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)

ClinicalTrials.gov Identifier: NCT03693300

CSR Synopsis

2. SYNOPSIS

Study centre(s)

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

Publications

Preliminary results of the study (as of 24 Aug 2020) were presented in the European Lung Cancer Congress on 27 Mar 2021 (Garassino MC, Mazieres J, Reck M, Delmonte A, Bischoff HG, Bernabe R, et al. 78MO - Early safety assessment of durvalumab after sCRT in patients with Stage III, unresectable NSCLC (PACIFIC 6) [abstract]. J Thorac Oncol. 2021;16 Suppl 4:S737).

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 for Primary Analysis

Objectives	Endpoints/Variables for Primary Analysis
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 treatment	• Grade 3 and Grade 4 TRAEs[a]
Secondary	
Efficacy objectives	
• To assess the efficacy of durvalumab 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 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 treatment in terms of lung cancer mortality	• Lung cancer mortality

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

a. TRAEs and PRAEs are used interchangeably, and PRAEs will be reported in the SAP, Tables, Figures, and Listings, and CSR.

b. This endpoint is intended to measure "PFS12 and PFS24 according to RECIST 1.1". This was erroneously described in the CSP, V4.0 (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".

Note: Toxicities were classified as per CTCAE grading system NCI CTCAE version 4.03. Analysis of ORR and DoR were based upon Investigator 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.

Note: 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.

Note: 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 etiology.

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; PFS=Progression-free survival; PFS12, PFS24=Proportion of patients progression-free at 12 months and 24 months, respectively, from first date of treatment; RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1; PFS=Progression-free survival; PRAE=Possibly related adverse event; SAE=Serious adverse event; SAP=Statistical analysis plan; TRAE=Treatment-related adverse event.

Study design

This is an ongoing 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 have not progressed following definitive, platinum-based sequential chemoradiotherapy (sCRT).

This study consists of a 4-week screening period, 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 the study drug in Europe and North America. Patients were treated in 2 cohorts: approximately 100-120 patients in the World Health Organisation/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 in this report as the study drug or investigational product [IP]) was administered via intravenous (IV) infusion once every 4 weeks (q4w), starting at 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 be delayed by up to 42 days from the end of the sCRT. Treatment with durvalumab will continue

for a maximum of 24 months from Cycle 1 Day 1, or until one of the following occurs: confirmed progressive disease (PD) (unless the patient continues to receive benefit from the IP, per the Investigator's judgment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

A primary analysis of data from this study was performed for this CSR, after the last patient dosed had the opportunity to receive six months of treatment follow-up (data cut-off [DCO]: 15 July 2021). The final DCO is planned to occur when the last patient has had the opportunity to receive durvalumab for a maximum of 24 months, followed by a 90-day safety follow-up period post the last dose of IP.

Target 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 had histologically- or cytologically-documented NSCLC with locally-advanced, unresectable Stage III disease, had a WHO/ECOG performance status of ≤ 2, had not progressed following platinum-based sCRT as per Investigator-assessed RECIST 1.1 criteria, had no prior exposure to CCI [redacted] agents, and had completed sCRT within 42 days prior to first IP dose administration, with adequate organ and marrow function at enrolment. Patients had 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 an allergy or hypersensitivity to durvalumab or any of the IP excipients, had disease progression following platinum-based sCRT, had received concurrent chemoradiation therapy (cCRT) for locally-advanced NSCLC, were eligible for surgical treatment, had mixed small-cell lung cancer and NSCLC histology or another malignancy, had a history of allogenic organ transplantation or active primary immunodeficiency, had active or prior documented autoimmune or inflammatory disorders, and had 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 and Grade 4 PRAEs within 6 months from the initiation of durvalumab treatment. Safety and tolerability of durvalumab were characterized for the cohorts of WHO/ECOG PS 0 to 1 and PS 2 patients.

Since this was a safety study, no formal sample size calculation was done. Between 100 and 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. As of DCO for the primary analysis, 117 patients (114 patients enrolled 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. Enrolment has been completed for the study.

Investigational product: dosage, mode of administration and batch numbers

Based on 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 will continue to receive this dose for up to a maximum of 24 months (26 doses) from Cycle 1 Day 1 with the last administration planned at Week 104.

Individual batch numbers and further information are included in the CSR (Appendix 16.1.6).

In the event that a patient's weight decreased 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 will continue for a maximum of 24 months from Cycle 1 Day 1 or until one of the following occurs: confirmed PD as per RECIST 1.1 (unless the patient continues to receive benefit from the IP, per the Investigator's judgment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is 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 summarized 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 groups.

Continuous variables were summarized by the number of observations (n), mean, standard deviation, median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category. For percentiles of survival times (eg, median survival) and point-estimates of survival (eg, PFS) based on the Kaplan-Meier method, confidence intervals (CIs) were calculated using the default method available in the SAS LIFETEST procedure. SAS® version 9.3 or higher will be 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 24.0 and graded according to the and 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 was 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 summarized.

Study population

This primary analysis CSR includes data as of the DCO of 15 July 2021 (data freeze, 14 October 2021). A total of 25 sites in 6 countries participated in this study and 117 patients received at least one dose of durvalumab as of DCO. At the time of DCO for the primary analysis, PPD of study treatment, 44 (37.6%) patients are continuing study treatment, and 73 (62.4%) patients had discontinued study treatment. The patients' demographic and disease characteristics were consistent with the study inclusion and exclusion criteria and were representative of the target population.

Summary of safety results

The PACIFIC 6 study assessed the safety and tolerability profile of durvalumab treatment, including all AEs, physical examinations, vital signs, ECGs, and laboratory findings, interventions and treatment, and outcome of treatment.

Sixty-two (53%) patients received the planned IP dose without any dose delay. The median actual treatment duration was 28.4 weeks.

Within 6 months from the initiation of durvalumab treatment, a total of 5 (4.3%) patients experienced Grade 3 or 4 AEs that were assessed as possibly related to the IP (95% CI: 1.40%, 9.69%) (primary objective). Most of the AEs that were possibly related to the IP were of Grade 1 or Grade 2 severity. The Grade 3 or Grade 4 AEs that were assessed as possibly related to the IP by the Investigator were leukopenia, adrenal insufficiency, hypothyroidism and pneumonitis (in 2 patients). 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 IP.

The most commonly observed AEs during the primary analysis for this study were similar to those observed in the PACIFIC study. However, the incidence of upper respiratory tract infection and radiation pneumonitis in this study, at the time of DCO for primary analysis, was

lower than in the PACIFIC study. Conversely, the incidence of asthenia and pneumonitis was higher than in the PACIFIC study. Nonetheless, a direct comparison between the two studies cannot be made as the study design, study populations, and analyses methodologies are different.

As of the DCO for primary analysis, 25 patients had died. The majority of deaths during the study were related to the disease under investigation (17 of the 25 patients). For one of these 17 patients, the primary cause of death was PPD and the secondary cause of death was PPD

Among the remaining 8 patients, one patient died due to PPD . One patient died due to PPD . Six patients died due to the following events which were reported during the survival follow-up, hence were not reported as SAEs: PPD

A total of 33 SAEs were reported in 23 (19.7%) patients at the time of DCO.
Six (5.1%) patients experienced SAEs that were assessed as possibly related to the IP by the Investigator. These SAEs were reported as pneumonitis (in 5 [4.3%] patients) and interstitial lung disease (in one patient).

The IP was discontinued because of AEs in 25 (21.4%) patients. The most frequently reported AEs (reported in ≥ 2.5% of patients) that led to discontinuation of the IP were pneumonitis, interstitial lung disease, and radiation pneumonitis.

Adverse events of special interest (AESIs) were reported in more than half of the study patients. The most common AESIs (reported in > 5% of patients) were pneumonitis, pruritus, arthralgia, diarrhoea, hypothyroidism, rash, hyperthyroidism, blood creatinine increased, and alanine aminotransferase increased. The AESIs observed in this study were similar to those described in the safety information for durvalumab (see the current version of the durvalumab Investigator's Brochure).

Immune mediated AEs (imAEs) were reported in 48 (41%) patients. Most of the imAEs were Grade 1 or Grade 2 in severity. The most frequently reported imAEs (reported in > 2.5% of patients) were pneumonitis, hypothyroidism, hyperthyroidism, arthralgia and interstitial lung disease.

A review of data available at the time of DCO, ie, after the last patient dosed had 6 months of follow-up, showed that a fixed-dosing regimen of durvalumab monotherapy, did not have a clinically significant effect on the likelihood of CCI mediated pneumonitis in patients who had not progressed after sCRT. The potential risk of CCI mediated pneumonitis in

this population will continue to be monitored at the final DCO for this study, and in future studies.

Overall, the safety data at the time of primary analysis suggest that the type of events were consistent with the known safety profile of durvalumab. The reported PRAEs, AEs, SAEs, AESIs, and imAEs were manageable with appropriate medical management (which included the use of corticosteroids, endocrine therapy, or other immunosuppressants), withholding study treatment until the event resolved, or permanent discontinuation of IP. There were no new safety concerns identified at the DCO for primary analysis. The incidence of AEs will be further evaluated at the final DCO and reported.

Summary of efficacy results

Median PFS was 10.9 months (95% CI: 7.33, 15.64). The PFS estimate at 12 months was 49.6% (95% CI: 39.50, 58.89). The PFS estimate at 24 months was not calculable. Median (range) duration of follow-up in all censored patients was 11 months (0.03, 22.28).

Median OS was 25 months (95% CI: 24.97, not calculable). The survival estimate at 12 months was 84.1% (95% CI: 75.62, 89.88). The survival estimate at 24 months was 69.8% (95% CI: 55.78, 80.18). The survival estimate at 36 months was not calculable. Median (range) duration of follow-up in all censored patients was 13.3 (4.40, 25.59) months.

At the time of DCO, the cause of death was assessed as related to disease under investigation (NSCLC) in 17 (14.5%) patients . NSCLC-related survival rate at 12 months and 24 months was 88.7% (95% CI: 80.86, 93.46) and 78.7% (95% CI: 64.03, 87.98), respectively.

Among 114 patients in the WHO/ECOG PS 0 or 1 cohort, confirmed objective response was observed in 20 (17.5%) patients (95% CI: 11.4, 26.4) and unconfirmed response was observed in 6 (5.3%) patients. Of the 3 patients in the WHO/ECOG PS 2 cohort, none showed confirmed or unconfirmed response. Median DoR from onset of confirmed response was not calculable (95% CI: 25.71, not calculable). Median time to onset of confirmed response from the first dose of IP was 3.6 months.

Conclusion(s)

The PACIFIC 6 study was designed to complement and expand the safety database from the Phase III PACIFIC study. Safety and efficacy data from the PACIFIC 6 study at the DCO for primary analyses are described in this CSR. In conclusion:

- Grade 3 or 4 AEs that were considered to be possibly related to durvalumab were reported in < 5% of patients. Most AEs, irrespective of their causality to the IP, were Grade 1 or Grade 2 in severity, 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, 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 from this study at the time of DCO for primary analysis.
- At the time of DCO for primary analysis, the durvalumab monotherapy following sCRT showed encouraging preliminary efficacy results. However, a longer duration of follow-up is required to further characterise the efficacy results.