40.4	14.1, 25.7	29.9, 40.1	14.4, 26.1
Progression-free survival rate at 60 months (%) [b]	N/A	N/A	N/A	N/A	33.1	19.0
95% CI for progression-free survival rate at 60 months [b]	N/A	N/A	N/A	N/A	28.0, 38.2	13.6, 25.2
Hazard ratio [c]	0.52		0.55		0.55	
95% CI for hazard ratio [c]	0.42, 0.65		0.44, 0.67		0.45, 0.68	

a Patients who did not progress or dye, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or day 1 if there were no non-missing visits. Patients who had no non-missing visits or did not have baseline data were censored at study day 1 unless they died within 2 visits of baseline.
b Calculated using the Kaplan-Meier technique.
c The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
RECIST version 1.1.

BICR=blinded independent central review, CI= confidence interval, DCO= data cut-off, N/A= not applicable, PFS= progression-free survival, RECIST= response evaluation criteria in solid tumours.
Source: Table 11.2.2.1.OSUP3, Table 11.2.2.1.OSUP2, and Table 11.2.2.1.

Figure 1 Progression-Free Survival (Based on BICR Assessments According to RECIST 1.1), Kaplan-Meier Plot at the 5-Year Update (Full Analysis Set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
MEDI4736	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

BICR= blinded independent central review. PFS= Progression-free survival, CI= confidence interval, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab.
Circles indicate a censored observation.
Source: Figure 11.2.1.5.OSUP3

Subgroup analysis

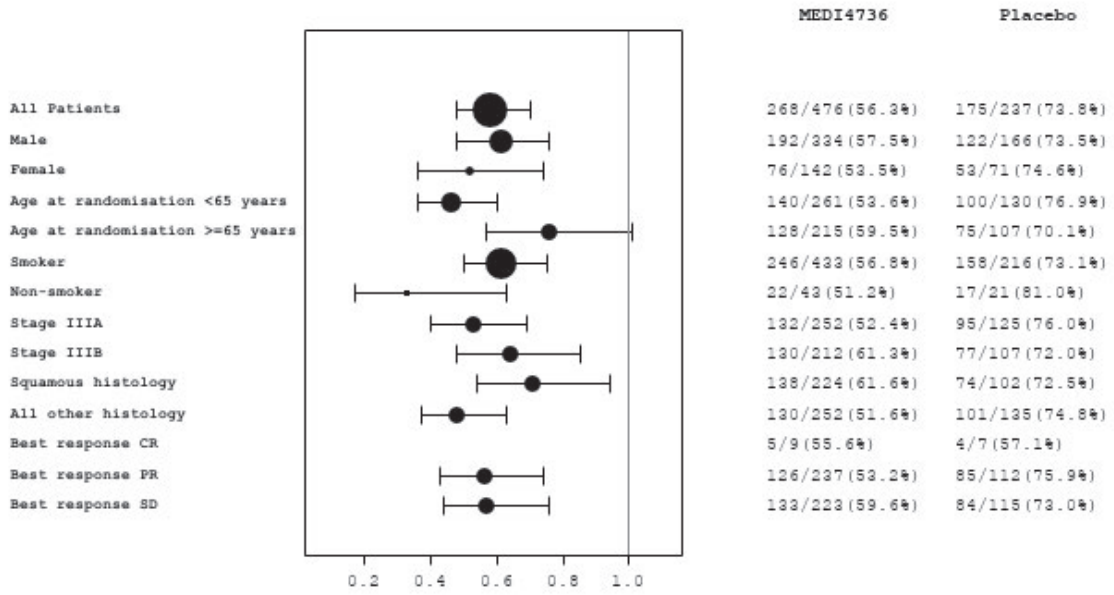
Subgroup analysis for the data at the primary PFS analysis is presented in the PACIFIC Interim CSR (see Figure 7 and Table 11.2.2.10 in the PACIFIC Interim CSR, Module 5.3.5.1).

At the 3-year follow-up update, PFS analysis or subgroup analysis were not performed.

At the 4-year follow-up update, improvement in PFS favouring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, baseline disease characteristics, and time from last dose of radiation to randomization (see Figure 2 in the PACIFIC CSR Addendum 3, Module 5.3.5.1). The results were generally consistent with that of the primary PFS analysis.

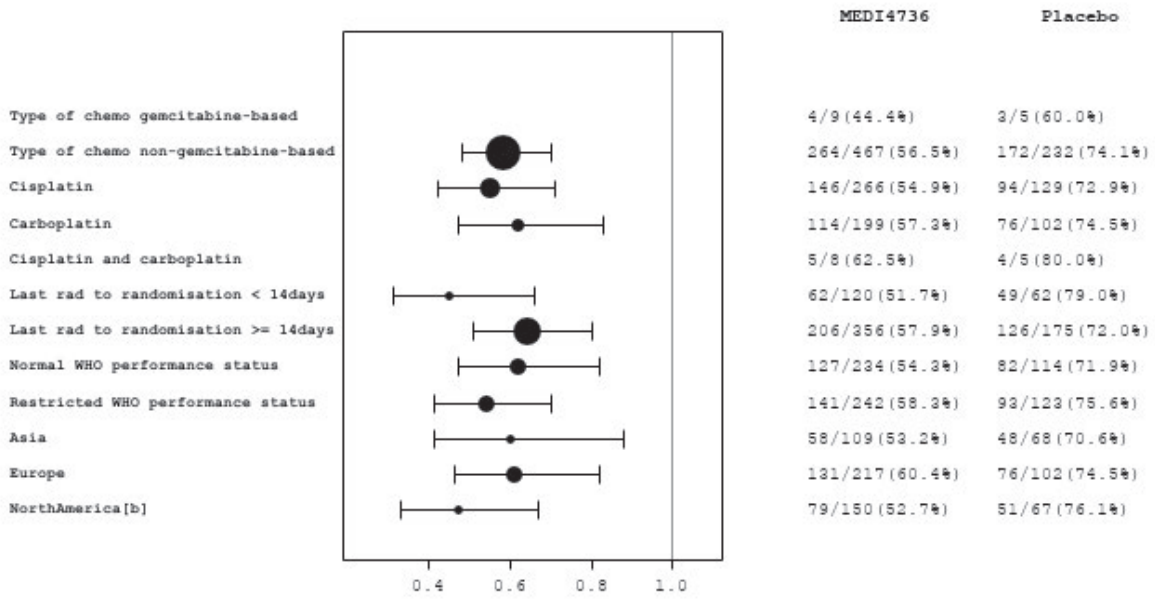
The PFS subgroup analysis at the 5-year follow-up update is presented in detail in Figure 2. The improvement in PFS favouring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, baseline disease characteristics, and time from last dose of radiation to randomization. The results are generally consistent with that of the primary PFS analysis.

Figure 2 Progression-Free Survival (Based on BICR Assessments According to RECIST 1.1), Forest Plot, by Subgroup (Full Analysis Set)



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or die, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.

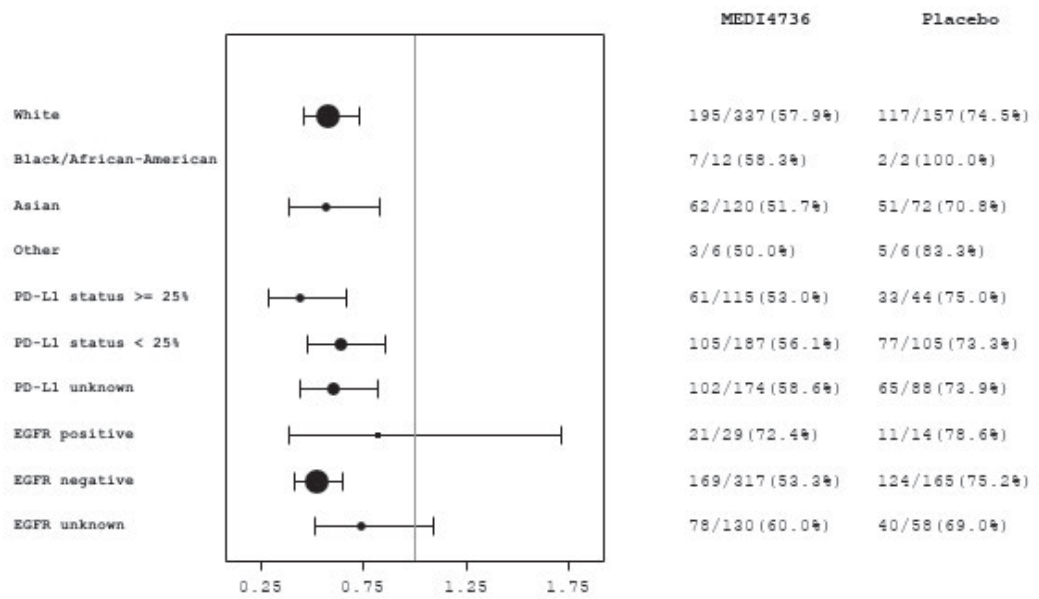
CI=Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab.
BICR= blinded independent central review, WHO= world Health Organization.
Source: Figure 11.2.1.9.OSUP3



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or die, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.

CI=Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab, BICR= blinded independent central review, WHO= world Health Organization.

Source: Figure 11.2.1.9.OSUP3



Hazard ratio (MEDI4736: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Progression includes deaths in the absence of RECIST progression.
Patients who did not progress or die, or who progressed or died after two or more missed visits, were censored at the latest non-missing RECIST assessment, or Day 1 if there were no non-missing visits.
Patients who have no non-missing visits or do not have baseline data will be censored at study Day 1 unless they die within 2 visits of baseline.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.
RECIST version 1.1.

CI=Confidence interval, CR= Complete response, PR= Partial response, SD= Stable disease, Rad= Radiation, RECIST= response evaluation criteria in solid tumours, MEDI4736 = durvalumab.
BICR= blinded independent central review, WHO= world Health Organization.
Source: Figure 11.2.1.9.OSUP3

7.1.1.2 Overall survival

At the time of the primary OS analysis, the study met the pre-defined criteria of the interim OS analysis (ie, statistical significance level of ≤ 0.00274). Durvalumab demonstrated a statistically significant and clinically meaningful benefit in OS over placebo, with a 32% reduction in the risk of death (HR: 0.68; 99.73% CI: 0.469, 0.997; 95% CI: 0.53, 0.87; p-value = 0.00251) (see Table 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). The Kaplan-Meier estimate of the median OS was 28.7 months in the placebo group, while it was not reached in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was observed early and was sustained over the treatment period (see Figure 11.2.1.1.OS, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at both the overall survival at 12 months (OS12) (83.1% vs 74.6%, respectively) and overall survival at 24 months (OS24) (66.3% vs 55.3%, respectively) landmarks. For a detailed description of the primary OS analysis results, see Section 7.1.1.2, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1.

At the time of the first OS follow-up analysis (3 years from LSI), a total of 45 new OS events were reported since the primary OS analysis (a total of 344 deaths [44.1% and 56.5% in the durvalumab and placebo groups, respectively]). For a detailed description of the first OS follow-up analysis results (Table 4 and Figure 3) (see Table 11.2.1.2.OSUP1, and Figure 11.2.1.3.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the second OS follow-up analysis (approximately, 4 years from LSI), a total of 52 new OS events were reported since the first OS follow-up analysis (a total of 396 deaths [51.9% and 62.9% in the durvalumab and placebo groups, respectively]). The survival benefit of durvalumab over placebo was consistent with the OS primary analysis, with a 29% reduction in the risk of death as compared to placebo (HR: 0.71; 95% CI: 0.57, 0.88) (Table 4). For a detailed description of the second OS follow-up analysis results (Table 4, Figure 3) (see Table 11.2.1.2.OSUP2, and Figure 11.2.1.3.OSUP2, PACIFIC Interim CSR Addendum 3, Module 5.3.5.1).

The OS results at the time of the 5-year follow-up update are summarized in Table 4, where the OS results at the primary OS analysis, at the time of the first OS follow-up analysis, and at the time of the second OS follow-up analysis are provided for the context.

At the time of the 5-year follow-up update (approximately, 5 years from LSI), a total of 23 new OS events were reported since the second OS follow-up analysis (a total of 419 deaths [264 and 155 in the durvalumab and placebo groups, respectively]). The survival benefit of durvalumab over placebo was consistent with the OS primary analysis, with a 28% reduction in the risk of death as compared to placebo (HR: 0.72; 95% CI: 0.59, 0.89) (Table 4).

The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group (Figure 3). The separation of OS curves between the durvalumab and placebo groups was sustained (Figure 3). This was supported by the

numerically higher OS rates for the durvalumab group vs the placebo group at the overall survival at 36 months (OS36) landmark (56.7% vs 43.6%, respectively), and the overall survival at 48 months (OS48) landmark (49.7% vs. 36.3%, respectively) (Table 4). At the 5-year analysis, the estimated overall survival rates for the durvalumab group vs the placebo group were 42.9% vs 33.4%, respectively (the 60-month landmark) (Table 4).

At the 5-year update (~5 years from LSI), the median duration of follow-up increased in both durvalumab and placebo groups. The median duration of follow-up in all patients was 34.2 months (range: 0.2 to 74.7); 40.0 months (range: 0.2 to 74.3) in the durvalumab group and 26.4 months (range: 0.3 to 74.7) in the placebo group (Table 11.2.1.2.OSUP3).

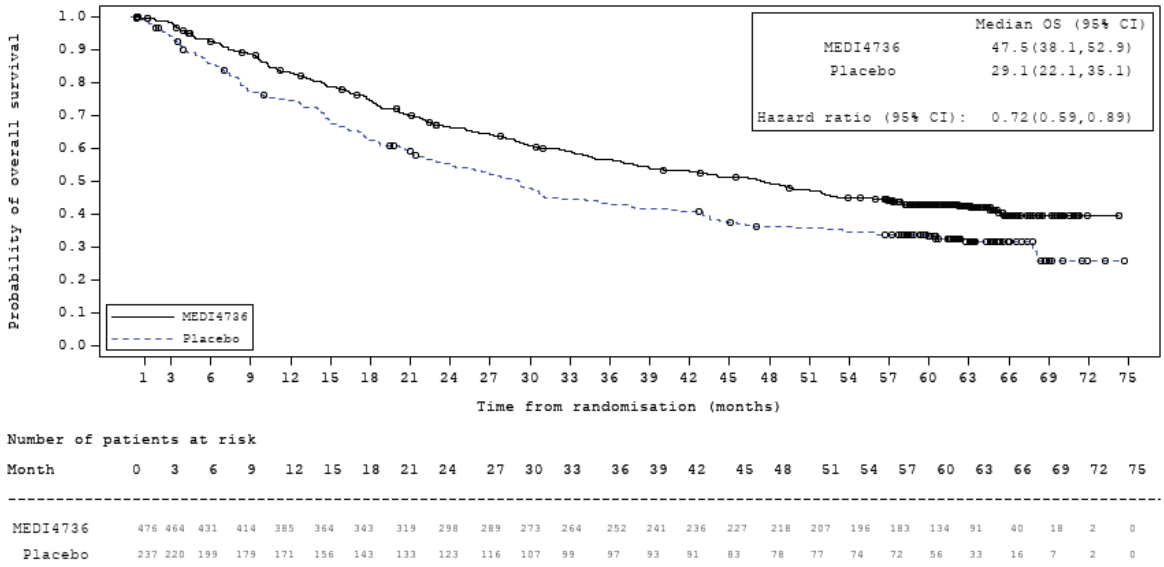
Table 4 Overall Survival at the 5-Year OS Update (Full Analysis Set)

	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)		Third OS follow-up Analysis (~5 years from LSI) (DCO: 11 January 2021)	
Survival status	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**
Death, n (%)	183 (38.4)	116 (48.9)	210 (44.1)	134 (56.5)	247 (51.9)	149 (62.9)	264 (55.5)	155 (65.4)
Median overall survival (months) [a]	NR	28.7	NR	29.1	47.5	29.1	47.5	29.1
95% CI for median overall survival [a]	34.7, NR	22.9, NR	38.4, NR	22.1, 35.1	38.4, 52.6	22.1, 35.1	38.1, 52.9	22.1, 35.1
Survival rate at 12 months (%) [a]	83.1	75.3	83.1	74.6	83.1	74.6	83.1	74.6
95% CI for survival rate at 12 months [a]	79.4, 86.2	69.2, 80.4	79.4, 86.2	68.5, 79.7	79.4, 86.2	68.5, 79.7	79.4, 86.2	68.5, 79.7
Survival rate at 24 months (%) [a]	66.3	55.6	66.3	55.3	66.3	55.3	66.3	55.3
95% CI for survival rate at 24 months [a]	61.7, 70.4	48.9, 61.8	61.8, 70.4	48.6, 61.4	61.8, 70.4	48.6, 61.4	61.8, 70.4	48.6, 61.4
Survival rate at 36 months (%) [a]	N/A	N/A	57.0	43.5	56.7	43.6	56.7	43.6
95% CI for survival rate at 36 months [a]	N/A	N/A	52.3, 61.4	37.0, 49.9	52.1, 61.1	37.1, 49.9	52.0, 61.1	37.1, 49.9
Survival rate at 48 months (%) [a]	N/A	N/A	N/A	N/A	49.6	36.3	49.7	36.3
95% CI for survival rate at 48 months [a]	N/A	N/A	N/A	N/A	44.9, 54.1	30.1, 42.6	45.0, 54.2	30.1, 42.6
Survival rate at 60 months (%) [a]	N/A	N/A	N/A	N/A	N/A	N/A	42.9	33.4

	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)		Third OS follow-up Analysis (~5 years from LSI) (DCO: 11 January 2021)	
Survival status	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**
95% CI for survival rate at 60 months [a]	N/A	N/A	N/A	N/A	N/A	N/A	38.2, 47.4	27.3, 39.6
Hazard ratio, comparing Durvalumab vs. Placebo [b]	0.68		0.69		0.71		0.72	
95% CI for hazard ratio [b]	0.53, 0.87		0.55, 0.86		0.57, 0.88		0.59, 0.89	

a Calculated using the Kaplan-Meier technique.
b The analysis was performed using stratified log-rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
CI = Confidence interval, NR = Not reached, DCO = data cut-off, LSI = last subject in, N/A = not applicable, OS = overall survival.
Source: Table 11.2.1.1.OSUP3, Table 11.2.1.1.OSUP2, Table 11.2.1.1.OSUP1(PACIFIC Interim CSR Addendum-2, Module 5.3.5.1), and Table 11.2.1.1.OS (PACIFIC Interim CSR Addendum-1, Module 5.3.5.1).

Figure 3 **Kaplan-Meier Plot of Overall Survival at the 5-Year OS Update (Full Analysis Set)**



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
MEDI4736	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Circles indicate a censored observation.
CI = confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.1.OSUP3.

Subgroup analysis

Subgroup analysis for the data at the primary OS analysis is presented in the PACIFIC Interim CSR Addendum 1 (see Figure 3 and Table 11.2.1.3.OS in the PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

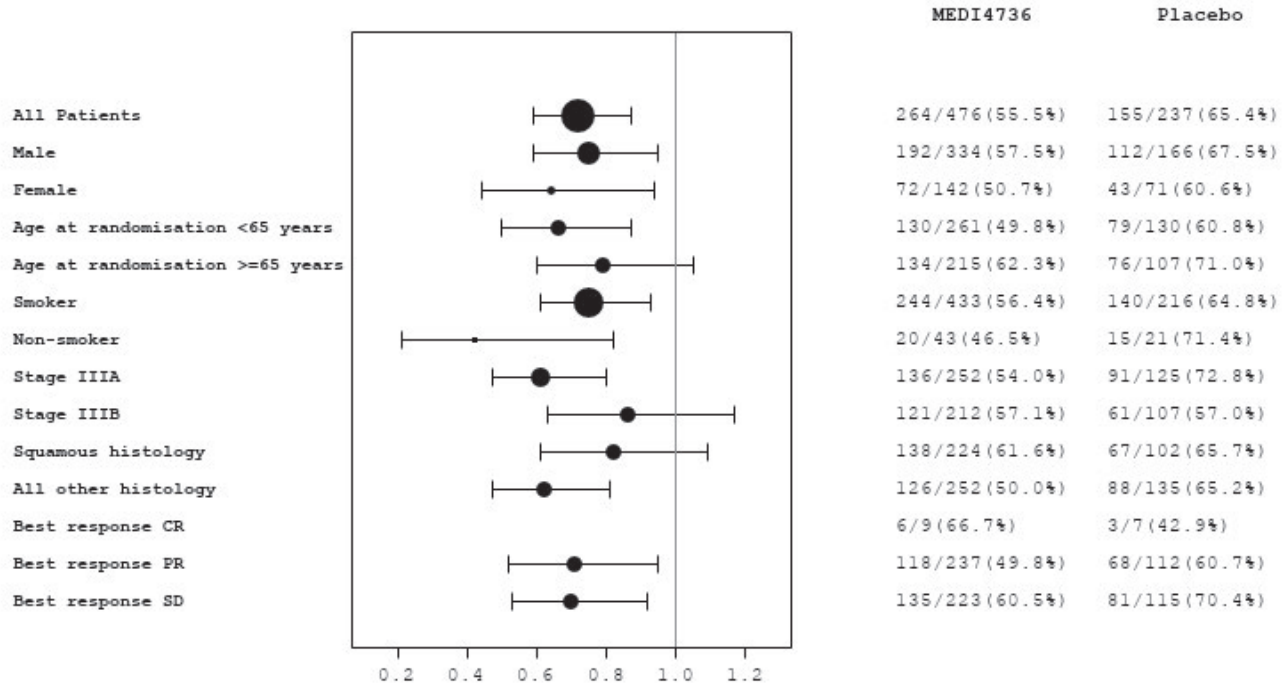
Subgroup analysis for the data at the first OS follow-up analysis is presented in detail in the PACIFIC Interim CSR Addendum 2 (See Figure 2, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1) and was generally consistent with that of the primary OS analysis. (see Figure 2 and Table 11.2.1.3.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

Subgroup analysis for the data at the second OS follow-up analysis is presented in detail in the PACIFIC Interim CSR Addendum 3 (See Figure 4, PACIFIC Interim CSR Addendum 3, Module 5.3.5.1) and was generally consistent with that of the primary OS analysis (see Figure 2 and Table 11.2.1.3.OSUP1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

Subgroup analysis for the data at the 5-year follow-up update is presented in detail in Figure 4 and was generally consistent with that of the primary OS analysis, the first OS follow-up analysis, and the second OS follow-up analysis. Improvements in OS favouring durvalumab over placebo were observed across all prespecified subgroups based on demography, geographical region, prior chemoradiation, and baseline disease characteristics (Figure 4, Table 11.2.1.3.OSUP3).

Further information and discussion on the exploratory *post-hoc* subgroup biomarker analysis by PD-L1 status at the 5-year update is provided in Appendix 12.1.14 in the PACIFIC CSR Addendum 4.

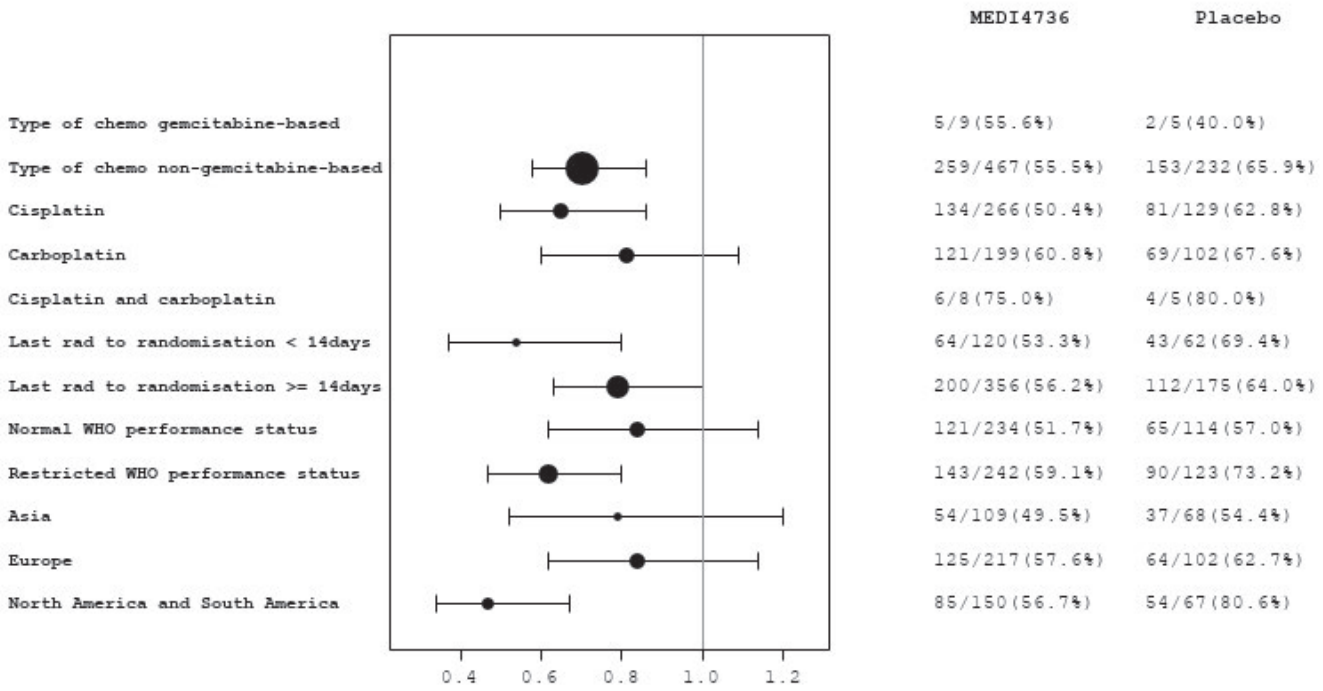
Figure 4 Overall Survival Forest Plot, by Subgroup at the 5-Year OS Update (Full Analysis Set)



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.

CI=Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

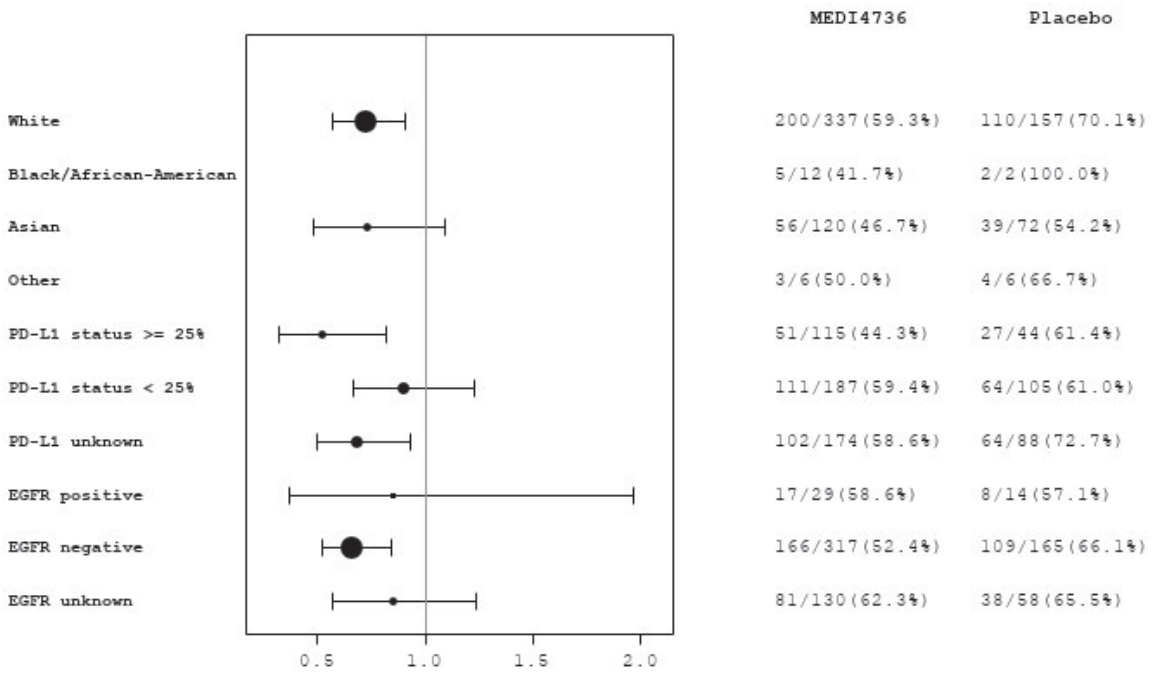
Source: Figure 11.2.1.4.OSUP3.



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.

CI=Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

Source: Figure 11.2.1.4.OSUP3.



Hazard ratio (DURVALUMAB: Placebo) and 95% CI. This is not calculated if the subgroup level has less than 20 events.
The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
Size of circle is proportional to the number of events.

CI=Confidence interval, WHO= World Health Organisation, CR= Complete response, PR= Partial response, SD= Stable disease, Chemo= chemotherapy, EGFR = estimated glomerular filtration rate, MEDI4736 = durvalumab, OS = overall survival, PD-L1= programmed death ligand 1.

Source: Figure 11.2.1.4.OSUP3.

7.1.2 Secondary efficacy variables

7.1.2.1 Time to first subsequent therapy or death (TFST)

The TFST results at the time of the first OS follow-up analysis and at the time of the OS primary analysis are presented in the PACIFIC Interim CSR Addendum 2 (See Table 4 and Figure 3, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the time of the 4-year update, treatment with durvalumab prolonged the TFST, as compared to placebo (HR: 0.62; 95% CI: 0.51, 0.76), consistent with the results at the time of the primary analysis and the 3-year update. The median TFST was 21.2 months in the durvalumab group, as compared to 10.4 months in the placebo group.

At the time of the 5-year follow-up update, treatment with durvalumab prolonged the TFST, as compared to placebo (HR: 0.65; 95% CI: 0.53, 0.79), consistent with the results at the time of the primary analysis, the 3-year update, and the 4-year update. The median TFST was 21.2 months in the durvalumab group, as compared to 10.4 months in the placebo group.

The TFST results at the time of the 5-year follow-up update, 4-year follow-up update, and 3-year follow-up update, as well as at the time of the primary analysis are presented in Table 5 and Figure 5.

Table 5 Time to First Subsequent Therapy or Death, Stratified Log-Rank Test at the 5-Year Update (Full Analysis Set)

	Number (%) of Patients							
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)		Third OS follow-up Analysis (~5 years from LSI) (DCO: 11 January 2021)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	267 (56.1)	169 (71.3)	283 (59.5)	183 (77.2)	310 (65.1)	186 (78.5)	324 (68.1)	188 (79.3)
Subsequent therapy	196 (41.2)	130 (54.9)	207 (43.5)	138 (58.2)	226 (47.5)	139 (58.6)	233 (48.9)	140 (59.1)
Death	71 (14.9)	39 (16.5)	76 (16.0)	45 (19.0)	84 (17.6)	47 (19.8)	91 (19.1)	48 (20.3)
Median time to first subsequent therapy or death (months) [b]	21.0	10.4	21.2	10.4	21.2	10.4	21.2	10.4
95% CI for median time to first subsequent therapy or death [b]	16.6, 25.5	8.3, 12.5	17.1, 25.8	8.4, 12.5	17.1, 25.8	8.4, 12.5	17.1, 25.8	8.4, 12.5
Hazard ratio	0.58		0.58		0.62		0.65	
95% CI for hazard ratio	0.47, 0.72		0.47, 0.71		0.51, 0.76		0.53, 0.79	

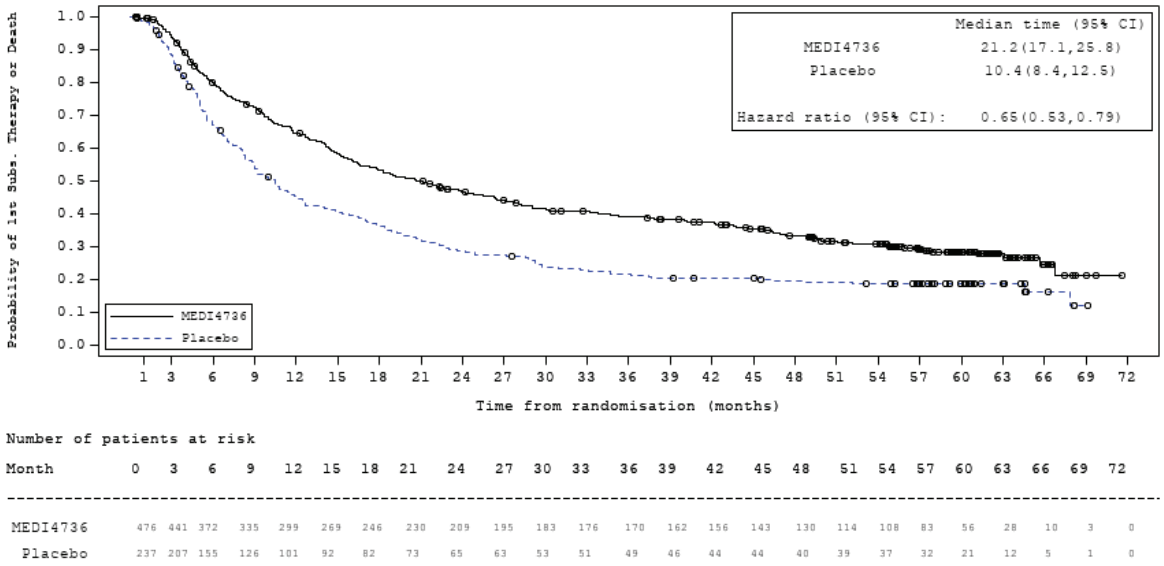
a Patients with first subsequent therapy or death (TFST). TFST is defined as the time from randomization to the start date of the first subsequent therapy after discontinuation of treatment, or death.

b Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

CI=Confidence interval, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.2.5.1.OSUP3, Table 11.2.5.1.OSUP2, Table 11.2.5.1.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.2.5.1.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Figure 5 Kaplan-Meier Plot of Time to First Subsequent Therapy or Death at the 5-year OS Update (Full Analysis Set)



Circles indicate a censored observation.
CI=confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.10.OSUP3.

7.1.2.2 Time to second subsequent therapy or death (TSST)

The TSST results at the time of the first (3-year update), second (4-year update), and third OS (5-year update) follow-up analyses, and at the time of the OS primary analysis are shown in Table 6.

At the time of the 5-year follow-up update, treatment with durvalumab prolonged the TSST, as compared to placebo (HR: 0.65; 95% CI: 0.53, 0.80; Table 6 and Figure 6), consistent with the results at the time of the primary OS analysis, the first OS follow-up analysis, and the 5-year update. The median TSST was 30.3 months in the durvalumab group, as compared to 17.8 months in the placebo group.

Table 6 Time to Second Subsequent Therapy or Death, Stratified Log-Rank Test at the 5-Year OS Update (Full Analysis Set)

	Number (%) of patients							
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)		Third OS follow-up Analysis (~5 years from LSI) (DCO: 11 January 2021)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n(%)	221 (46.4)	139 (58.6)	250 (52.5)	162 (68.4)	275 (57.8)	170 (71.7)	291 (61.1)	172 (72.6)
Subsequent therapy	83 (17.4)	61 (25.7)	109 (22.9)	79 (33.3)	117 (24.6)	82 (34.6)	122 (25.6)	82 (34.6)
Death	138 (29.0)	78 (32.9)	141 (29.6)	83 (35.0)	158 (33.2)	88 (37.1)	169 (35.5)	90 (38.0)
Median time to second subsequent therapy or death (months) [b]	29.3	18.6	30.2	17.8	30.2	17.8	30.3	17.8
95% CI for median time to second subsequent therapy or death [b]	26.0, 34.9	14.8, 23.9	26.0, 38.4	14.1, 22.9	26.0, 38.9	14.1, 22.9	26.0, 38.9	14.1, 22.9
Hazard ratio	0.63		0.61		0.62		0.65	
95% CI for hazard ratio	0.50, 0.79		0.49, 0.75		0.51, 0.77		0.53, 0.80	

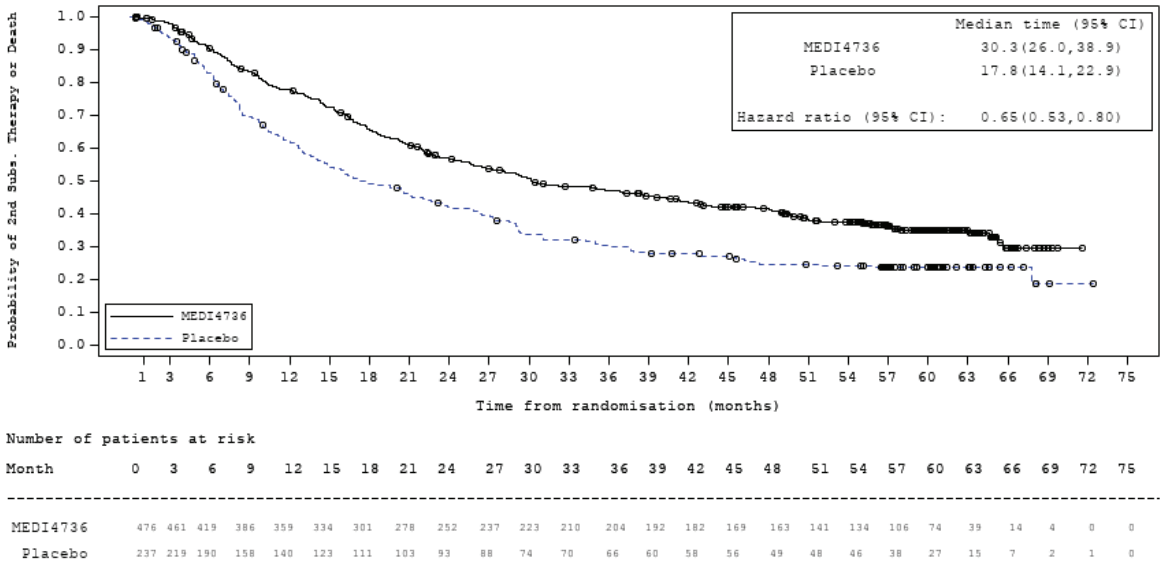
a Patients with second subsequent therapy or death (TSST). TSST is defined as the time from randomization to the start date of the second subsequent therapy after discontinuation of treatment, or death.

b Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomization (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

CI=Confidence interval, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.2.9.1.OSUP3, Table 11.2.9.1.OSUP2, Table 11.2.9.1.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.2.9.1.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

Figure 6 **Kaplan-Meier Plot of Time to Second Subsequent Therapy or Death at the 5-Year OS Update (Full Analysis Set)**



Circles indicate a censored observation.
CI = confidence interval, MEDI4736 = durvalumab, OS = overall survival.
Source: Figure 11.2.1.13.OSUP3.

7.2 Efficacy evaluation conclusions

At the time of the 5-year follow-up update (approximately 5 years from LSI), the PFS analysis results were consistent with that reported at the time of the primary PFS analysis:

- The PFS benefit of durvalumab over placebo (5-year analysis) was consistent with the PFS primary analysis (HR: 0.55; 95% CI: 0.45, 0.68).
- The Kaplan-Meier estimate of median PFS was 16.9 months in the durvalumab group (95% CI: 13.0, 23.9), as compared to 5.6 months in the placebo group (95% CI: 4.8, 7.7).
- The separation in the Kaplan-Meier curves between the treatment groups was observed early and was sustained. At the 5-year analysis, the estimated PFS rates for the durvalumab group vs the placebo group were 33.1% vs 19.0%, respectively (the 60-month landmark).

At the time of the 5-year follow-up update (approximately 5 years from LSI), the survival benefit of durvalumab over placebo was consistent with the OS primary analysis, with a 28% reduction in the risk of death as compared to placebo (HR: 0.72; 95% CI: 0.59, 0.89).

- The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group.
- The separation of OS curves between the durvalumab and placebo groups was sustained. This was supported by the numerically higher OS rates for the durvalumab group vs the placebo group at the OS36 landmark (56.7% vs 43.6%, respectively), OS48 landmark (49.7% vs 36.3%, respectively). At the 5-year analysis, the estimated OS rates at the 60-month landmark for the durvalumab group vs the placebo group were 42.9% vs 33.4%, respectively

8. SAFETY EVALUATION

The safety analyses at the 22 March 2018 DCO were conducted based on the safety analysis set, which included 475 patients in the durvalumab group and 234 patients in the placebo group (See Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

By May 2017, all patients had completed their protocol-defined 12 months of study treatment or had discontinued prior to the defined 12 months of treatment. Therefore, a comprehensive safety presentation was provided in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1.

At the date of the first OS follow-up (approximately 3 years from LSI) analysis, there were no safety updates to be provided (except for deaths), as compared to the primary OS analysis (see Section 8, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). The listings of deaths on treatment are presented in Section 11 (see Table 11.3.3.1.6.OSUP1, and Table 11.3.3.1.8.OSUP1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the date of the second OS follow-up (approximately 4 years from LSI) analysis, there were no safety updates to be provided (except for deaths), as compared to the first OS analysis (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

At the date of the 5-year follow-up update (approximately 5 years from LSI) analysis, there were no safety updates to be provided (except for deaths), as compared to the first OS analysis (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1).

No patients recorded an AE related to COVID-19 and there were no deaths related to COVID-19.

8.1 Deaths, serious adverse events, discontinuation of study treatment due to adverse events, and other significant adverse events

8.1.1 Deaths

At the time of the 5-year follow-up update, a total of 419 deaths were observed, with 264 (55.5%) patients in the durvalumab group and 155 (65.4%) patients in the placebo group. This was an addition of 23 deaths compared to the previous analysis. The majority of deaths were solely related to disease under investigation (208/264 [78.8%] in durvalumab group and 118/155 [76.1%] in the placebo group, respectively). There have been no new fatal adverse events.

All deaths for the full analysis set is presented in Table 7 (see Table 11.3.3.1.8.OSUP3 for deth listings). Details of deaths at the time of the primary OS analysis is presented in the PACIFIC Interim CSR Addendum 1 (Section 8.3.1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1). Details of deaths at the time of the first OS follow-up analysis is presented in the PACIFIC Interim CSR Addendum 2 (Section 8.1.1, PACIFIC Interim CSR Addendum 2, Module 5.3.5.1). Details of deaths at the time of the second OS follow-up analysis is presented in the PACIFIC Interim CSR Addendum 3 (Section 8.1.1, PACIFIC Interim CSR Addendum 3, Module 5.3.5.1).

Table 7 All Deaths at the 5-Year Update (Full Analysis Set)

	Number (%) of patients							
	Primary OS analysis (DCO: 22 March 2018)		First OS follow-up Analysis (~3 years from LSI) (DCO: 31 January 2019)		Second OS follow-up Analysis (~4 years from LSI) (DCO: 20 March 2020)		Third OS follow-up Analysis (~5 years from LSI) (DCO: 11 January 2021)	
Category	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**	**Durvalumab (N=476)**	**Placebo (N=237)**
Total number of deaths	183 (38.4)	116 (48.9)	210 (44.1)	134 (56.5)	247 (51.9)	149 (62.9)	264 (55.5)	155 (65.4)
Death related to disease under investigation only [a]	147 (30.9)	86 (36.3)	169 (35.5)	101 (42.6)	196 (41.2)	114 (48.1)	208 (43.7)	118 (49.8)
Death related to disease under investigation [a] and an AE with outcome of death	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)	10 (2.1)	7 (3.0)
AE onset prior to subsequent therapy [b]	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)	10 (2.1)	6 (2.5)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
AE with outcome of death only	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)	11 (2.3)	10 (4.2)
AE onset prior to subsequent therapy [b]	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)	11 (2.3)	9 (3.8)
AE onset after start of subsequent therapy [c]	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Death not due to either disease progression or an AE with a start date whilst on treatment or within the safety follow-up period	8 (1.7)	6 (2.5)	10 (2.1)	8 (3.4)	16 (3.4)	9 (3.8)	18 (3.8)	10 (4.2)
Unknown reason for death	7 (1.5)	6 (2.5)	10 (2.1)	7 (3.0)	12 (2.5)	8 (3.4)	14 (2.9)	9 (3.8)
Other deaths [d]	0	1 (0.4)	0	1 (0.4)	2 (0.4)	1 (0.4)	3 (0.6)	1 (0.4)

a Deaths related to disease under investigation as determined by the Investigator.

b Includes adverse events with an onset date (or pre-treatment AEs that increase in severity) on or after the date of first dose and up to and including 90 days following the last dose of study medication, or AE start date <= the date of initiation of the first subsequent therapy (whichever occurs first).

c AE start date >90 days following the last dose of study medication and AE start date > the date of initiation of the first subsequent therapy (whichever occurs first).

d Patients who died and are not captured in the earlier categories and patients who died due to AE with onset date in the re-treatment phase and up to and including 90 days following the last dose of study medication in the re-treatment phase.

AE=adverse event, DCO = data cut-off, LSI = last subject in, OS = overall survival.

Source: Table 11.3.3.1.6.OSUP3, Table 11.3.3.1.6.OSUP2, Table 11.3.3.1.6.OSUP1 (PACIFIC Interim CSR Addendum 2, Module 5.3.5.1), and Table 11.3.3.1.6.OS (PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

8.2 Safety evaluation conclusions

At the time of the 5-year follow-up update (DCO: 11 January 2021), there was no change in safety conclusions from those reported at the time of the primary OS analysis.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

A comprehensive discussion of the efficacy, safety, and pharmacokinetic results of the PACIFIC study, and the substantial clinical benefit of durvalumab treatment in patients with Stage III, locally advanced, unresectable, NSCLC is outlined in the PACIFIC Interim CSR and PACIFIC Interim CSR Addendum 1 (see Section 9.1, PACIFIC Interim CSR Addendum 1, Module 5.3.5.1).

At the time of the 5-year follow-up update, the PFS benefit of durvalumab over placebo was consistent with the PFS primary analysis and sustained with the longer duration of follow-up (60-month PFS rate for durvalumab of 33.1% vs 19.0% for placebo). The durvalumab survival benefit over placebo was consistent with that reported at the time of the primary OS analysis as well as the first OS follow-up analysis. Similarly, TFST and TSST results were consistent with the previous analyses performed on an annual basis.

At the time of the 5-year follow-up update, the Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was 47.5 months in the durvalumab group. The separation of OS curves between the durvalumab and placebo groups was sustained, which was supported by the higher OS rates for the durvalumab group vs the placebo group at the OS12 landmark (83.1% vs 74.6%, respectively), OS24 landmark (66.3% vs 55.3%, respectively), OS36 landmark (56.7% vs 43.6%, respectively), and OS48 landmark (49.6% vs 36.3%, respectively). At the 5-year analysis, the estimated overall survival rates for the durvalumab group vs the placebo group were 42.9% vs 33.4%, respectively (the 60-month landmark).

9.2 Overall conclusion

In the pre-planned interim analyses of the 2 primary endpoints of PFS (DCO: 13 February 2017) and OS (DCO: 22 March 2018), durvalumab treatment demonstrated a clinically meaningful benefit compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after concurrent platinum-based chemoradiation.

The results of the second OS follow-up (approximately 4 years from LSI) analysis (DCO: 20 March 2020) were consistent with those reported at the time of the OS primary analysis

and first OS follow-up analysis.

The results of the 5-year follow-up (approximately 5 years from LSI) analysis (DCO: 11 January 2021) were consistent with those reported at the time of the OS primary analysis and first OS follow-up analysis.

Overall, durvalumab treatment demonstrated a well-tolerated and manageable safety profile that was generally consistent with the established safety profile to date.

Taken together, the 5-year survival follow-up analyses demonstrated that the overall benefit: risk of durvalumab treatment remains highly favourable and consistent with that previously reported in this patient population.

10. REFERENCE LIST

Not Applicable

11. SUMMARY TABLES AND FIGURES AND LISTINGS

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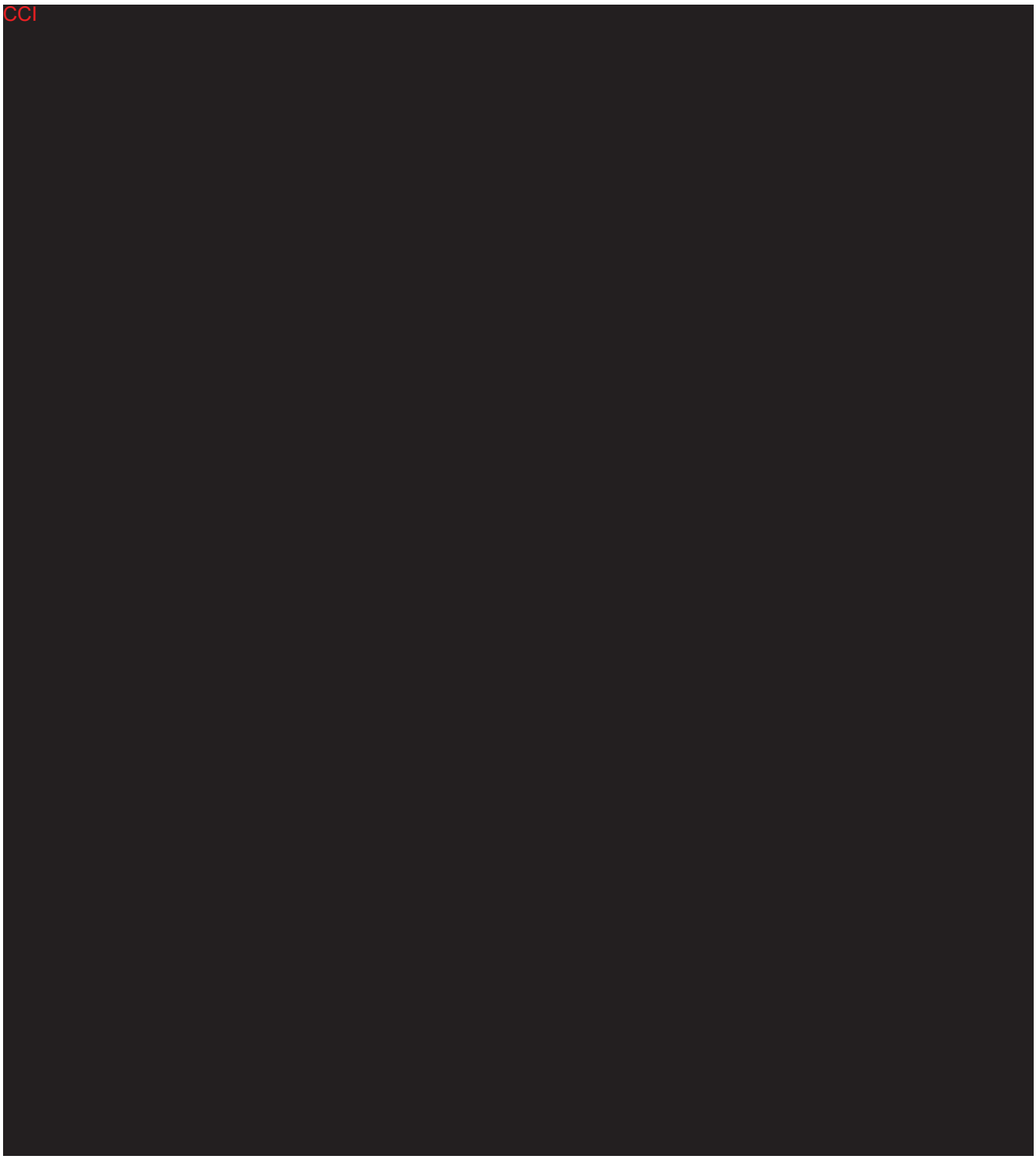


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