A Phase II, Open-Label, Multi-Centre, International Safety Study of Durvalumab Following Sequential Chemotherapy and Radiation Therapy in Patients with Stage III, Unresectable Non-Small Cell Lung Cancer (PACIFIC 6)

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Final Clinical Study Report Synopsis

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Drug Substance	Durvalumab (MEDI4736)
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A Phase II, Open-Label, Multi-Centre, International Safety Study of Durvalumab Following Sequential Chemotherapy and Radiation Therapy in Patients with Stage III, Unresectable Non-Small Cell Lung Cancer (PACIFIC 6)

Study Dates:	First patient enrolled: 16 April 2019 Last patient enrolled: 05 January 2021 (study completed on 21 April 2023 [last patient last visit]) The analyses presented in this report are based on a clinical data lock date of 16 June 2023.
Phase of Development:	Therapeutic exploratory (II)
International Co-ordinating Investigator:	PPD
Sponsor's Responsible Medical Officer:	PPD

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

Study centres

The study was conducted at 25 sites in the United States of America (USA), France, Germany, Italy, Spain, and the United Kingdom. Of note, site initiation was done at 29 sites; however, 4 sites were not active and did not recruit any patients.

Publications

The final study results have not been published at the time of writing this report. They were presented at the European Society for Medical Oncology Congress on 20-24 October 2023 (Garassino M, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab [durva] after sequential chemoradiotherapy [CRT] in patients [pts] with unresectable Stage III NSCLC: Final analysis from PACIFIC-6. Annals of Oncology. 2023;34[2]:S1301-02).

The preliminary study results (as of the data cut-off [DCO] of 15 July 2021) are publicly available (Garassino MC, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab after sequential chemotherapy in Stage III, unresectable NSCLC: The Phase 2 PACIFIC-6 trial. J Thorac Oncol. 2022;17[12]:1415-27).

Objectives and criteria for evaluation

The primary and secondary objectives and endpoints are presented in Table S1 below. Exploratory objectives and endpoints are described in the clinical study report (CSR).

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To assess the safety and tolerability profile of durvalumab (MEDI4736) as defined by Grade 3 and Grade 4 TRAEs [a] within 6 months from the initiation of durvalumab (MEDI4736) treatment	• Grade 3 or Grade 4 TRAEs [a]
Secondary	
Efficacy	
• To assess the efficacy of durvalumab (MEDI4736) treatment in terms of PFS and OS	• Median PFS according to RECIST 1.1 as assessed by the Investigator • PFS12 and PFS24 according to RECIST 1.1 as assessed by the Investigator [b] • Median OS, OS12, OS24, and OS36
• To further assess the efficacy of durvalumab (MEDI4736) treatment in terms of ORR and DoR	• ORR according to RECIST 1.1 as assessed by the Investigator • DoR according to RECIST 1.1 as assessed by the Investigator
• To assess the efficacy of durvalumab (MEDI4736) treatment in terms of lung cancer mortality	• Lung cancer mortality

Objectives	Endpoints/Variables
Safety	
• To further assess the safety and tolerability profile of durvalumab (MEDI4736) treatment, including all AEs	• AEs, SAEs, AESIs, imAEs, physical examinations, vital signs including BP, pulse, temperature, respiratory rate, ECGs, and laboratory findings including clinical chemistry, haematology, and urinalysis

[a] TRAEs and PRAEs are used interchangeably and PRAEs are reported in the SAP, Tables, Figures, and Listings, and primary as well as final CSRs.

[b] This endpoint is intended to measure "PFS12 and PFS24 according to RECIST 1.1." This was erroneously described in the CSP, version 4.0 (Appendix 16.1.1) as "Median PFS12 and PFS24 according to RECIST 1.1" and has been correctly represented in this CSR as "PFS12 and PFS24 according to RECIST 1.1."

Toxicities were classified as per CTCAE grading system NCI CTCAE version 4.03.

Analysis of ORR and DoR were based upon the Investigator's assessment according to RECIST 1.1.

Prior irradiated lesions were considered measurable and selected as target lesions, provided they fulfilled the other criteria for measurability.

An AESI is an AE of scientific and medical interest specific to the understanding of the IP. AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring, and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy.

An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action, and that has no clear alternate aetiology.

Abbreviations: AE = Adverse event; AESI = Adverse event of special interest; BP = Blood pressure; CSP = Clinical study protocol; CSR = Clinical study report; CTCAE = Common Terminology Criteria for Adverse Event; DoR = Duration of response; ECG = Electrocardiogram; imAE = Immune-mediated adverse event; IP = Investigational product; NCI = National Cancer Institute; ORR = Objective response rate; OS = Overall survival; OS12, OS24, OS36 = Proportion of patients alive at 12 months, 24 months, 36 months, respectively, from first date of treatment; PFS = Progression-free survival; PFS12, PFS24 = Proportion of patients progression-free at 12 months and 24 months, respectively, from first date of treatment; PRAE = Possibly related adverse event; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1, SAE = Serious adverse event; SAP = Statistical analysis plan; TRAE = Treatment-related adverse event.

Study design

This was a Phase II, open-label, multi-centre study to determine the safety of a fixed dose of durvalumab (1500 mg) monotherapy in patients with unresectable Stage III non-small cell lung cancer (NSCLC) who had not progressed following definitive, platinum-based sequential chemoradiotherapy (sCRT).

This study consisted of a 4-week screening period, a 24-month treatment period, a 90-day post-treatment safety follow-up period, and an overall survival follow-up period.

Up to 150 patients were planned to be treated with durvalumab (1500 mg) in Europe and North America in 2 distinct cohorts: approximately 100-120 patients in the World Health

Organization/Eastern Cooperative Oncology Group Performance Status (WHO/ECOG PS) 0 to 1 Cohort and up to 30 patients in the WHO/ECOG PS 2 Cohort.

Durvalumab (1500 mg; also referred to as MEDI4736, and as the study drug or investigational product [IP] in this report) was administered via intravenous (IV) infusion once every 4 weeks (q4w), starting on Week 1 of the study, after confirmation of patient eligibility. Treatment initiation within the first 14 days after sCRT therapy was encouraged. For patients who were recovering from toxicities associated with prior treatment, administration of the first IP dose could have been delayed by up to 42 days from the end of the sCRT. Treatment with durvalumab continued for a maximum of 24 months from Cycle 1 Day 1, or until one of the following occurred: confirmed progressive disease (PD) (unless the patient continued to receive benefit from the IP, per the Investigator's judgement), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

This CSR presents the analyses of data captured up to the final analysis DCO for this study (20 March 2023) and the database lock date was 16 June 2023. Of note, primary analysis of data from this study was performed after the last patient dosed had 6 months of follow-up (DCO: 15 July 2021). These data were presented in a separate primary CSR dated 30 March 2022, which is referenced in this CSR for comparison purposes between data obtained at primary versus final analysis DCOs.

Target subject population and sample size

Patients included in this study had a life expectancy of at least 12 weeks at enrolment and were aged ≥ 18 years at the time of screening. Eligible patients also had:

- Histologically- or cytologically-documented NSCLC with locally-advanced, unresectable Stage III disease
- A WHO/ECOG PS ≤ 2
- Not progressed following platinum-based sCRT as per Investigator assessed Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) criteria
- No prior exposure to anti-programmed cell death-1 (anti-PD-1) or anti-PD ligand 1 (anti-PD-L1) agents
- Completed sCRT within 42 days prior to first IP dose administration, with adequate organ and marrow function at enrolment
- A body weight of > 30 kg at enrolment and before the first dose of IP administration

Patients were not eligible to participate in the study if they had or were:

- An allergy or hypersensitivity to durvalumab or any of the IP excipients
- A disease progression following platinum-based sCRT

- Received concurrent chemoradiation therapy (cCRT) for locally-advanced NSCLC
- Eligible for surgical treatment
- Mixed small cell lung cancer and NSCLC histology or another malignancy
- A history of allogenic organ transplantation or active primary immunodeficiency
- Active or prior documented autoimmune or inflammatory disorders
- Uncontrolled intercurrent illness, or active infection

The primary objective of this study was to assess the safety and tolerability of durvalumab as defined by Grade 3 or Grade 4 possibly related adverse events (PRAEs) within 6 months from the initiation of durvalumab treatment.

Since this was a safety study, no formal sample size calculation was done. Between 100-120 patients were planned to be enrolled in the WHO/ECOG PS 0 to 1 Cohort and up to 30 patients in the WHO/ECOG PS 2 Cohort, depending on recruitment.

Study enrolment was already completed as of primary analysis DCO: 117 patients (114 patients in the WHO/ECOG PS 0 to 1 Cohort and 3 patients in the WHO/ECOG PS 2 Cohort) received at least one dose of durvalumab.

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

Based on an average body weight of 75 kg, a fixed dose of 1500 mg of durvalumab q4w (equivalent to a weight-based dose of 20 mg/kg) was administered in this study. Patients received 1500 mg durvalumab monotherapy via IV infusion q4w and continued to receive this dose for up to a maximum of 24 months (26 doses) from Cycle 1 Day 1 with the last administration planned on Week 104.

Individual batch numbers and further information are included in the CSR.

In the event of a patient's weight decreasing to ≤ 30 kg, the weight-based dosing equivalent to 20 mg/kg of durvalumab q4w was administered after consultation between the Investigator and Study Physician, until the weight improved to > 30 kg, at which point the patient was administered the planned fixed dosing of durvalumab 1500 mg q4w.

Duration of treatment

Durvalumab treatment continued for a maximum of 24 months from Cycle 1 Day 1 or until one of the following occurred: confirmed PD as per RECIST 1.1 (unless the patient continued to receive benefit from the IP, per the Investigator's judgement), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Statistical methods

No formal statistical hypothesis testing was planned for this single arm study.

All data, demography, baseline characteristics, safety, efficacy, and biomarkers, were summarised using descriptive statistics, as appropriate for the type of data. In addition, all efficacy and safety data and some selected relevant data (eg, patient disposition, demography, and baseline characteristics) were summarised separately for the WHO/ECOG PS 0 to 1 and PS 2 Cohorts.

Continuous variables were summarised by the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min), and maximum (max). Categorical variables were summarised by frequency counts and percentages for each category. For percentiles of survival times (eg, median survival) and point-estimates of survival (eg, progression-free survival [PFS]) based on the Kaplan-Meier method, confidence intervals (CIs) were calculated using the default method available in the Statistical Analysis Software (SAS) LIFETEST procedure. SAS® version 9.3 or higher was used for all analyses.

For all summaries of adverse events (AEs), only treatment-emergent AEs (TEAEs) were included. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 26.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE), version 4.03 and were reported using system organ class (SOC) and preferred term (PT) and NCI CTCAE grade, as appropriate. All concomitant and previous medications were coded using the WHO drug dictionary and were reported using anatomical therapeutic chemical classification and generic term.

Baseline was defined as the last assessment of the variable under consideration prior to the first dose of durvalumab regardless of whether the assessment was on Day 1, at screening or unscheduled.

Protocol deviations reported during the coronavirus disease 2019 (COVID-19) pandemic were assessed if they were COVID-19 related. The study disruptions due to the pandemic were also summarised.

Study population

A total of 25 sites in 6 countries participated in this study and 117 patients received at least one dose of durvalumab: 114 patients in the WHO/ECOG PS 0 to 1 Cohort and 3 patients in the WHO/ECOG PS 2 Cohort.

At the time of the final DCO, all 117 patients had discontinued the study drug. The main reasons were a worsening of condition under investigation for 44 (37.6%) patients, AEs for 31 (26.5%) patients, and completion of the maximum study treatment duration for 28 (23.9%) patients. All 117 patients terminated the study. Of these, 57 (48.7%) patients

completed the study, 52 (44.4%) patients died, 6 (5.1%) patients withdrew their consent, and 2 (1.7%) patients were lost to follow-up.

Overall, in this study, the patient's demographic and disease characteristics were consistent with the inclusion and exclusion criteria and were representative of the target population.

Summary of safety results

The PACIFIC-6 study assessed the safety and tolerability of durvalumab treatment, including the AE profile, laboratory findings, vital signs, electrocardiograms, and physical examinations.

In this study, the median total treatment duration was 41.0 weeks, with 65 (55.6%) patients treated for ≤ 12 months and 52 (44.4%) for > 12 months. Overall, 42 (35.9%) patients received ≥ 18 cycles and 29 (24.8%) patients received ≥ 24 cycles. Fifty-eight (49.6%) patients received the planned starting dose of study drug without any delay.

Within 6 months since the initiation of durvalumab treatment, 5 (4.3%) patients experienced AEs of CTCAE Grade 3 or 4 that were assessed as possibly related to the study drug (95% CI: 1.40%, 9.69%) (primary study objective). At the final DCO, 7 (6.0%) patients were reported with PRAEs of CTCAE Grade 3 or 4 (95% CI: 2.44%, 11.94%).

The AEs of CTCAE Grade 3 or 4 AEs that were assessed as possibly related to the study drug by the Investigator were pneumonitis, pneumonia, leukopenia, adrenal insufficiency, hypothyroidism, and hyperkalaemia. Among these Grade 3 or 4 PRAEs, pneumonitis, leukopenia, adrenal insufficiency, and hypothyroidism were reported with an onset date within 6 months of the first dose date. None of the patients in the WHO/ECOG PS 2 Cohort had Grade 3 or 4 AEs that were assessed as possibly related to the study drug. The AEs experienced by most patients were of CTCAE Grade 1 or 2.

Although a direct comparison between this study and the PACIFIC study cannot be made because of differences in study design and other features, in general, the AE profile observed in these 2 studies were similar and consistent with the safety profile of durvalumab monotherapy. At PT level, the main differences in AEs incidence (ie, differences > 10%) between the PACIFIC-6 and PACIFIC studies were observed for asthenia, reported with a higher frequency in the PACIFIC-6 study (26.5% versus 10.7% of patients), and for upper respiratory tract infection and radiation pneumonitis, reported with a lower frequency in the PACIFIC-6 study (0.9% versus 12.4% of patients, and 5.3% versus 20.2% of patients, respectively) (Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. N Engl J Med. 2018;379:2342-50).

At the final DCO, 51 patients had died. The majority of deaths were related to the disease under investigation (41 of 51 patients). For one of these 41 patients, the primary cause of

death was PPD and the secondary cause of death was PPD Among the remaining 10 patients, one death had PPD and the other 9 were PPD : one patient died due to PPD PPD (primary cause of death) and PPD (secondary cause of death), one patient died due to PPD , and 7 patients died due to the following events: PPD The following 6 out of these 9 fatal events were not reported as serious adverse events (SAEs) as occurred during the survival follow-up period: PPD PPD

A total of 32 (27.4%) patients were reported with SAEs and 7 (6.0%) of them experienced SAEs that were assessed as possibly related to the study drug by the Investigator. These possibly related SAEs were pneumonitis (in 5 [4.3%] patients), and PPD PPD

The study drug was discontinued due to AEs in 32 (27.4%) patients. Of note, in disposition/study population data, one of these patients was classified as having discontinued study drug following clinical decision and not due to AEs. The most common AEs leading to study drug discontinuation (ie, reported in more than one patient) were pneumonitis, interstitial lung disease, radiation pneumonitis and lung disorder.

Overall, adverse events of special interest (AESIs)/adverse events of potential interest (AEPIs) were reported in 89 (76.1%) patients. The most common AESIs/AEPIs (ie, reported in ≥ 5% of patients) were diarrhoea, arthralgia, pneumonitis, pruritus, hypothyroidism, rash, hyperthyroidism, blood creatinine increased, and alanine aminotransferase increased. The AESI PTs observed in this study were similar to those seen in the PACIFIC study.

Immune-mediated AEs (imAEs) were reported in 50 (42.7%) patients, with adjudicated imAEs reported in 66 (56.4%) patients. Most of the imAEs were of CTCAE Grade 1 or 2. The most common imAEs (ie, reported in ≥ 5% of patients) were pneumonitis and hypothyroidism.

In conclusion, the safety data observed in this study at the final DCO were consistent with those seen during the primary analysis and with the overall safety profile known for durvalumab. The reported PRAEs, AEs, SAEs, AESIs, and imAEs were manageable with appropriate medical management (which included the use of corticosteroids, high-dose steroids, and endocrine therapy), interruption of study drug until the patient's recovery, or permanent discontinuation of study drug. There were no new safety concerns identified in this study.

Summary of efficacy results

In this PACIFIC-6 final analysis, the median PFS (95% CI) was 13.1 months (7.36, 19.91). The PFS estimates (95% CI) were 50.6% (40.97, 59.45) at 12 months and 35.3% (26.46, 44.32) at 24 months. Median (range) duration of follow-up in all censored patients was 30.2 months (0.03, 43.27).

The median PFS and the PFS estimate at 12 months were slightly higher in this final analysis compared to the primary analysis, which showed a median PFS of 10.9 months and a PFS estimate of 49.6% at 12 months (PFS estimate at 24 months could not be determined in the primary analysis). However, both median PFS and PFS estimate at 12 months were lower in this study compared to those observed in the PACIFIC study, where a median PFS of 16.8 months and a PFS estimate of 55.9% at 12 months were seen (Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. N Engl J Med. 2017;377:1919-29). This was expected for this patient population as sCRT is generally reserved for patients who cannot tolerate treatment with cCRT.

In this PACIFIC-6 final analysis, the median overall survival (OS) (95% CI) was 39.0 months (30.59, not calculable [NC]). The survival estimates (95% CI) were 83.5% (75.36, 89.15) at 12 months, 67.2% (57.73, 75.08) at 24 months, and 56.5% (46.41, 65.46) at 36 months. Median (range) duration of follow-up in all censored patients was 32.6 months (4.40, 45.73).

The median OS was higher here compared to the PACIFIC-6 primary analysis (25 months) whereas the survival estimates at 12 months were comparable between the 2 analyses (83.5% versus 84.1%).

The PACIFIC-6 final analysis showed similar 12-, 24- and 36-month OS to those observed in the PACIFIC study, where the 12-, 24- and 36-month OS rates were 83.1%, 66.3% and 56.7%, respectively (Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. J Clin Oncol. 2022;40[12]:1301-11). However, a conclusive comparison between the 2 studies cannot be made because of the differences in the study design, study populations, and analytical methodologies.

At the time of DCO, the cause of death was assessed as related to disease under investigation (NSCLC) in 41 (35.0%) patients. NSCLC-related survival rates (95% CI) were 87.6% (79.90, 92.45) at 12 months, 75.0% (65.67, 82.16) at 24 months, and 63.1% (52.46, 71.93) at 36 months.

In the WHO/ECOG PS 0 or 1 Cohort, confirmed and unconfirmed objective responses (95% CI) were observed in 24 (21.1%) and 5 (4.4%) patients (14.0, 29.7), respectively. PPD PPD Among the 24 patients with a confirmed objective response, 21 (18.4%) had a partial response and 3 (2.6%) had a complete response. Median duration of response

from onset of confirmed response was NC and the median (range) time to onset of response from the first dose of study drug was 3.8 months PPD

These results were similar to those observed in the primary analysis, where confirmed and unconfirmed responses were seen in 20 (17.5%) and 6 (5.3%) patients respectively, from the WHO/ECOG PS 0 or 1 Cohort. Similarly, a median time to onset of confirmed response of 3.6 months from the first dose of study drug was observed in the primary analysis.

Conclusions

The PACIFIC-6 study was designed to complement and expand the safety database from the Phase III PACIFIC study. The following conclusions could be drawn from the study:

- Adverse events of CTCAE Grade 3 or 4 that were assessed possibly related to durvalumab were reported in a small percentage of patients (6.0% over the course of the study and 4.3% within the first 6 months of treatment with study drug). Most AEs, irrespective of their causality to the study drug, were of Grade 1 or 2 as CTCAE grade, which was consistent with the known safety profile of durvalumab. The majority of deaths during the study were related to the disease under investigation.
- The safety profile of durvalumab monotherapy using a fixed-dosing regimen (1500 mg), in patients with unresectable Stage III NSCLC who had not progressed after sCRT, was manageable and generally consistent with the known safety profile of durvalumab and PACIFIC study. There were no new safety and tolerability findings identified in this study.
- The durvalumab monotherapy following sCRT investigated in this study showed positive efficacy results. Encouraging efficacy was seen here in a frailer population than that enrolled in the PACIFIC study, with a median OS of 39.0 months and 56.5% of patients estimated to remain alive at 36 months and with a median PFS of 13.1 months and 35.3% of patients estimated to remain alive and progression-free at 24 months.
- These findings demonstrated that durvalumab after sCRT is well tolerated and could be a reasonable therapeutic strategy for patients when cCRT is not possible. Confirmatory results from Phase III development are awaited from the ongoing PACIFIC-5 study (NCT03706690) that is assessing the efficacy and safety of durvalumab after either cCRT or sCRT.