26 July 2018
EMA/CHMP/548232/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: durvalumab

Procedure No. EMEA/H/C/004771/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1-L	First-line
2-L	Second-line
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event(s) of special interest
ALK	Anaplastic lymphoma kinase
APF12	Proportion of patients alive and progression-free at 12 months from randomisation (also abbreviated as PFS12)
APF18	Proportion of patients alive and progression-free at 18 months from randomisation (also abbreviated as PFS18)
AUC	Area under the concentration-time curve
BICR	Blinded Independent Central Review
CI	Confidence interval
C_{max}	Maximum serum concentration
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung cancer 13 items
FAS	Full analysis set
FDA	Food and Drug Administration (US Department of Health and Human Sciences)
FTIH	First-time-in-human
GCP	Good Clinical Practice
HR	Hazard ratio
Ig	Immunoglobulin
IM	Immunogenicity
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	The Medical Dictionary for Regulatory Activities
NSCLC	Non-small cell lung cancer

ORR	Objective response rate
OS	Overall survival
OS24	Proportion of patients alive at 24 months from randomization
PD	Progression of disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PFS2	Time from randomization to second progression
PI	Prescribing information
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcomes
PS	Performance status
Q2W	Every 2 weeks
RECIST 1.1	Response Evaluation Criteria In Solid Tumors (Version 1.1)
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCLC	Small-cell lung cancer
SD	Stable disease
SOC	System organ class
TFST	Time to start of first subsequent therapy or death
TSST	Time to start of second subsequent therapy or death
TTDM	Time to death or distant metastasis
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 1 September 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Imfinzi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: treatment of adults with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance durvalumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	**date**	**Area**
EMA/CHMP/SAWP/140265/2014	20 March 2014	Quality non-clinical and clinical
EMA/CHMP/SAWP/693252/2014	20 November 2014	Quality and clinical
EMA/CHMP/SAWP/243370/2015	23 April 2015	Clinical
EMA/CHMP/SAWP/596562/2015	24 September 2015	Clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Jorge Camarero Jiménez

The application was received by the EMA on	1 September 2017
The procedure started on	28 September 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 December 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	22 December 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 December 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
A GCP inspection at three sites, one clinical investigator site in Australia, one clinical investigator site in Japan and a CRO site in the United Kingdom between January and February 2018. The outcome of the inspection carried out was issued on 16 April 2018.	N/A
The Rapporteurs circulated the Joint Assessment Report on the	04 May 2018

responses to the List of Questions to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 July 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Imfinzi on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant seeks approval in the following indication: Durvalumab is indicated for the treatment of patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

2.1.2. Epidemiology

Primary lung cancer is the most common form of cancer worldwide (13% of all new cancers) and the fourth most common form of cancer in the European Union (Ferlay et al 2015)[1]. Lung cancer remains the leading cause of cancer-related death globally (19.4% of all cancer deaths), with only 17.7% of patients surviving for 5 years, irrespective of stage (Novello et al 2016, SEER 2016)[2]. Approximately 85% of all lung cancers are NSCLC, of which the major histological types are adenocarcinoma (representing 35% to 40% of all lung cancers), squamous cell carcinoma (25% to 30%), and large cell carcinoma (10% to 15%) (GLOBOCAN 2012)[3]. Stage III NSCLC consists of a heterogeneous population with two subsets: Stage IIIA and IIIB. Approximately one-third of the patients with Stage IIIA disease are considered operable. The majority of

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015, 136:E359-86.
[2] Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016; 27(suppl 5): v1-27.
[3] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality, and Prevalence Worldwide in 2012. Available from URL: http://globocan.iarc.fr/Default.aspx. Accessed 07 July 2017.

patients with Stage IIIA/B have inoperable (unresectable) disease, but are amenable to receiving curative intention chemoradiation treatment.

2.1.3. Biologic features, aetiology and pathogenesis

The biological characteristics of locally advanced Stage III disease are poorly defined, although the clinical characteristics known to be associated with prognosis are nodes or nodes station involved, size of primary tumour, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status.

Historically, NSCLC has been considered a non-immunogenic disease (Brahmer 2013)[4]. However, emerging evidence has demonstrated that the lack of an effective immune response is, in fact, often the result of specific, active immune-evasive mechanisms. These mechanisms, if understood, can be overcome therapeutically with meaningful clinical efficacy (Carbone et al 2016)[5]. The most significant advances in NSCLC immunotherapy have been made in metastatic setting by targeting the PD-1/PD-L1 immune checkpoint (Shu and Rizvi 2016)[6]. The PD-1/PD-L1 checkpoint inhibitors shift the balance of immune activity from a tumour-induced immune suppressive state toward an active antitumor immune response.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Approximately 70% of subjects with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. The 5-year relative survival rates for lung cancer overall and metastatic lung cancer have been reported to be 17.7% and 4.3%, respectively (SEER stat facts. 2016). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects.

2.1.5. Management

The current standard-of-care for patients with locally advanced, unresectable NSCLC is concurrent chemoradiation with a platinum-based doublet and 60 Gy of radiation daily over 6 weeks administered with a curative intent (NCCN® Clinical Practice Guidelines in Oncology 2017;[7] Eberhardt et al (ESMO) 2015;[8] Saijo et al 2010)[9]. While chemoradiation can achieve initial disease control, the majority of patients eventually progress. More than 50% of patients develop distant metastasis (Bezjak et al 2015)[10], and up to 40% can experience local recurrence (Bradley et al (RTOG 0617) 2015)[11]. The standard-of-care for patients with locally advanced, unresectable, NSCLC has remained unchanged for the past 2 decades. Several randomized studies have confirmed that additional induction chemotherapy (prior to chemoradiation) or consolidation

[4] Brahmer JR. Harnessing the immune system for the treatment of non-small-cell lung cancer. J Clin Oncol. 2013; 31 (8): 1021-8.
[5] Carbone DP, Gandara DR, Antonia SJ et al. Non-Small-Cell Lung Cancer: Role of the Immune System and Potential for Immunotherapy. J Thorac Oncol. 2015; 10 (7): 974-84.
6 Shu CA and Rizvi NA. Into the clinic with nivolumab and pembrolizumab. Oncologist. 2016; 21 (5): 527-8.
[7] National Comprehensive Cancer Network®, Clinical Practice Guidelines in Oncology, Version 5.2017; 16 March 2017.
[8] Eberhardt WE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015; 26 (8): 1573-88.
[9] Siajo N, Fukuoka M, Thongprasert S, et al. Lung cancer working group report. Jpn J Clin Oncol. 2010; 40 Suppl 1:i7-12.
[10] Bezjak A, Temin S, Franklin G, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence- Based Clinical Practice Guideline. J Clin Oncol. 2015; 33 (18): 2100-5.
[11] Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015; 16 (2): 187-99.

chemotherapy (after chemoradiation) in this setting does not improve clinical outcomes. The prognosis remains poor, and the 5-year survival rate is approximately 15% (Aupérin et al 2010)[12]. Therefore, new therapies are needed to prevent disease progression after delivery of definitive chemoradiotherapy.

Patients whose disease does not progress after chemoradiation are carefully monitored and followed up without treatment. The uncertainty of knowing whether chemoradiation will provide long term benefit causes great psychological stress and anxiety, which is associated with lung cancer mortality (Vodermaier et al 2017)[13]. While advances have been made in improving survival by optimizing locoregional control, a significant majority of these patients eventually progress. Most patients experience local and/or distant metastasis and thereby present a clinical challenge for improving outcomes. Brain metastasis disease is a major cause of morbidity and mortality in patients with locally advanced NSCLC. Approximately one third of NSCLC patients develop brain metastasis, including nearly two-thirds of patients who have a systemic relapse. Moreover, the brain as the sole site of release occurred in approximately 20% of patients (Govindan et al 2008)[14]. For patients with distant metastatic disease who have relapsed, treatment is similar to management of Stage IV disease; first-line platinum-based chemotherapy is provided if the patient has been disease-free for more than a year, and second-line single agent chemotherapy or immunotherapy is provided if the patient has been disease free for less than a year [15].

Despite continuing improvement in therapy of advanced disease, little progress has been made in locally advanced, unresectable NSCLC. Many randomized Phase III trials investigating the clinical benefit of maintenance therapy post chemoradiation failed to demonstrate OS benefits. Therefore, a significant unmet medical need exists for the development of new treatment strategies that can prolong these patients' favourable clinical state after achieving initial disease control with chemoradiation.

About the product

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.

Durvalumab is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses.

The applicant applied for the following indication:

[12] Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28 (13): 2181-90.
[13] Vodermaier A, Lucas S, Linden W, Olson R. Anxiety After Diagnosis Predicts Lung Cancer-Specific and Overall Survival in Patients With Stage III Non-Small Cell Lung Cancer: A Population-Based Cohort Study. J Pain Symptom Manage. 2017 Jun;53(6):1057-1065
[14] Govindan R, Bogart J, Vokes EE. Locally advanced non-small cell lung cancer: the past, present, and future. J Thorac Oncol. 2008 Aug;3(8):917-28
[15] National Comprehensive Cancer Network®, Clinical Practice Guidelines in Oncology, Version 5.2017; 16 March 2017.

Imfinzi as monotherapy is indicated for the treatment of adults with locally advanced, unresectable non small cell lung cancer (NSCLC) whose disease has not progressed following platinum based chemoradiation therapy.

The recommended indication is:

Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on $\geqslant$ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy.

The recommended dose of Imfinzi is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months.

It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability.

Guidelines for management of immune-mediated adverse reactions are described in the table below.

Table 1: Recommended treatment modifications for Imfinzi and management recommendations

Adverse reactions	**Severity**[a]	**Imfinzi treatment modification**	**Corticosteroid treatment unless otherwise specified**
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1 to 4 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT > 5-≤ 8 x ULN or total bilirubin > 3-≤ 5x ULN		
	Grade 3 with AST or ALT > 8 x ULN or total bilirubin > 5 x ULN	Permanently discontinue	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause		

Adverse reactions	**Severity**[a]	**Imfinzi treatment modification**	**Corticosteroid treatment unless otherwise specified**
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment, see section 4.8
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	
Immune-mediated rash or dermatitis	Grade 2 for > 1 week	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2	Withold dose[b]	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	

Adverse reactions	**Severity**[a]	**Imfinzi treatment modification**	**Corticosteroid treatment unless otherwise specified**
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose	Initiate 1 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue[c]	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	
Infection	Grade 3 or 4	Withold dose until clinically stable	
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue	

[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[b] If no improvement within 3 to 5 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which Imfinzi can be resumed based on clinical judgment.

[c] Permanently discontinue Imfinzi if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. After withhold, Imfinzi can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. Imfinzi should be permanently discontinued for recurrent Grade 3 or 4 (severe or life-threatening) immune-mediated adverse reactions.

For non-immune-mediated adverse reactions, withholding Imfinzi should be considered for Grade 2 and 3 adverse reactions until ≤ Grade 1 or baseline. Imfinzi should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment) (see section 4.2 of the SmPC).

Type of Application and aspects on development

The company has received the following scientific advice from the SAWP with regard the design and clinical development of Imfinzi in NSCLC.

Date of adoption of the CHMP scientific advice	Key Agreements
20 March 2014	The applicant requested scientific advice from the CHMP regarding quality development, pre-clinical development and clinical development (Procedure No. EMEA/H/SA/2752/1/2014/III). The following aspects were discussed: • A comparability exercise to bridge Process 1 to Process 2 material in support of the MA application. • The approach for implementation of a new bioassay for release and stability testing. • The acceptability of the non-clinical programme to support the MAA. • The acceptability of the Phase 2/3 clinical development plan to support an indication for durvalumab in 3rd/4th line NSCLC patients • The acceptability of the Phase 3 clinical study to support an indication for 1st line sequential therapy. • The proposed dose to be used in the Phase 2/3 studies. • The proposed Health Related Quality of Life and Patient Reported Outcome measures as additional measures of clinical benefit to support the risk benefit evaluation.
20 November 2014	The applicant requested scientific advice from the CHMP regarding quality development and clinical development (Procedure No. EMEA/H/SA/2752/1/FU/1/2014/III). The following aspects were discussed: • Follow-up comparability advice for the ongoing NSCLC pivotal trials • MEDI4736 and tremelimumab combination therapy in NSCLC: The approach and acceptability of clinical development for the proposed combination indication • The proposal to investigate the role of PD-L1 and the plan to provide assurance of technical performance of the diagnostic intended to support approval of durvalumab
23 April 2015	The applicant requested scientific advice from the CHMP regarding clinical development (Procedure No. EMEA/H/SA/2752/1/FU/2/2015/II). The following aspects were discussed: •The clinical relevance of data generated to date from study CD-ON-MEDI4736-1108 and totality of data that would be required to support Conditional Marketing Authorisation (CMA) in the proposed indication. • The specific criteria to fulfil an unmet medical need for a CMA.
24 September 2015	The applicant requested scientific advice from the CHMP regarding clinical development (Procedure No. EMEA/H/SA/2752/1/FU/3/2015/II). The following aspects were discussed: • Two, randomised, open-label, global studies of first-line durvalumab in combination with tremelimumab or durvalumab monotherapy versus SoC platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC, one study with a primary endpoint of PFS to support initial registration and a post-approval study with a primary endpoint of OS • Demonstration of the need for each of the monotherapy components (durvalumab and tremelimumab) in the combination and the posology for combination and monotherapy in the first-line NSCLC setting. • The suitability of the overall package to support future registration in Europe.

2.2. Quality aspects

2.2.1. Introduction

Imfinzi is presented as a sterile concentrate for solution for infusion containing 50 mg/ml of active substance durvalumab formulated with histidine, histidine hydrochloride monohydrate, trehalose dehydrate, polysorbate 80 and water for injections.

The product is available in a single-use Type I glass vial containing 2.4 mL or 10 mL of concentrate, corresponding to 120 mg or 500 mg durvalumab, respectively. It is diluted with 0.9% sodium chloride or 5% glucose prior to administration.

The pack size of Imfinzi is 1 vial.

2.2.2. Active Substance

General information

Durvalumab is a human IgG1κ monoclonal antibody that blocks the binding of PD-L1 to PD-1 and CD-80, resulting in enhanced anti-tumor activity by eliminating the immunosuppressive effects of PD-L1 on cytotoxic T-cells. The heavy chain CH2 domain of durvalumab was engineered to contain three amino acid substitutions that are referred to as triple mutation (TM); a leucine to a phenylalanine at residue 238, a leucine to a glutamatic acid at residue 239, and a proline to a serine at residue 335. These TM amino acid substitutions were introduced to reduce Fc-mediated effector functions of the antibody molecule such as antibody-dependent cellular cytotoxicity (ADCC) and complement fixation.

Durvalumab is a human IgG1κ monoclonal antibody of approximately 149 kDa, including oligosaccharides. The antibody is composed of two identical heavy chains of approximately 49 kDa each (theoretical mass without glycosylation), and two identical light chains of approximately 24 kDa each. Durvalumab has primarily N-linked biantennary complex-type oligosaccharides attached to each heavy chain at Asn-301. The average size of the oligosaccharide moiety is approximately 1500 Da per heavy chain.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Durvalumab active substance is manufactured at AstraZeneca Pharmaceuticals LC (formerly MedImmune LLC) Frederick, Maryland, USA. This is also the site for storage and testing of active substance, except for mycoplasma testing which occurs at Charles River Laboratories, Malvem, Pennsylvania, USA.

Both sites are covered by valid EU GMP certificates. No issues have been identified during the review of the dossier calling for an inspection.

The durvalumab active substance production process includes cell culture process in Chinese Hamster Ovary (CHO) cells, harvest and a series of purification steps.

The cell culture and harvest process consists of five steps: working cell bank (WCB) vial thaw; inoculum expansion in shake flasks of increasing size and rocker bags; seed bioreactors; durvalumab production in bioreactor, and cell removal and clarification during harvest. The production bioreactor is operated in a fed-batch mode. When the bioreactor reaches the target product concentration, the target culture duration, or

the lower limit for cell viability, the harvest is initiated. Overall, the upstream (cell culture and harvest) process and the process controls has been described in sufficient detail. A few minor concerns were raised during the procedure regarding the criterion for initiation of harvest. These issues were adequately addressed in the responses provided.

The purification process consists of three chromatography steps: a product capture step and to remove process-related impurities; anion exchange chromatography is designed to bind and remove process-related impurities and putative viruses; cation exchange chromatography is carried out in bind and elute mode to remove product- and process-related impurities. Two virus clearance steps are conducted: a low pH treatment step and a virus filtration step. Finally, a concentration and diafiltration step is conducted to achieve a specific target protein concentration. The formulated bulk is prepared by dilution and excipient addition to achieve a specific target protein concentration and formulation composition. The formulated bulk is 0.2 micron filtered and filled directly into a storage container, after which it is designated active substance. The active substance is stored at 2-8℃ prior to shipment at 2-15℃ to a finished product manufacturing site for fill and finish.

Two purification process steps are qualified as reprocessing steps for the manufacture of the active substance. Overall, the description of the harvest and isolation process and the product purification is sufficient. During the procedure, the applicant was asked to provide additional details on the column steps (dimensions and volumes, process times, and conditions for discard/collection of eluate). Furthermore, the applicant was asked to specify post-use integrity test of bioburden filters. Finally, the applicant was asked to indicate the sterile filtration steps in the process flow diagrams. All issues were sufficiently addressed in the responses provided.

Control of materials

Raw materials

Raw materials used in the manufacture of durvalumab active substance have been listed appropriately, identifying where each raw material is used in the process. For non-compendial materials internal quality standards exists. Raw materials are tested and released according to approved specifications and require a minimum of appearance and identification testing.

A risk assessment on the use of FBS in the culture and banking of the host cell line has been performed and concludes that the risk posed for potential Bovine Spongiform Encephalopathy (BSE) infectious agent introduction is low. The raw materials therefore do not pose a Transmissible Spongiform Encephalopathy (TSE) risk or viral risk. No formal TSE risk or virus risk assessment in accordance with Ph. Eur was initially presented so the information was requested during the procedure. Although not presented in the format requested (risk-assessment for each individual raw material), the response provided is considered to cover the information requested and the issue is resolved.

Source, history and generation of the cell substrate

The Chinese Hamster Ovary cell line, is used as the host cell line, . The source history and generation of cell substrate is considered adequately described and in accordance with current guidelines. A minor concern on the potential use of porcine trypsin in the early stages of development of the host cell line was raised during the procedure. With the response provided, the requested information regarding the potential use of porcine trypsin in the early stages of the host cell development has been provided.

The cell banking system employed for durvalumab is a standard two-tiered system including a MCB from which multiple WCBs are derived. Active substance lots are generated from the WCB. Testing of MCB and

WCBs was performed according to relevant guidelines (ICH Q5A and ICH Q5D). All results complied with the acceptance criteria, demonstrating that the cell banks are microbiologically and virologically safe for clinical and commercial applications. The potential relevance of including specific tests for porcine viruses (from trypsin) was raised during the procedure. In the response the applicant confirmed that the Master Cell Stock has been tested for porcine viruses.

The cell line stability was tested according to ICH Q5B and ICH Q5D.

Criteria are listed for the qualification of new WCBs.

In general, the cell banking system, including establishment of the MCB, WCB and generation of EOP cells, the characterisation and testing are considered adequately described and in accordance with current guidelines.

Process validation

The proposed manufacturing control strategy for the durvalumab active substance is considered appropriate to ensure process consistency and product meeting the required quality attributes. A risk-based approach in line with ICH Q8 has been used for the identification of CQAs and CPPs.

Process characterisation studies for the production of active substance have been carried out. These studies determined the impact of the process parameters on product quality, resulting in their classification as Critical Process Parameters (CPPs) or non-Critical Process Parameters (NCPPs). Impacts of process parameters on process performance were also determined. The process characterisation studies were performed using scale-down models that were verified to adequately predict the performance of the commercial scale process.

The approach for manufacturing process characterisation is described in sufficient detail and is found acceptable. No design space is claimed and no significant or unusual flexibility in the manufacturing process has been requested.

The control strategy for durvalumab is based on a systematic risk assessment which was presented. The control strategy has been sufficiently described and found acceptable.

The commercial manufacture of durvalumab active substance at the AstraZeneca Pharmaceuticals LP, Frederick Manufacturing Center (FMC) has been validated. The process validation included CPPs, some NCPPs, In-Process Controls (IPCs), Microbial Controls (MCs), and Performance Attributes (PAs).

Validation was performed on five consecutive process validation lots. Except for one out-of-specification result (OOS), all process validation study results met the pre-approved validation criteria. OOS root cause was investigated and corrective actions were taken as a result of the investigation. There was no impact to product quality.

Overall, the process validation confirmed that the active substance manufacturing process is robust, adequately controlled, and consistently able to produce quality product. Minor concerns were raised during the procedure. These issues have been clarified.

Manufacturing process development

Two manufacturing processes have been used during the development of durvalumab.

Evaluation of the comparability of the durvalumab active substance between manufacturing changes during manufacturing process development, including routine and extended characterization, supports that the process changes implemented from clinical batches to conformance batches did not impact product

characteristics or the process consistency. Process robustness studies conducted during process development and characterisation generally confirmed that the described manufacturing process is suitable for the production of durvalumab active substance meeting the required quality attributes.

Characterisation

Durvalumab is characterised with the standard analytical methods for a monoclonal antibody. The classical IgG1 structure is confirmed with identification of the higher order structure, glycosylation profile, charge and size heterogeneity and biological activity.

Durvalumab is classified as a Class II antibody (binding to cell bound antigen with blocking function) and with minimised effector function potential due to the engineered Fc mutations. The overall characterisation of durvalumab has been performed with a sufficient level of detail.

The characterisation of the product-related impurities has been described in sufficient detail. Request for further information was raised for process-related impurities, with a request to describe in more detail. This information has been provided by the applicant on the methods used for detection of product related impurities.

Specification

The active substance specification is provided and includes control of identity, purity and impurities, bioactivity and other general tests.

The analytical procedures have been described in sufficient detail and adequate system suitability tests with suitable acceptance criteria have been composed for the methods. The applicant was requested to include representative chromatograms, electropherograms and electrophoresis profiles where relevant. This has been done. For the AP-1 reporter gene bioassay, the statistical approach for analysis of data and setting of suitability test was requested to be clarified. This has been sufficiently addressed in the response provided.

The extent of the validation of the analytical procedures is found sufficient.

The active substance and finished product specifications are part of the control strategy composed based on the product quality attribute risk assessment. The attributes included in the release and shelf-life specifications have been found adequate. The justification of the limits for the attributes in the active substance specification is found satisfactory and the limits are acceptable. The justification of the limits are based on compendial limits/guidance and literature, clinical experience, nonclinical toxicology experience, and characterisation of the structure-function relationship for the relevant quality attributes. In addition, the stability data and manufacturing process capability have been considered.

Batch analysis

The batch data presented demonstrate manufacturing consistency. All lots produced met the specifications in place at the time of release.

Reference materials

The applicant has established a two-tiered (primary and working) reference standard system as recommended in ICH Q6B. The reference standards are prepared in-house.

In the dossier, the preparation, qualification and stability of the current primary reference standard have been described. This includes the description of the preparation, qualification and summary of the stability

data. In addition, a description of the historical reference standard used during the pre-clinical and toxicology studies has been included.

The future establishment of primary and working reference standards has been described, including preparation, routine characterisation/qualification and stability programme. Overall, the description is found adequate. However, the applicant was requested during the procedure to perform further characterisation of future reference standard unless otherwise justified. The applicant has confirmed that future reference standards will be characterised with the same panel of tests that will adequately describe both primary and working standard. In addition, the statistics behind the assignment of potency to future reference standard was requested to be discussed and justified. With the response provided, the applicant has sufficiently explained the statistic behind assignment of potency and acceptance criteria for future reference standards.

Stability

The primary packaging component for the durvalumab active substance is a disposable, single-use bag intended for long-term storage of the active substance at 2-8° C. The commercial container provides protection from microbial contamination and environmental effects. The materials used for the container are in compliance with compendial requirements for plastic containers, as specified in relevant Ph. Eur. monographs.

Leachables and extractables from the container were assessed by performing a simulation study at the intended long-term storage temperature (2-8°C), and under accelerated (23-27°C/55-65 % residual humidity (RH)) and stressed (38-42°C/70-80 % RH) storage conditions for six months. The results presented support the safety of long-term, 2-8°C active substance storagefor at least 24 months.

Real-time, real-temperature long-term stability studies of durvalumab active substance were performed at 2-8°C for 24 months using three primary lots and supporting lots according to the definitions in ICH Q1A (R2).

Comparability has been demonstrated between Clinical and Commercial lots.

Three different container closure systems are represented in the stability studies. Material from all processes demonstrated similar stability in the commercial container closure.

The proposed active substance shelf life is 24 months at the long-term storage condition of 2-8°C in commercial container. Twenty-four months of real-time, real-temperature data are presented for the primary stability studies as well as 24 months of data for supporting stability studies. Stability test results meet the commercial acceptance criteria at the long-term storage condition for all primary and supporting stability lots.

In addition to this, each year of manufacturing, one representative batch of active substance will be placed into the ongoing stability program. A minor concern regarding the lack of references to the methods used in the stability study was raised. This has been clarified.

Stability data have been provided, supporting an active substance shelf-life of 24 months when stored at 2-8°C in commercial container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Composition

The durvalumab finished product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. It is supplied as a single-dose vial in two presentations: 500 mg of durvalumab per vial with a 10.0 mL nominal volume (10.77 mL target fill volume) and 120 mg of durvalumab per vial with a 2.4 mL nominal volume (2.77 mL target fill volume). Minimum fill volumes are described. The finished product contains 50 mg/mL durvalumab in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80 and water for injections, pH 6.0.

Both presentations of the finished product are aseptically filled into 10R glass vials and closed with a latex-free elastomeric stopper. The finished product vial is then capped with an aluminium seal.

Pharmaceutical development

The formulation development has been thoroughly described and the rationale for the selection of the formulation has been adequately addressed and justified. The same formulation composition was used throughout the clinical and commercial development of the product. The dosage form has changed from a lyophilised form to a liquid form through clinical development. A fill overage is added to the two vial presentations and justified.

The manufacturing process development has been described in detail. CQAs and commercial control strategy have been described. The durvalumab finished product is presented in single-use vials without preservative. The measures to control microbiological quality and sterility of the finished product are considered acceptable. The container closure system and the assessment of the suitability of the components have been described. Results of extractable and leachable studies revealed no unexpected components.

The results of the finished product comparability studies have been presented in the dossier. All results met the comparability acceptance criteria. The results demonstrate that batches are comparable. Both routine and characterisation test results showed that the quality of the material intended for commercial use is similar to material used in clinical studies. Degradation rates and/or profiles from accelerated and stressed stability of durvalumab finished product batches were comparable over 3 months of stability.

A compatibility study with the infusion system demonstrated that the finished product diluted into 0.9% (w/v) saline or 5% (w/v) glucose was compatible with the infusion system and the diluents. Comparability has been adequately described.

Overall, the pharmaceutical development of durvalumab finished product has been described in sufficient detail.

Manufacture of the product and process controls

The active substance is pre-filtered into a mixing vessel and pooled. During filling, pooled active substance is continuously 0.2 µm sterile filtered as it is aseptically filled into sterile vials, closed with sterile stoppers and sealed. The resulting finished product is 100% visually inspected, labelled and packaged, and stored at 2-8°C. The description of manufacture of durvalumab finished product is acceptable.

The proposed manufacturing control strategy for the durvalumab finished product manufacturing process and the performed process validation are considered appropriate to ensure process consistency and product meeting the required quality attributes.

On request, missing information on validation of the secondary manufacturing (labeling and packaging) at the AstraZeneca site was provided.

Container Closure System

The primary packaging for finished product is a colourless Ph. Eur. Type I glass vial sealed with a 20 mm Teflon-coated rubber stopper and crimped with a 20 mm aluminium seal fitted with a plastic flip-off cap. All product-contacting materials comply with relevant pharmacopeia requirements.

The container-closure system used for durvalumab finished product is adequately described. Compatibility of the container-closure system with durvalumab is demonstrated with the stability information. Extractables from the container and closure are evaluated to be non-toxic. The container closure integrity is demonstrated.

The sterilisation methods and conditions for the primary packaging materials are described.

Product specification

The finished product specification includes control of identity, purity and impurities, bioactivity and other general tests.

The finished product release and shelf-life specifications are considered adequate to ensure the quality of the finished product. It was requested that the finished product release and shelf-life specifications should include reference to relevant monographs or internal methods. Tables have been provided with the method references.

Validation studies are presented for the methods that are only applicable for the finished product. The validations presented and the transfer qualification information presented are considered acceptable. A short summary of the robustness study for the container closure integrity including the parameters investigated and the conclusion was requested and has been provided.

An evaluation of elemental impurities, as required according to the ICH Q3D Guideline, has been submitted.

The justification for the limits for the finished product specific specification parameters are in line with the specification for active substance and are found acceptable.

Batch analysis

The lot release test results were presented. All lots produced met the specifications in place at the time of release. The batch data presented demonstrate manufacturing consistency.

Reference materials

The reference standard used for finished product is the same as that used for active substance.

Stability of the product

The intended shelf life for durvalumab finished product is 36 months, when stored at 2-8°C. Real-time long term stability studies are designed according to ICH guidance, including a minimum of three primary lots of each presentation (120 mg and 500 mg) of durvalumab finished product as well as supporting lots. All

primary and supporting studies were performed using durvalumab finished product material in the final formulation, and the same container closure system (10R glass vials with Teflon-coated rubber stoppers), which is also intended for storage and distribution.

The stability studies performed, the protocols used, and the results of the studies are presented. In short, real-time, long term studies were performed at 2-8°C. The results obtained to date comply with the acceptance criteria. A discrepancy regarding the time-points for which long-term stability data was provided, was detected between the information given in the finished product Quality Overall Summary and Module 3, which has to be addressed by the applicant. This has been done.

Stability studies at accelerated (23-27°C/55-65% RH, 6 months) and stressed (38-42°C/70-80% RH, 3 months) storage conditions have been performed. These studies are completed.

Based on the stability data presented the claimed shelf life of 3 years (2°C – 8°C) for the finished product can be accepted. Regarding the diluted solution, if not used immediately, chemical and physical in-use stability of Imfinzi has been demonstrated for no more than 24 hours at 2°C to 8°C or 4 hours at room temperature up to 25°C from the time of vial puncture to the start of administration.

Photostability

A photostability study was performed according to ICH Q1B using one commercial scale batch of each presentation (). It was demonstrated that the marketing pack satisfactorily protects the finished product material from the effects of light exposure, as all results obtained complied with the acceptance criteria.

Water loss

A study was conducted for determination of water loss during storage at recommended long-term conditions and accelerated conditions, for which 24 months of results have been obtained. To date, no water loss has been detected from the primary packaging.

Elemental purities

Finally, elemental purities studies were performed, using three commercial scale lots representing both presentations. Results obtained through the 24 month time point are below the dose-adjusted Permissible Daily Exposure level established according to ICH Q3D.

Adventitious agents

Non-viral adventitious agents

As required, a risk assessment of the transmission of BSE from FBS used in the culture and banking of the host cell line has been performed and concludes that the risk posed for potential BSE infectious agent introduction is low. However, a TSE risk assessment on the remaining biologically derived raw materials could not be located in the dossier. These documents were requested and have been provided.

Viral adventitious agents

Assurance of viral safety of durvalumab active substance and finished product is based on the following approaches as defined by ICH Q5A: control of raw materials used in manufacturing, virus testing and characterisation of the cell banks used in GMP manufacturing, virus testing of unprocessed bulk, and inactivation assessment of the purification process.

For the FBS used, this risk is considered very low as no viruses were detected in any of the virus assays including the *in vitro* assay for bovine adventitious viral agents (Modified 9 CFR) applied for testing of the

MCB. For the cholesterol used, the preparation process is evaluated to minimise the risk of transmitting infectious viruses.

Testing of both MCB and WCB cell banks was performed according to current guidelines (ICH Q5A and ICH Q5D), including testing for cell identity, mycoplasma, sterility (bacteria, fungi), endogenous and adventitious viruses. The cell banks have been extensively tested for presence of endogenous and adventitious viruses according to ICH Q5A, using both unspecific and specific *in vitro* and *in vivo* assays. All results complied with the acceptance criteria, demonstrating that the WCB is microbiologically and virologically safe for clinical and commercial applications. A question was posed to the potential relevance of including specific testing for porcine viruses. The applicant confirmed specific testing for porcine viruses.

Aseptic processing of the inoculum train and closed system processing of the rest of the steps adds to minimising the risk of potential virus contamination or process carry-over during manufacturing.

The measures applied in order to minimise the risk of introducing adventitious viruses and for contamination by process carry-over are considered acceptable.

The capability of the durvalumab downstream purification process for viral clearance has been validated using four model viruses with different physicochemical properties. Five steps, including four orthogonal steps, of the purification process were evaluated, including the Capture chromatography, the low pH treatment, the anion and cation exchange chromatography, and the virus filtration (20 nm) step.

The virus clearance studies have demonstrated significant clearance of all four model viruses by the manufacturing process. A safety margin for clearance of endogenous RVLPs of > 8.3 $\log_{10}$ corresponding to less than 1 retrovirus particle for every 2.0 x 10^8 doses was obtained, which is considered acceptable. The design of and the safety margin obtained from the performed virus clearance studies are in accordance with ICH Q5A.

In addition to the viral clearance capability demonstrated for the manufacturing process, the extensive testing of cell substrates and unprocessed bulk, the control of raw materials and manufacturing process, and the environmental monitoring and pest control programs enable the durvalumab active substance and finished product to be considered as virologically safe.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No Major Objection was identified during the procedure.

Overall, the quality of Imfinzi is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The cell culture and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Imfinzi is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Imfinzi is approvable.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Durvalumab is a human IgG1 kappa monoclonal antibody (mAb) that targets human (h)PD-L1. It contains 3 point mutations in its constant domain that reduce binding of C1q as well as the affinity of the Fc domain for the antibody-dependent cell mediated cytotoxicity-inducing Fcγ receptors (Oganesyan et al, 2008). The binding of durvalumab to PD-L1 inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumour immunity.

PD-L1 is a member of the B7 family of ligands that normally regulate the activation of T cells through binding to the PD-1 receptor (Keir et al, 2008). PD-L1 is aberrantly expressed in malignancies of several origins at a high frequency (Dong et al, 2002). PD-L1 represses antitumour T-cell responses in tumours and secondary lymphoid organs and protects tumours from immune elimination (Zou and Chen, 2008). Expression of PD-L1 in tumours is associated with reduced survival and unfavorable prognosis (Mu et al, 2011; Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007; Nomi et al, 2007; Loos et al, 2008; Wang et al, 2010; Hamanishi et al, 2007). Inhibition of the PD-L1 /PD-1 axis has demonstrated antitumour activity in several preclinical studies (Hirano et al, 2005; Iwai et al, 2002; Okudaira et al, 2009; Zhang et al, 2008).

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro:

Analysis of sequence homology of human, mouse, rat and cynomolgus monkey PD-L1 (ONC4736-0012) and confirmation that binding of durvalumab to recombinant human PD-L1 depends on arginine at position 95 in PD-L1 (ONC4736-0014).

Extracellular domain sequences of hPD-L1 were compared to its homologous for other species (cynoPD-L1, rPD-L1 and mPD-L1). After comparison, the identity of the protein sequence was established as follows: hPD-L1 vs. cynoPD-L1 (95.9%); hPD-L1 vs. mPD-L1 (73.5%) and hPD-L1 vs. rPD-L1 (74.4%).

In addition, arginine at position 95 in B7-H1 (PD-L1), which is critical for the binding of MEDI4736 to recombinant human B7-H1 (PD-L1), is conserved only in human and cynomolgus monkey B7-H1 (PD-L1). Thus, the likelihood of binding of MEDI4736 to cynomolgus monkey B7-H1 (PD-L1) is high. In contrast, the binding of MEDI4736 to mouse and rat B7-H1 is unlikely.

Durvalumab affinity and specificity [ONC4736-0001 and -0007]: Durvalumab Binds to Human and Cynomolgus Monkey PD-L1 with High Affinity (ONC4736-0001) and does not Bind to Human Proteins of Related Sequence or Function or Mouse PD-L1 (ONC4736-0007). The affinity (represented by the equilibrium

dissociation constant [KD]) of durvalumab for rhPD-L1 and rcynoPD-L1 in solution was measured using KinExA label-free technology). The KD values for binding of durvalumab to rhPD-L1 and rcynoPD-L1 were 22 and 78 pM, respectively. Based on these results, durvalumab has a high affinity and specificity for both rhPD-L1 and rcynoPD-L1.

Durvalumab inhibits the interaction of PD-L1 with PD-1 or CD80 (ONC4736-0002) and overcomes the PD-L1-mediated inhibition of primary human T Cells in vitro (ONC4736-0003): The half-maximal inhibitor concentration (IC50) values were 0.10 (PD-L1) and 0.04 (CD80) nM, respectively.

When anti-CD3, anti-CD28 and CAT004 (mouse IgG1) were incorporated to the cultures of primary human T cells, an increase of proliferation and IFN-γ was observed. In this study, the effect of rhPD-L1 was confirmed by reducing both T-cell proliferation and IFN-γ releasing. This reducing effect was reverted with durvalumab, which was not observed in the case of incubation with CAT254 (isotype control).

The in vitro potency of durvalumab varies when using primary T Cells from different donors (ONC4736-0020): A CHO cell line expressing a membrane bound form of the anti-CD3 antibody and hPD-L1 was treated with Mitomycin-C and cultured with primary human CD3+ T cells. Durvalumab increased the proliferation of T cells, while the incorporation of the isotype matched control antibody (NIP228) did not affect T cells proliferation. The EC90 value could be estimated at 0.99 μg/mL. The cumulative frequency distribution indicated that concentrations above 3 μg/mL achieved 90% of maximal response.

Durvalumab does not inhibit the activity of antigen-presenting cells or trigger effector function (ONC4736-0005, ONC4736-0015): No effect of durvalumab was observed in an *in vitro* antigen-recall assay. These results showed that durvalumab did not affect the activity of antigen-presenting cells.

Assessment of durvalumab-induced release of cytokines (IFN-γ, IL-2, IL-6 and TNF-α) in human whole blood (ONC4736-0004). Cultures of plasma-depleted human whole blood were incubated during 24 hours in the presence of durvalumab or anti-human CD3, as a control positive. No cytokines were released in the presence of durvalumab.

Assessment of release of cytokines induced by durvalumab in combination with tremelimumab (a fully humanized anti-CTLA-4 antibody, which blocks CD80 and CD86) (ONC4736-0017): The combination of durvalumab and tremelimumab did not increase the levels of cytokines in supernatants.

Cellular PD-L1 (ONC4736-0013) and soluble PD-L1 (ONC4736-0008) are present in a range of human cancers: The PD-L1 expression was investigated by using the chimeric 2.14H9 mIgG1 antibody. The higher number of positive samples to 2.14H9 mIgG1 were obtained in gastric (6/6), colorectal (7/8), renal (9/10) and lung (7/9). In this study, some nontumour cells, including infiltrating mononuclear and stroma cells, showed a positive membranous and cytoplasmic staining for PD-L1. An additional study showed that levels of soluble PD-L1 in plasma of patients with cancer (NSCLC-ADC, NSCLC-SCC and CRC) were higher than in healthy subjects.

10F.9G2 (surrogate antimouse PD-L1 antibody) binds mouse PD-L1 with high affinity and inhibits the binding of mouse PD-L1 to PD-1 and CD80 (ONC4736-0009, ONC4736-0010): The aim of this study was to validate this antibody to test in an *in vivo* mouse models of human cancer. The KD value for binding of 10F.9G2 to rmuB7-H1 was 7.66 pM.

In vivo

Durvalumab was evaluated *in vivo* murine models of human cancer.

Durvalumab inhibits the growth of human tumours in mice via an immune-mediated killing mechanism (ONC4736-0006): The Applicant used A375 (human melanoma) and HPAC (human pancreatic adenocarcinoma) cells enriched for CD4+ and CD8+ T cells. Treatment with durvalumab reduced the tumour volume in the HPAC xenograft model, resulting in a maximum tumour growth inhibition of 74%. In the case of A375 xenograft model, durvalumab inhibited tumour growth in the presence of T cells.

The antitumor activity of anti-mouse PD-L1 is dose dependent in the CT26 mouse colorectal cancer model (ONC4736- 0019): Animals administered with 10F.9G2 (a surrogate antimouse PD-L1 antibody) improved median survival time compared to control group, although only 1, 10 and 20 mg/Kg dose levels showed significant differences (1 mg/Kg (p=0.006), 10 mg/Kg (p=0.0003), and 20 mg/Kg (p=0.006) of 10F.9G2). The dose of 5 mg/Kg did not significantly increase the median survival rate (p=0.111). The highest survival rate was recorded in the group treated at 10 mg/Kg (87.5%), followed by 1 and 20 mg/Kg (62.5%); and finally 5 mg/Kg of 10F.9G2 (37.5%).

Combination of anti-mouse PD-L1 antibody with oxaliplatin (ONC4736-0011) or with anti-mouse CTLA-4 antibody (ONC4736-0018). All treatments given alone increased the median survival time. The combination (PD-L1 antibody with oxaliplatin or PD-L1 antibody with CTLA-4) prolonged the values obtained with the individual components.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies with durvalumab were conducted.

Safety pharmacology programme

Safety pharmacology parameters were evaluated following administration of durvalumab in the GLP 4- and 13-week repeat-dose toxicity studies in cynomolgus monkeys (Study VMM0008 and Study VMM0033).

These included neurological parameters (assessed by clinical observations), cardiovascular parameters (electrocardiogram [ECG; including heart rate, wave form morphology, ST segment and PR and QT interval, corrected QT interval (QTcM or QTcB)] and blood pressure parameters, and respiration rate.

Cardiovascular measurements were conducted pre-dose, days 8 and 29, 1h post dose. T_{max} was 1.5 or 6.5 hours in VMM0008 on day 1. The lowest dose of 30 mg/kg provided similar C_{max} (mean 625 and 634 µg/ml, male and female monkey, respectively) to C_{max} in clinic (mean 364, range 200-1221 µg/ml). The highest dose administered provided a C_{max} of 3780 and 3810 µg/ml, in male and female monkey, respectively, providing a safety margin of approximately 10 compared to the clinically relevant plasma concentrations.

Neurobehavioural screening was performed on all animals at three occasions, before treatment, on Days 1 and 29 of treatment at 1 hour post dose (±15 mins) and during Week 8 of the treatment-free period. There were no treatment-related effects on any of the neurobehavioural parameters investigated.

The safety pharmacology endpoint assessments (Study VMM0008 and Study VMM0033) did not lead to any changes for either cardiovascular, respiratory or central nervous system measurements.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with durvalumab.

2.3.3. Pharmacokinetics

No dedicated pharmacokinetic studies were performed, but kinetic samples were taken in all the *in vivo* toxicity studies. A comprehensive evaluation of the PK/TK and PK/PD relationships was reported by referring to the four toxicity studies conducted in cynomolgus monkey:

- 302833; A PK/PD dose range finding study (Non-GLP).
- VMM0008; A four weeks toxicity study with eight-weeks recovery period (GLP).
- VMM0033; A thirteen weeks toxicity study with eight-weeks recovery period (GLP).
- 8291365; ePPND study (GLP).

302833: The study design involved dosing at pharmacologically relevant doses (0.1 or 1 mg/kg durvalumab) on Day 1, followed by 2 weeks off dose and then repeat dosing at potential toxicologically relevant doses (10 or 100 mg/kg) on Day 15, 22, and 29.. Animals were immunized with 10 mg Keyhole Limpet Hemocyanin (KLH) on Day 1 and 29 to monitor potential effects of durvalumab on the antibody response to a T cell-dependent antigen. Non-linear kinetics was evident between doses 0.1 and 1 mg/kg due to target-mediated drug disposition as expected, but also between 10 and 100 mg/kg. The nonlinear PK at 10 and 100 mg/kg correlated with all animals in the low dose group and 4 out of 5 animals in the high dose group were tested positive for antidrug antibodies. Regarding pharmacodynamics, almost complete suppression of sPD-L1 was observed after the first dose (including 0.1 mg/kg). The target suppression was dose dependent but also time dependent, as after the last dose, target suppression decreased faster than after the first dose. A similar outcome was observed for the membrane bound PD-L1, measured by flow cytometry. Almost complete occupancy (>97%) after the first dose of durvalumab was observed in animals administered a low dose of 0.1 mg/kg, a complete suppression of target can be achieved at a plasma concentration of approximately 2 µg/mL serum (C_0 = 1.77 µg/ml for 0.1 mg/kg) in the absence of antidrug antibodies in monkeys.

Table 2 Pharmacokinetics of durvalumab in cynomolgus monkey shown as mean (standard deviation).

Study ID	N	Dose (mg/kg)	Day	AUC_{0-t} µg/kg*days	$t_{½}$ (days)	V_{ss} (mL/kg)	CL (mL/d/kg)	C_0 µg/mL
302833	4	0.1	1	2.1 (0.165)	0.926 (0.211)	49.1 (18.3)	43.8 (3.27)	1.77 (0.424)
302833	5	1	1	80.3 (14.7)	3.05 (0.995)	40.5 (7.00)	11.1 (1.11)	20.8 (1.27)
302833	4	10	29	70 (57.9)	ND	ND	ND	124 (26.9)
302833	5	100	29	7370 (7240)	ND	ND	ND	2660 (692)

VMM0008: Dosing was initiated with a loading dose in order to minimize formation of antidrug antibodies leading to the following dose groups: 30/15, 60/30 and 200/100 mg/kg administered one week apart. Exposure was linear between the doses on Day 1 and was consistent with 100 mg/kg dose in study 302833. The clearance was lower and $t_{½}$ higher compared to study 302833, as these doses were designed to be in the linear segment (target mediated clearance saturated) of the previously tested dose range of durvalumab. Volume of distribution was consistent with plasma volume and data from study 302833. The number of animals that tested positive for presence of ADA increased with time. Prior to the last dose (Day 29), 11 of 12 animals in the 30/15 mg/kg dose group tested positive for the presence of ADA. The number of animals that tested positive for presence of ADA on Day 29 was lower in the 60/30 and 200/100 mg/kg dose groups (5 of

12 animals in each group). Anti-drug antibodies in animals treated with durvalumab persisted throughout the 8-week recovery period. By the end of the recovery period, ADA was detectable in all animals in Groups 2 and 3 and in 4 of 6 animals in Group 4. The presence of ADA had variable impact on pharmacokinetics and PK data from animals with obvious impact of ADAs were excluded from summary statistics calculations. ADAs were not detected in any sample from any control animal (Group 1).The PD measure sPD-L1 was suppressed from Day 1 to day 32 in 9 out of 12 animals in group 2 (30/15 mg/kg), in all animals in group 3 (60/30 mg/kg) and in 11 out of 12 animals in group 4 (200/100 mg/kg).

VMM0033: In-study pharmacokinetic linearity was demonstrated on Day 1. Comparable AUC_T between VMM0033 and 8291365 is observed, whereas a factor of 1.4, 1.4 and 1.6 fold increase is observed for the three dose levels 30, 60 and 200 mg/kg, respectively, between VMM0008 and VMM0033. The only difference between the studies, was the age of the animals, consequently the weight was higher and therefore also the dose. The older animals, which showed higher exposure, were of higher body weight, especially the males. Clearance was determined in VMM0008 and in 8291365, the ePPND study using sexually mature female animals. Clearance was determined to be higher in the young animals used in study VMM0008 (6-7 mL/kg/day) and lower in study 8291365 (3 L/kg/day). Thirty-three percent (33%, 4 of 12 animals) of the control Group 1 animals were positive for ADA.

8291365: Pregnant females received a loading dose (double the maintenance dose) of 60 or 200 mg/kg durvalumab by IV infusion upon confirmation of pregnancy on gestation day 20 (GD20). This was followed by weekly doses of 30 or 100 mg/kg durvalumab from GD27 until delivery. Control animals received vehicle following the same dosing schedule. Transfer of durvalumab from dam to infant was shown to occur during gestation and demonstrates the existence of a placental transfer mechanism. Also durvalumab excretion into milk in lactating mothers was demonstrated, although in low concentration not anticipated to induce pharmacological activity in infants. The serum concentrations in infants was likely due to placental transfer illustrated by the relatively high and pharmacological relevant mean serum concentrations of 7.85 and 42.2 µg/mL at day 90 post partum.

In general, after the first dose of durvalumab, a biphasic decline in serum durvalumab concentration was reported. The highest durvalumab concentrations were achieved by the end of product infusion. Median T_{max} for all dose levels ranged from 1.5 to 6 hours post dose. Mean elimination half-life estimated for the concentration declined out to 7 days post dose and was approximately 6 to 8 days. In the 13 week repeated dose study C_{max} and AUC_T, was approximately dose proportional to dose from 30- to 200 mg/kg with a mean accumulation ratio of 1.56 to 1.91.

Table 3 lists selected pharmacokinetic parameters from Day 1 of all studies conducted with durvalumab. Vz and Clearance were not reported for VMM0033 and 8291365, however comparing data from VMM0008 with 302833, dose dependent changes in clearance and $t_{½}$ is demonstrated due to target mediated clearance at lower doses, whereas volume of distribution is largely conserved over the whole dose range of 0.1 to 200 mg/kg as expected.

Table 3 List of mean IV pharmacokinetic parameters in cynomolgus monkey after loading dose (Day 1) in studies 302833, VMM0008, VMM0033 and 8291365.

Study ID	N	Dose (mg/kg)	AUC_{0-t} (µg/mL*day)	C_{max} (µg/mL)	$t_{½}$ (days)	V_z (mL/kg)	CL (mL/d/kg)
302833	4	0.1	2.1 80.165)	1.77 (0.424)	0.926 (0.211)	49.1 (18.3)	43.8 (3.27)
302833	5	1	80.3 (14.7)	20.8 (1.27)	3.05 (0.995)	40.5 (7.00)	11.1 (1.11)
302833	4	10*	70 (57.9)	124 (26.9)	ND	ND	ND

302833	5	100*	7370 (7240)	2660 (692)	ND	ND	ND
VMM0008	12	30	2490 (313)	630 (64.6)	5.93 (NA)	52.1 (NA)	6.10 (NA)
VMM 0008	12	60	4530 (776)	1180 (181)	6.75 (NA)	73.0 (NA)	7.49 (NA)
VMM 0008	12	200	14500 (2560)	3800 (928)	6.29 (0.114)	65.6 (12.5)	7.24 (1.4)
VMM 0033	12	30	3590 (1030)	833 (171)	6.44 (1.82)	NC	NC
VMM 0033	12	60	6210 (1380)	1720 (325)	6.78 (2.16)	NC	NC
VMM 0033	12	200	23200 (4400)	6420 (1490)	8.27 (12.7)*	NC	NC
8291365	20	60	6760 (1160)	1610 (323)	NC	NC	NC
8291365	20	200	21000 (5430)	5060 (1180)	NC	NC	NC

Note: For study 302833 C_{max} is extrapolated C_0. For the three GLP studies, mean C_{max} is reported.
*: Not drug naïve animals

Durvalumab is showing dose linear exposure on Day 1 of studies VMM0008 and VMM0033, which demonstrates saturated target mediated clearance for doses used in pivotal toxicity studies, see Table 4.

Table 4 Assessment of dose linearity on Day 1 in pivotal toxicity studies

Study	Dose	Dose increment	AUC_{0-t} increment	C_{max} increment
Vmm0008	30	NA	NA	NA
Vmm0008	60	2	1.8	1.9
Vmm0008	200	6.7	5.8	6.0
Vmm0033	30	NA	NA	NA
Vmm0033	60	2	1.7	2.1
Vmm0033	200	6.7	6.5	7.7

PK parameters in the pivotal toxicity studies were comparable between male and female animals. Therefore tables and summaries are reporting result pooled across sex.

2.3.4. Toxicology

The nonclinical toxicology package completed with durvalumab is considered in accordance with ICH S6(R1) and ICH S9 guidance. The IV route of administration was used for all in vivo toxicology studies as this is the intended route of administration.

The cynomolgus monkey was found to be the only pharmacological relevant nonclinical species for evaluation of local and systemic toxicities of durvalumab.

Table 5: List of the toxicology studies performed with durvalumab

Study Number	Study Title	Species/ROA	GLP
302833	MEDI4736: A Pharmacokinetic/pharmacodynamic and Dose Range Finding Intravenous Toxicity Study in Cynomolgus Monkeys	Cynomolgus monkey/IV	No
VMM0008	MEDI4736: A 4 Week Intravenous Toxicity Study in the Cynomolgus Monkey with an 8 Week Treatment-Free Period	Cynomolgus monkey/IV	Yes
20019776	A Biodistribution Study in Select Cynomolgus Monkey Tissues Following Intravenous Injection of MEDI4736 for 4 Weeks with an 8 Week Recovery	In vitro	No
VMM0033	MEDI4736: A 13 Week Repeat Dose Intravenous Toxicity Study in the Cynomolgus Monkey Followed by an 8 Week Treatment-Free Period	Cynomolgus monkey/IV	Yes
8291365	MEDI4736: An Enhanced Pre- and Postnatal Development Study in Cynomolgus Monkeys	Cynomolgus monkey/IV	Yes
20014789	A Tissue Cross-Reactivity Study of MEDI4736 in Normal Human Tissues	In vitro	Yes

Study Number	Study Title	Species/ROA	GLP
20014791	A Tissue Cross-Reactivity Study of MEDI4736 in Normal Cynomolgus Monkey Tissues	In vitro	Yes

Single dose toxicity

No single dose administration studies were carried out.

Repeat dose toxicity.

Studies 302833, VMM0008 and VMM0033

The main aims of the non-GLP PK/PD and DRF toxicity study (Study 302833) were to determine the PK/PD relationship and a preliminary toxicity profile of durvalumab upon IV bolus administration. Scheduled necropsies were carried out on Day 39 and tissues were taken for microscopic analysis.

Two GLP repeat-dose IV toxicity studies were conducted with durvalumab, a 4-week (Study VMM0008) and a 13-week (Study VMM0033) repeat-dose toxicity study. To mitigate the high incidence of immunogenicity and ADA-mediated adverse effects observed in the non-GLP repeat-dose toxicity study (Study 302833), in both studies a loading dose (double the maintenance dose) of 30, 60, or 200 mg/kg durvalumab was administered on Day 1, and followed by 4 or 13 weekly doses of 15, 30, or 100 mg/kg, respectively. In addition, animals were dosed by 30 min IV infusion rather than IV bolus administration to reduce the risk of anaphylactic reactions. The majority of animals were tested positive for ADAs, however, exposure was maintained in most animals and serum levels of sPD-L1 were generally fully suppressed within 24 hours following the first administration of durvalumab and throughout the dosing period for both studies.

Table 6 below lists the findings, considered to be drug related in the DRF study 302833 and the two GLP pivotal toxicity studies VMM0008 and VMM0033.

Table 6: Summary of key findings in IV repeat-dose toxicity studies

Study ID	Number/ Group/Sex	Dose (mg/kg/week)	Duration	NOAEL (mg/kg/week)	Major findings
302833	5M	0.1/10	4 weeks	100	Mortality: Male 203 died on Day 22. This death, suspected to be due to an ADA-associated anaphylactic reaction, occurred shortly following administration of the second dose of 10 mg/kg durvalumab. Clinical observations: decreased activity, labored breathing, lying on the side for Male 203 (0.1/10 mg/kg durvalumab). There were no treatment-related findings in the remaining animals. Microscopic pathology: lung edema and hemorrhage for Male 203 (0.1/10 mg/kg durvalumab) that died on Day 22 following a suspected ADA-linked anaphylactic response. There were no treatment-related findings in the remaining animals.
302833	5M	1/100	4 weeks	100	No treatment related changes
VMM0008	6M/6F	30/15	4 weeks	200/100	No treatment related changes
VMM0008	6M/6F	60/30	4 weeks	200/100	No treatment related changes

VMM0008	6M/6F	200/100	4 weeks	200/100	Clinical observations: Male 645 (200/100 mg/kg durvalumab) presented with rash on the legs, ears, arms, ocular regions, and head and had red stained urine beginning on Day 29 shortly following administration of the final dose of 100 mg/kg durvalumab. Red stained urine was also observed in the home cage of this animal on Day 30. The rash had completely resolved by Day 32. There were no toxicology significant findings in the remaining animals. Gross pathology: small thymus in all animals administered 200/100 mg/kg durvalumab. Enlarged kidneys for Male 645 (200/100 mg/kg durvalumab). Organ weights: thymi of animals administered 200/100 mg/kg of durvalumab were generally of lower weight than concurrent controls (without reaching statistical significance). There were no treatment-related changes in the remaining animals. Microscopic pathology: slight to moderate reduction in cellularity of the thymic cortex in some animals (1 of 3 M and 2 of 3 F) in 200/100-mg/kg dose group, which was absent in animals examined after the 8-week treatment-free period. Bilateral, marked, tubular ischemic necrosis and multifocal vasculitis with fibrinoid necrosis (one with a small thrombus) in Male 645 (200/100-mg/kg dose group). This animal also had inflammation in the choroid plexus, a medium-sized artery in the heart, in a complex of vessels in one epididymis, and slight inflammatory cell infiltration in the section of sciatic nerve.
VMM0033	6M/6F	30/15	13 weeks	200/100	Microscopic pathology: In the thymus, an increase in incidence and/or severity of involution/atrophy (cortex and medulla or cortex) was observed in males and females.
VMM0033	6M/6F	60/30	13 weeks	200/100	Microscopic pathology: In the thymus, an increase in incidence and/or severity of involution/atrophy (cortex and medulla or cortex) was observed in males and females.
VMM0033	6M/6F	200/100	13 weeks	200/100	Microscopic pathology: In the thymus, an increase in incidence and/or severity of involution/atrophy (cortex and medulla or cortex) was observed in males and females. In the mesenteric lymph node, decreased germinal center development was noted in two males treated at 200/100 mg/kg/occasion. Following the 8-week treatment-free period, no difference from control was observed in either of these tissues. These findings were not associated with any changes in peripheral-blood T cells counts, were considered to have an uncertain relationship to treatment and given their incidence or severity, if they were related to treatment, they were considered not to be adverse.

The selection of the high dose in all three studies is therefore also accepted as NOAEL (200/100 mg/kg) in the pivotal toxicity studies.

Genotoxicity

No genotoxicity studies were carried out.

Carcinogenicity

No carcinogenitity studies were carried out.

Reproduction Toxicity

To assess the potential effects of durvalumab on embryofetal and postnatal development, an ePPND study (Study 8291365) was conducted in cynomolgus monkeys. Pregnant females were administered durvalumab IV from confirmation of pregnancy (GD20) until parturition, and development of the infants was monitored in a 6-month postnatal phase, which included an assessment of immune-competence of the infants by inclusion of a challenge with a T cell-dependent antigen (KLH).

Table 7 Summary of findings in studies of reproductive and developmental toxicity

Study type/Endpoint/ Study ID	Species; Number/group	Route & dose	Dosing period	Findings	NOAEL (mg/kg &AUC)
13 weeks toxicity study Surrogate endpoints for Male fertility VMM0033	Cynomolgus monkey N=4	IV 30/15, 60,30 or 200/100 mg/kg/week	13 weeks	Epididymis: Infiltration, Inflammatory cells in dosed groups, not dose related, reversible Prostate: Infiltration, Inflammatory cells in 50% of animals, including control group Seminal vesicles: Mineralization in >50% of animals including control group Testes: No findings	NOEL for reversible inflammatory cell infiltration not attained
13 weeks toxicity study Surrogate endpoints for Female fertility VMM0033	Cynomolgus monkey N=4	IV 30/15, 60,30 or 200/100 mg/kg/week	13 weeks	Uterine cervix: Mucoid change in 1 animals in mid and high dose group Uterus: Infiltration, Inflammatory cells in 1 animals in mid and high dose group, Hemorrhage in 1 animal in low dose group Vagina: Infiltration, Inflammatory cells in 88% of animals, including control group	200/100 mg/kg
ePPND Embryo-fœtal development 8291365	Cynomolgus monkey N=20	60,30 or 200/100 mg/kg/week		Total pregnancy loss for low dose group higher than control (25 vs. 5%), however lower than historical control of 31%	200/100 mg/kg
ePPND Peri & postnatal 8291365	Cynomolgus monkey infants N=14-19	Infants not dosed, exposure is from mother during gestation	180 days	% infant deaths day 1-7: 5% for low dose, 10% for high dose, but 9.8% for historical controls. Infant external examination, morphological measurements, neurobehavioural assessment, grip strength, skeletal development: no treatment-related findings.	200/100 mg/kg

Table 8 Histopathology – group distribution of findings for animals killed after 13 weeks of treatment

Group	1	2	3	4
Compound	Control	MEDI4736	MEDI4736	MEDI4736
Dose 1 (mg/kg/occasion)	0	30	60	200
Dose 2-14 (mg/kg/occasion)	0	15	30	100

		Number of animals affected							
Tissue/Organ and Findings	Group/Sex No. of animals	1M 4	2M 4	3M 4	4M 4	1F 4	2F 4	3F 4	4F 4
Cecum	No. examined	4	4	4	4	4	4	4	4
Parasites		0	0	1	0	0	0	0	0
Infiltration, Fatty, Mucosal/Submucosal		0	1	0	0	0	0	0	0
Colon	No. examined	4	4	4	4	4	4	4	4
Infiltration, Fatty, Mucosal/Submucosal		0	1	0	0	0	0	0	1
Duodenum	No. examined	4	4	4	4	4	4	4	4
Epididymides	No. examined	4	4	4	4	-	-	-	-
Infiltration, Inflammatory Cells		0	3	1	4	-	-	-	-
Esophagus	No. examined	4	4	4	4	4	4	4	4
Infiltration, Inflammatory Cells, Submucosa		1	0	2	2	0	0	2	1
Infiltration, Inflammatory Cells, Muscle		1	0	0	0	0	0	0	0

Table 9 Incidence of Infiltration, Inflammatory cells in Epididymides at Envigo

Historical Histopathology Data 03/01/2018

Incidence of selected findings in control Cynomolgus monkeys from studies conducted at Envigo UK

MALES

code number	cyn39 0810	cyn02 0811	cyn04 0904	cyn04 0904	cyn26 0909	cyn26 0909	cyn26 1202	cyn26 1202	cyn39 1507	cyn39 1507	cyn26 1508	cyn26 1508	cyn06 1511	cyn06 1704	
start date	Oct-08	Nov-08	Apr-09	Apr-09	Sep-09	Sep-09	Feb-12	Feb-12	Jul-15	Jul-15	Aug-15	Aug-15	Nov-15	Apr-17	
route of admin.	og	og	og	og	iv	iv	sc	sc	sc	sc	ih	ih	sc	og	
study type	tox	tox	tox	tox	tox	tox	tox	tox	tox	tox	tox	tox	tox	tox	
supplier	Hart	n/a	Hart	Hart	Hart	Hart	Hart	Hart	Hart	Hart	BS	BS	BS	BS	
country of origin	Ch	Ch	Ch	Ch	Ch	Ch	Ch	Ch	Viet	Viet	Viet	Viet	Viet	Viet	
age at start of study	34 - 59M	5Y	4 - 5Y	4 - 5Y	57 - 64M	57 - 64M	74 - 96M	74 - 96M	44 - 54M	44 - 54M	80 - 91M	80 - 91M	4 - 6Y	6 - 9Y	
study duration (weeks)	39	2	4	4 + 4	26	26 + 26	26	26 + 13	39	39 + 8	26	26 + 4	6	6	
															totals
number of animals	4	3	3	2	4	2	3	2	4	2	4	2	3	3	41
Epididymides															
No examined	4	3	3	2	4	2	3	2	4	2	4	2	3	3	41
Infiltration, Inflammatory Cells															
minimal	0	0	0	1	0	0	0	0	0	0	1	0	0	0	2
percentage *	0.0%	0.0%	0.0%	50.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	25.0%	0.0%	0.0%	0.0%	4.88%

Toxicokinetic data

Toxicokinetics (TK) was monitored in all three toxicity studies including ADA and pharmacological relevant biomarkers. Based on study 302833, the doses chosen for the pivotal toxicity studies were all in the pharmacokinetic linear range which was confirmed by toxicokinetics. As no gender differences were determined in the studies, TK was pooled across sex. Accumulation of durvalumab in repeat dose studies was lower or as expected (theoretical accumulation ratio is approximately 1.8) for the selected dosing schedule

(QW) and observed half-life (approximately 6 days). Maximum accumulation ratio observed was 1.9, which is very close to the theoretical value.

Exemplifying and assessing impact of antidrug antibodies on TK can be done using the table of accumulation ratios from the TK report of VMM0008. The exposure after day 15 was severely impacted in the low dose group, but seems to be reliable in group 3 and 4 until Day 29. See Table 10 of accumulation ratios below:

Table 10: Individual Accumulation ratios determined using AUCτ and Cmax (VMM0008).

Group	MEDI4736 Dose (mg/kg)		Gender	Animal ID	AR Cmax		AR AUC_τ	
	Loading	Maintenance			Day 22	Day 29	Day 22	Day 29
2	30	15	FEMALE	614	1.18	ND	1.53	ND
				616	0.859	ND	0.476	ND
				618	0.583	ND	0.198	ND
				620	ND	0.370	ND	0.130
				622	ND	0.133	ND	0.000
				624	ND	0.910	ND	0.883
2	30	15	MALE	613	1.49	ND	1.89	ND
				615	1.05	ND	0.673	ND
				617	1.36	ND	1.62	ND
				619	ND	1.11	ND	1.20
				621	ND	0.512	ND	0.311
				623	ND	1.70	ND	1.81
3	60	30	FEMALE	626	1.58	ND	1.56	ND
				628	1.31	ND	1.55	ND
				630	0.883	ND	1.14	ND
				632	ND	1.09	ND	1.09
				634	ND	0.531	ND	0.291
				636	ND	1.07	ND	1.32
3	60	30	MALE	625	1.30	ND	1.25	ND
				627	1.15	ND	1.29	ND
				629	1.19	ND	1.16	ND
				631	ND	1.40	ND	1.43
				633	ND	0.984	ND	1.69
				635	ND	1.15	ND	0.972
4	200	100	FEMALE	638	0.768	ND	0.846	ND
				640	1.35	ND	1.94	ND
				642	1.14	ND	1.19	ND
				644	ND	1.50	ND	1.93
				646	ND	1.02	ND	1.06
				648	ND	0.934	ND	0.889
4	200	100	MALE	637	1.40	ND	1.68	ND
				639	1.01	ND	1.33	ND
				641	1.91	ND	1.91	ND
				643	ND	1.22	ND	1.27
				645	ND	0.631	ND	0.0230
				647	ND	1.48	ND	1.73

AR = Accumulation Ratio calculated using the following equation:

$$AR_{AUC} = \frac{AUC_{\tau,Dose\_n}}{AUC_{\tau,Dose\_1}}$$

$$AR_{C_{max}} = \frac{C_{max,Dose\_n}}{C_{max,Dose\_1}}$$

A more direct way of determining validity of the toxicity study with antidrug antibodies, is to monitor target occupancy. Soluble PD-L1 was below Lower limit of quantification (LLOQ) in all animals in group 3, all except animal 645 up to day 29 in group 4, which correlates with toxicokinetics. In group 2, three animals showed signs of neutralising antibodies as sPD-L1 increased to near normal levels in the third week of the study.

A few samples obtained pre-study initiation (week-3 samples), were determined ADA positive: 631 group 3, negative day 8, positive thereafter, 645 group 4, positive thereafter, 646 group 4, negative thereafter. One sample from group 1 were tested ADA positive in this study: 609 Day 56 of recovery.

A similar picture was observed for the 13-week toxicity study with decreasing number of animals with PK affected by ADAs for higher doses.

Table 11 Exposure at end of study at NOAEL and margin to human:

Study ID	Duration	Weekly Dose (mg/kg)	Mean AUC_{ss0-7d} µg/mL*day monkey	Mean $AUC_{ss0-14d}$ µg/mL*day human	Animal:human Exposure Multiple
VMM0008	4 weeks	200/100	20500	3816*	11
VMM0033	13 weeks	200/100	34900	3816*	18

*: From clinical report entitled "Exposure-response report for efficacy and safety", page 16. Dose = 10 mg/kg every two weeks.

Local Tolerance

A dedicated local tolerance study with durvalumab was not conducted. Injection sites were evaluated as part of the repeat-dose toxicity studies with durvalumab in cynomolgus monkeys (Studies 302833, VMM0008, and VMM0033). In the non-GLP PK/PD and DRF toxicity study with durvalumab (Study 302833), local tolerance was assessed by microscopic evaluation of the IV injection site 10 days after the final dose. In the GLP 4- and 13-week repeat-dose toxicity studies with durvalumab (Studies VMM0008 and VMM0033), local tolerance at the IV infusion site was assessed by dermal Draize evaluation throughout the dosing period and by microscopic evaluation of the injection site 3 days after the final dose.

Arteritis/periarteritis, subcutaneous inflammation, subcutaneous haemorrhage and thrombus were observed at the injection sites (left and right saphenous veins) of treated animals and controls in study Study VMM0033. Occasional incidences of bruising, oedema, erythema and acanthosis were recorded at the injection sites. The Applicant stated that all of these signs were observed in both control and treated animals and there was no evidence of an increase in severity, incidence or duration in treated animals and these signs are therefore considered to be related to the injection procedure and not associated with treatment with durvalumab.

Other toxicity studies

Tissue cross reactivity (TCR studies 20014789 and 20014791) was studied in a panel of tissues from humans and cynomolgus monkeys. In human tissues, staining with durvalumab was present in the membrane and cytoplasm of mononuclear cells and trophoblastic epithelium. Cytoplasmic staining only was also present with durvalumab in pituitary epithelium. In the placenta, durvalumab stained extracellular proteinaceous material. PD-L1 expression has been reported in mononuclear cells, including dendritic cells, lymphocytes, monocytes, and macrophages and placenta trophoblasts. The soluble form of PD-L1 may account for the staining of extracellular proteinaceous material in the placenta. The expression of PD-L1 has not specifically been reported in pituitary epithelium; however, other epithelial cell types have been reported to express PD-L1. TCR in cynomolgus monkey showed similar staining patterns as compared to human tissues.

2.3.5. Ecotoxicity/environmental risk assessment

Durvalumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), durvalumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Durvalumab was found to only bind to human and cynomolgus monkey PD-L1, and the cynomolgus monkey was found to be the only relevant nonclinical species for the safety and toxicity studies. For the PD studies, either a model of immunodeficient mice inoculated with a mixture of human tumour cell lines expressing B7-H1 (PD-L1) and human T-cells alloreactive to the human tumour cell lines or in a syngeneic mouse model using a mouse surrogate monoclonal antibody against mouse PD-L1. Both models showed dose related tumour reducing effects and in vivo proof of concept is accepted.

In the set of in vitro studies, the binding affinity and specificity of Durvalumab with the proposed target, i.e. human PD-L1, was calculated. In this regard, the action of Durvalumab (nM range) on hPD-L1 was reported by inhibiting the binding to its ligands, both hPD-1 and hCD80 receptors. This action was also estimated in T cells obtained from donors. In this assay, the serum concentration of Durvalumab with 90% of the maximal response observed was 3 µg/mL. As PD-L1 mechanism of action is to re-activate the host immune response to tumours overexpressing PD-L1, there is also a risk that autoimmune reactions could be stimulated following treatment with durvalumab.

No dedicated PK studies were performed, but samples for PK/TK were taken in the DRF toxicity study as well as in the pivotal toxicity studies in cynomolgus monkeys. Durvalumab administration resulted in Cmax generally reached after fist dose. A relatively dose proportional increase of AUC was seen at low doses and with a more than dose proportional increase a high doses (100x). This non-linear PK at high doses may be influenced by a saturable target-mediated clearance which is not unexpected in antibodies that have membrane targets. A very high variability exposure was reported with increased dose frequency and this variability is attributed to the high presence of ADAs when the last dose is administered. PK variability was reduced in those animals that did not present ADA formation. Durvalumab administration resulted in total suppression of free sPD-L1 as expected due to the pharmacology of the product. Almost complete occupancy (> 97%) of membrane PD-L1 in various cell subsets CD4+ also on CD8+ lymphocytes and CD14+ monocytes. Maximal suppression was seen from dose of 0.1mg/kg. Although the first doses resulted in free sPD-L1 suppression, this was later diminished or abolished after repeated administration due to the presence of ADAs. Not surprisingly ADA formation increased with time.

Durvalumab was administered by the intravenous route in pivotal toxicity studies, therefore the applicant did not evaluate absorption. Distribution studies were not conducted for durvalumab which is acceptable as according to ICH S6(R1), distribution studies are not needed for monoclonal antibodies. It should be noted that the volume of distribution is in the range of 40.5 to 73.0 mL/kg, which is expected for large protein molecules as these primarily resides in the plasma volume. The absence of classical distribution studies are considered acceptable. No studies of metabolism or excretion of durvalumab have been conducted. According to ICH S6(R1), the expected metabolism and clearance of monoclonal antibodies is degradation to small peptides and individual amino acids, which are taken up by the body and incorporated into other proteins or catabolised. Therefore, the metabolism and clearance pathways are generally understood. Classical biotransformation and excretion studies are therefore not needed.

In the toxicity studies where safety pharmacology endpoints were included, no clinically relevant adverse effects were observed. Two monkeys showed ADA-associated reactions, one which died in the non-GLP DRF study, and one animal in the 4 week toxicity study showed clinical signs and histopathological findings consistent with immune complex depositions. Further to the submission of an additional study designed to assess this issue together with information from published literature, it was considered that immune complex deposition is the plausible cause of enlarged kidneys and potentially responsible as well of the epididymis

toxicity reported. These findings in the nonclinical studies were not considered to be predictive of the potential for clinical adverse reactions, as human immunogenicity is not well predicted in the nonclinical setting.

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in foetal loss. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery, at exposure levels approximately 18 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC), was associated with placental transfer but not with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development. Negligible levels of durvalumab were found in milk of cynomolgous monkey on Day 28 after birth (see sections 4.6 and 5.3 of the SmPC).

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for durvalumab, were considered adequate and acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, mutagenicity, fertility and early embryonic development was well justified.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The PK of durvalumab has been investigated in patients enrolled in the Phase 3 study D4191C00001 (hereafter referred to as PACIFIC), in the Phase 1/2 study CD-ONMEDI4736-1108 (hereafter referred to as Study 1108), and in the Phase 2 study D4191C00003 (hereafter referred to as ATLANTIC) following administration by IV infusion.

Table 12: Listing of clinical trials

Table 1 Listing of clinical pharmacology studies

Type of study	Study identifier	Objectives of study	Study design and type of control	Route of administration and dosage regimen
Phase 3, multi-centre, 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	D4191C00001 (PACIFIC)	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life	Randomized, double-blind, placebo-controlled	IV at 10 mg/kg Q2W for up to 12 months
Phase 1/2, dose escalation, dose-exploration, and dose-expansion study to investigate durvalumab monotherapy in adult patients with various advanced solid tumors	CD-ON-MEDI4736-1108 (Study 1108)	Safety, tolerability, PK, and immunogenicity	Open-label, non-randomized	Dose-escalation phase: IV at 0.1, 0.3, 1, 3, and 10 mg/kg Q2W and 15 mg/kg Q3W for up to 12 months Dose-exploration phase: IV at 20 mg/kg Q4W for up to 12 months Dose-expansion phase: IV at 10 mg/kg Q2W for up to 12 months
Phase 2 multi-center, international study of durvalumab monotherapy in patients with locally advanced or metastatic non-small cell lung cancer (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens, including 1 platinum-based chemotherapy regimen	D4191C00003 (ATLANTIC)	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, non-randomized	IV at 10 mg/kg Q2W for up to 12 months

2.4.2. Pharmacokinetics

The PK of durvalumab was studied in 1902 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered intravenously once every two, three or four weeks.

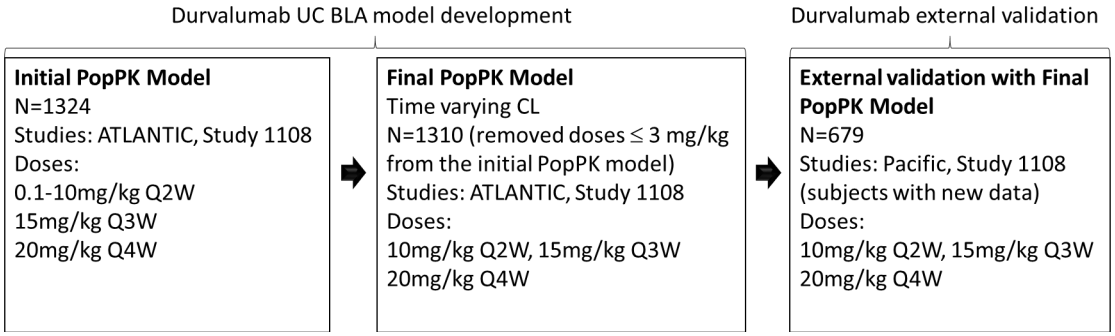
Analytical methods: The immuno-assays for quantification of durvalumab and soluble PD-L1 in human serum samples were adequately validated.

The flow cytometry methods for quantification of T, B, NK cells and for quantification of proliferating T cells in human whole blood, were only partly validated and included inter-assay precision, short-term stability and drug tolerance. The immuno-assays for detection of ADAs, neutralising anti-bodies and for ADAs specific to TM were all qualitative methods and the testing limited. The nAb assay was tested for selectivity as matrix interference in serum from healthy individuals and cancer patients. The ADA methods were not tested for matrix interference as this had been accounted for in the cut point calculation based on serum from patients with different types of cancer.

Pharmacokinetic data analysis: No single dose study has been conducted with durvalumab. Non-compartmental analysis (NCA) was used to analyse the PK of multiple dose durvalumab in study 1108. Sparse PK samples (C_{trough}) were available from the ATLANTIC and PACIFIC study conducted in patients with NSCLC. A Pop PK model has been developed with data from the 3 clinical studies: PACIFIC, Study 1108, and ATLANTIC. The PopPK model has been validated with 679 patients with 3408 samples from PACIFIC and Study 1108 with at least 1 new PK sample that were not used for the previous PK model development. All studies included male and female patients ≥18 years of age with advanced solid tumours. The ATLANTIC and PACIFIC studies were conducted in patients with NSCLC. No PK data are available in healthy volunteers.

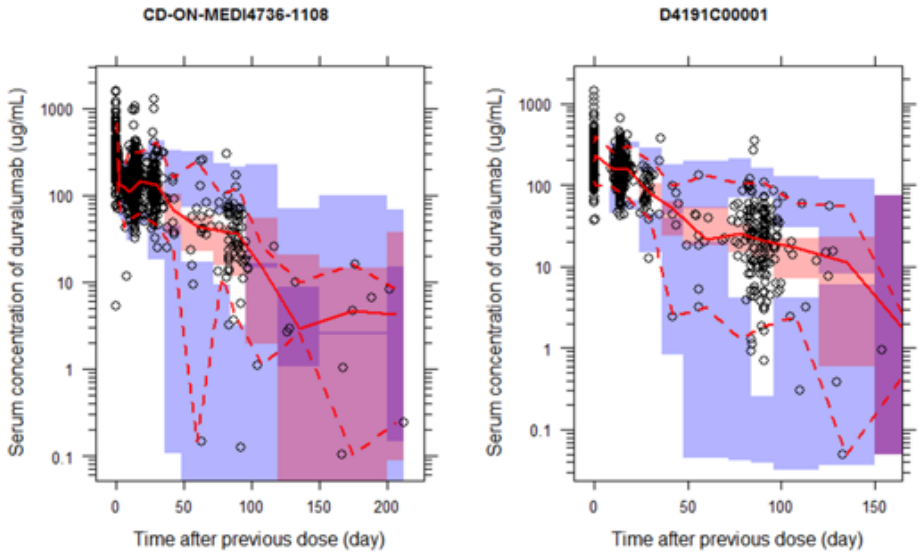
The population PK modelling was used to describe durvalumab serum concentrations in patients (NSCLC and other solid tumours) and to evaluate the need for dose adjustment in special populations based on patients' baseline characteristics.

The durvalumab final population PK model was externally validated with 679 patients with 3408 samples from PACIFIC and Study 1108 with at least 1 PK sample that was not used in the model development.



BLA biologics licence application; CL clearance; popPK population pharmacokinetics; Q2W every 2 weeks; Q3W every 3 weeks; Q4W every 4 weeks; UC urothelial carcinoma
Source: Figure A, External Model Validation of the Population Pharmacokinetics for Durvalumab, Module 5.3.3.5.

Figure 1 Data and patients used for model building and external validation



Note: Circles are observed durvalumab serum concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5 percentile and 97.5 percentile of the observed values. Pink shaded areas represent the spread (5 percentile and 95 percentile) of the median predicted values, and purple shaded areas represent the spread of the 5th and 95th predicted percentile concentrations

Source: Figure 6, External Model Validation of the Population Pharmacokinetics for Durvalumab, Module 5.3.3.5.

Figure 2 Prediction-corrected visual predictive check of durvalumab concentration versus time profiles for validation patients

Absorption

Durvalumab is administered intravenously and the bioavailability 100 %.

Bioequivalence

No bioequivalence studies have been conducted. Full comparability has been demonstrated between the formulation used in the clinical studies and the product to be commercialized.

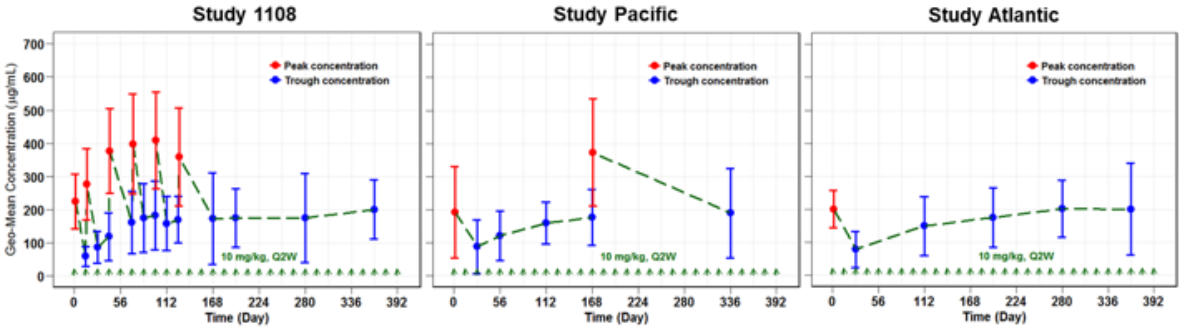
Distribution

Distribution studies were not conducted for durvalumab.

The population PK model adequately described durvalumab PK profiles. A 2-compartmental population PK model with both linear and Michaelis Menten nonlinear elimination components was initially developed for patients across all dose levels and was later updated to a final population PK model with linear elimination at doses doses ≥10 mg/kg Q2W IV in a posthoc analysis.

Based on this final model, the mean systemic linear CL and central volume of distribution (V1) were 0.266 L/day and 3.51 L with a modest between-patient variability of 27.3% and 22.1% expressed as CV%, respectively. Based on the analysis population that included all of the patients in the final model development and in the external validation (1878 patients), the geometric mean (CV%) V_{ss} was 5.64 L (17.6%).

The PK parameters estimated by popPK analysis were consistent with the non-compartmental analysis in study 1108.



C_{max} maximum concentration; C_{trough} trough concentration; IV intravenous; PK pharmacokinetics; Q2W every 2 weeks; SD standard deviation.
Note: Red and blue dots indicate geometric mean peak and trough concentrations (N ≥15 at each time point), respectively; green arrows indicate the scheduled time of durvalumab administrations..
Source: Table 2.7.2.1.

Figure 3 Geometric mean (geometric SD) PK profile of durvalumab after 10 mg/kg Q2W IV administration inPACIFIC, Study 1108, and ATLANTIC

The estimates of AUCss, Cmin,ss and Cmax,ss following durvalumab 10 mg/kg Q2W were predicted in the Pop PK analysis to be: AUCss (ug*day/mL):3816 [1562,17800], Cmax,ss (µg/mL) 364.1 [200.4,1221] and Cmin,ss (µg/mL) 160 [55.4,839.2].

Elimination

No studies regarding durvalumab metabolism have been conducted. No mass balance studies have been conducted. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system (RES) or target-mediated disposition. Durvalumab is not metabolized in the liver and not subject to elimination by P450 enzymes.

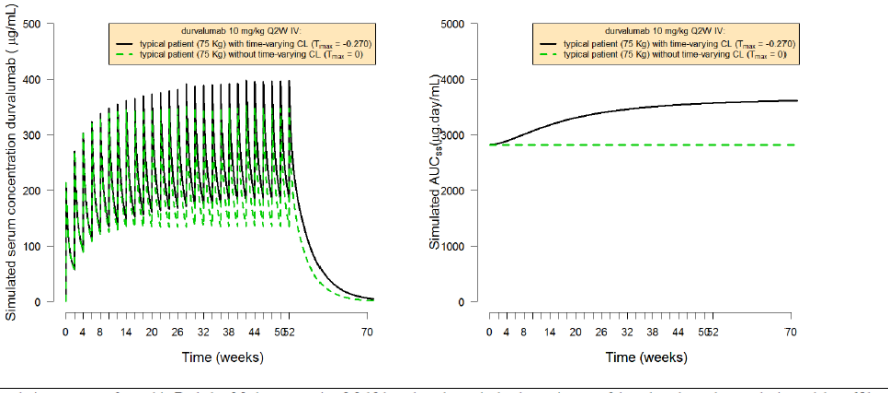
For the 3 studies (PACIFIC, Study 1108 and ATLANTIC), the durvalumab serum PK data at the durvalumab dose of 10 mg/kg Q2W IV were similar (Figure 4).

The Km estimate was 0.533 mg/L (95% CI: 0.072 – 1.58 mg/L). Vmax was 0.931 mg/day. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CL_{ss}) of 8.16 mL/h at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The terminal half-life ($t_{1/2}$), based on baseline CL, was approximately 18 days. Steady state was achieved at approximately 16 weeks.

Exposure-response

The Exposure-response evaluation was conducted with data from the PACIFIC study where all patients were treated with the same durvalumab dose of 10 mg/kg Q2W and PK sampling was sparse. The exposure parameters were simulated from the POP PK model.

The final pop PK model included time varying clearance. A semi-mechanistic model including disease state variable such as lactate dehydrogenase (LDH), neutrophil lymphocyte ratio (NLR), albumin (ALB) and tumour size supported a biological explanation for the deceased clearance as a matter of improvements in diseases state over time. The higher exposure as a result of the time dependent decrease in clearance of approximately 23 % is not associated with a higher incidence of AEs.



The simulations were performed in Berkeley Madonna, version 8.3.18 based on the typical value estimates of durvalumab posthoc analysis model run651.mod assuming a 10 mg/kg Q2W IV dosing scheme and a typical patient of 75 Kg body weight. The simulations were deterministic, with the magnitude of change of CL over time (T_{max} = θ) being evaluated as either fixed to 0 (no time-varying CL) or set to the typical value estimate (T_{max} = -0.270). This simulation was set to examplify the impact of time-varying CL on the levels of durvalumab concentration time-course at the population level. Note that AUC_{ss} was computed according to the analytical solution of dose over systemic clearance.

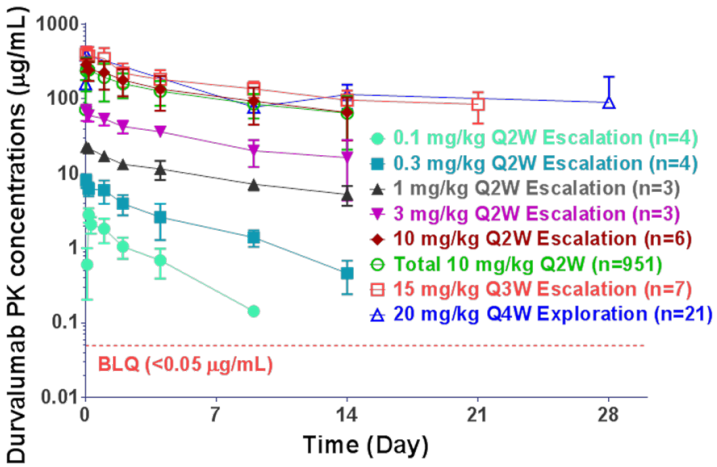
Figure 4: Simulated serum concentration (left panel) and AUCss (right panel) time profiles of two typical patients (one with time-varying CL, one without) following 10 mg/kg Q2W IV of durvalumab for one year based on final PK model (run651.mod)

Inter-individual variability in the target population was moderate (CL CV=27.3% and V1 CV=22.1%) and the intra-subject variability also relatively small (proportional residual error σ1 (CV%) and the additive error standard deviation σ2 (CV%) 21.3% (2.2%) and 4.91 µg/mL (13%), respectively.

Dose proportionality and time dependencies

Dose proportionality

The PK time profile of the low-dose cohorts in the dose-escalation phase of Study 1108 (0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg) show a faster CL. Following the first IV dose, mean maximum serum concentration following the first dose (C_{max1}) increased in a dose-proportional manner over the dose range of 0.1 to 20 mg/kg (Table 13). Exposure levels at 20 mg/kg Q4W provide similar AUC_{ss} levels as 10 mg/kg Q2W over a period of 28 days, but a higher C_{max} to C_{trough} ratio. Mean area under the concentration-time curve from time 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner with doses <3 mg/kg and reached linearity at dose ≥ 3 mg/kg Q2W.



BLQ below the limit of quantification; CSR clinical study report; IV intravenous; PK pharmacokinetics; n sample size; Q2W every 2 weeks; Q3W every 3 weeks; Q4W every 4 weeks; SD standard deviation.
Source: Figure 11.4.4.1-1, Study 1108 Third Interim CSR, Module 5.3.5.2.

Figure 5: Mean (±SD) durvalumab serum concentration-time profile following the first IV administration of 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W to 20 mg/kg Q4W (log scale) (Study 1108)

Table 13: Mean durvalumab pharmacokinetic parameters following the first dose (Study 1108)

Dose (mg/kg)	Schedule	Geometric Mean (n, geometric %CV)								
		T_{max1} (day)	C_{max1} (µg/mL)	C_{max1}_D (µg/mL/mg)	$C_{trough1}$[a] (µg/mL)	$C_{trough1}\_D$ (µg/mL/mg)	AUC_{last} (µg·day/mL)	AUC_{last}_D (µg·day/mL/mg)	AUC_{0-14} (µg·day/mL)	AUC_{0-14}_D (µg·day/mL/mg)
0.1	Q2W	0.170 (4, 1.80)	2.78 (4, 22.1)	0.341 (4, 27.9)	NC	NC	5.14 (4, 45.1)	0.632 (4, 39.8)	6.03 (4, 41.1)	0.741 (4, 39.7)
0.3	Q2W	0.0444 (4, 7.30)	7.97 (4, 23.0)	0.294 (4, 40.3)	0.431 (3, 49.9)	0.0168 3, 57.1	25.1 (4, 65.5)	0.926 (4, 80.2)	25.8 (4, 57.4)	0.952 (4, 71.6)
1	Q2W	0.0777 (3, 79.8)	22.8 (3, 11.3)	0.305 (3, 31.8)	5.11 (3, 34.1)	0.0685 (3, 9.40)	131 (3, 20.1)	1.75 (3, 23.9)	135 (3, 17.1)	1.82 (3, 18.1)
3	Q2W	0.129 (3, 518)	70.8 (3, 17.0)	0.397 (3, 13.3)	12.4 (3, 135)	0.0694 (3, 214)	400 (3, 21.7)	2.25 (3, 53.0)	402 (3, 22.0)	2.25 (3, 53.3)
10 (Escalation)	Q2W	0.0780 (5, 222)	294 (5, 23.4)	0.351 (5, 26.0)	53.8 (6, 92.3)	0.0637 (6, 99.1)	1780 (5, 39.1)	2.13 (5, 37.5)	1770 (5, 38.5)	2.12 (5, 37.1)
10 (Escalation +expansion)	Q2W	NC	225[b] (872, 36.8)	NC	57.6[b] (744, 48.3)	NC	NC	NC	NC	NC
15	Q3W	0.103 (7, 168)	427 (7, 25.5)	0.351 (7, 38.4)	77.4[c] (7, 50.1)	0.0635[c] (7, 38.0)	2940 (7, 36.3)	2.42 (7, 34.5)	2320 (7, 34.4)	1.91 (7, 34.7)
20	Q4W	0.0443 (18, 86.3)	416 (18, 23.9)	0.268 (18, 37.6)	63.0[d] (19, 47.4)	0.0409[d] (19, 44.2)	4500 (18, 23.1)	2.90 (18, 29.5)	3290 (18, 21.3)	2.12 (18, 31.4)

Time dependency

Accumulation of durvalumab was observed following repeated dosing. The mean C_{max_ss} and $C_{trough,ss}$ increased in an approximately more than dose-proportional manner at doses ≤1 mg/kg Q2W. Accumulation of durvalumab was evaluated by the ratio of steady state C_{max} and C_{trough} (on Day 84 or beyond) to those at first dose. Following 0.1 to 10 mg/kg Q2W dose, the mean accumulation ratio for Cmax (ARC_{max}) from the first to eighth dose ranged from 0.64 to 1.87, whereas mean accumulation ratio for C_{trough} (ARC_{trough}) ranged from 3.16 to 4.93.

Table 14: Mean durvalumab pharmacokinetic parameters at steady state (Study 1108)

Dose (mg/kg)	Schedule	Geometric mean (n, geometric%CV)				Accumulation ratio (n, geometric%CV)	
		C_{max_ss} (µg/mL)	$C_{max\_ss\_D}$ (µg/mL/mg)	C_{trough_ss} (µg/mL)	$C_{trough\_ss\_D}$ (µg/mL/mg)	ARC_{max} (Ratio)	ARC_{trough} (Ratio)
0.1	Q2W	1.85 (3, 37.6)	0.230 (3, 83.9)	NC	NC	0.639 (3, 54.0)	NC
0.3	Q2W	15.1 (2, 16.4)	0.511 (2, 13.3)	2.18 (2, 82.5)	0.0737 (2, 86.6)	1.68 (2, 26.0)	4.93 (2, 5.60)
1	Q2W	42.5 (3, 19.6)	0.579 (3, 5.00)	19.2 (3, 23.6)	0.262 (3, 1.20)	1.87 (3, 26.4)	3.77 (3, 9.90)
3	Q2W	NC	NC	NC	NC	NC	NC
10 (Escalation)	Q2W	324 (1, NC)	0.349 (1, NC)	91.9 (1, NC)	0.0988 (1, NC)	1.49 (1, NC)	4.32 (1, NC)
10 (Escalation +expansion)[a]	Q2W	409 (34, 35.7)	NC	182 (27, 57.3)	NC	1.82[b]	3.16[b]
15	Q3W	582 (3, 54.8)	0.504 (3, 48.9)	140 (3, 70.4)	0.121 (3, 79.1)	1.43 (3, 28.5)	2.05 (3, 67.5)
20	Q4W	489 (9, 32.7)	0.294 (9, 27.3)	99.6 (10, 50.1)	0.0611 (10, 32.1)	1.07 (9, 41.4)	1.44 (10, 47.6)

[a] Parameters are directly taken from pre-infusion and end-of-infusion data of first dose. No NCA was performed for total 10 mg/kg Q2W group (escalation + expansion).

[b] ARC_{max} is calculated as the ratio of $C_{max.ss}/C_{max}$; ARC_{trough} is calculated as the ratio of $C_{trough.ss}/C_{trough.}$

ARC_{max} Accumulation index for C_{max}; ARC_{trough} Accumulation index for C_{trough}; C_{max_ss} maximum serum concentration at steady state; $C_{max\_ss\_D}$ dose-normalized maximum serum concentration at steady state; CSR clinical study report; C_{trough_ss} trough serum concentration at steady state; $C_{trough\_ss\_D}$ dose-normalized trough serum concentration at steady state; CV coefficient of variation; n sample size; NC not calculated; NCA non-compartmental analysis; PK pharmacokinetics; Q2W every 2 weeks; Q3W every 3 weeks; Q4W every 4 weeks.

Note: Steady state was defined as the 8th dose (Day 98) for Q2W regimen, 6th dose (Day 105) for Q3W regimen, and 4th dose (Day 84) for Q4W regimen.

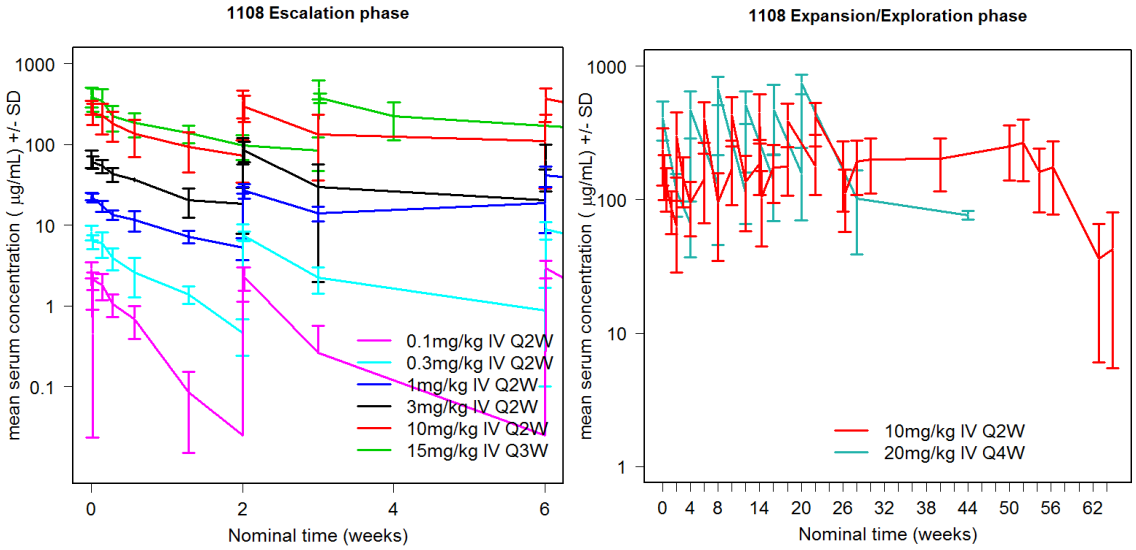
Note: The PK analysis set included all patients who received at least 1 dose of durvalumab per the protocol, for whom any post-dose PK data are available, and who do not deviate from the protocol in a manner that would significantly affect the PK analysis.

Note: The 3 mg/kg PK data were not available for steady state PK parameter calculations since all 3 patients discontinued from the study due to disease progression or death.

Source: Table 11.4.4.1-2, Study 1108 Third Interim CSR, Module 5.3.5.2.

In the Pop PK analysis a statistically significant decrease in durvalumab linear clearance (CL) was observed over time with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%) resulting in a geometric mean steady state clearance CL_{ss} (CV%) of 8.24 mL/h (37.3%). The time-varying clearance was included in the updated pop PK model (model 2).

The decrease in CL_{ss} was not considered clinically relevant since changes in PK parameters ((AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) were <30% for a typical patient with time-varying CL (reduced CL with an estimate of T_{max} = -0.270) compared to a typical patient with time-independent CL (T_{max} = 0, CL = 0.266).



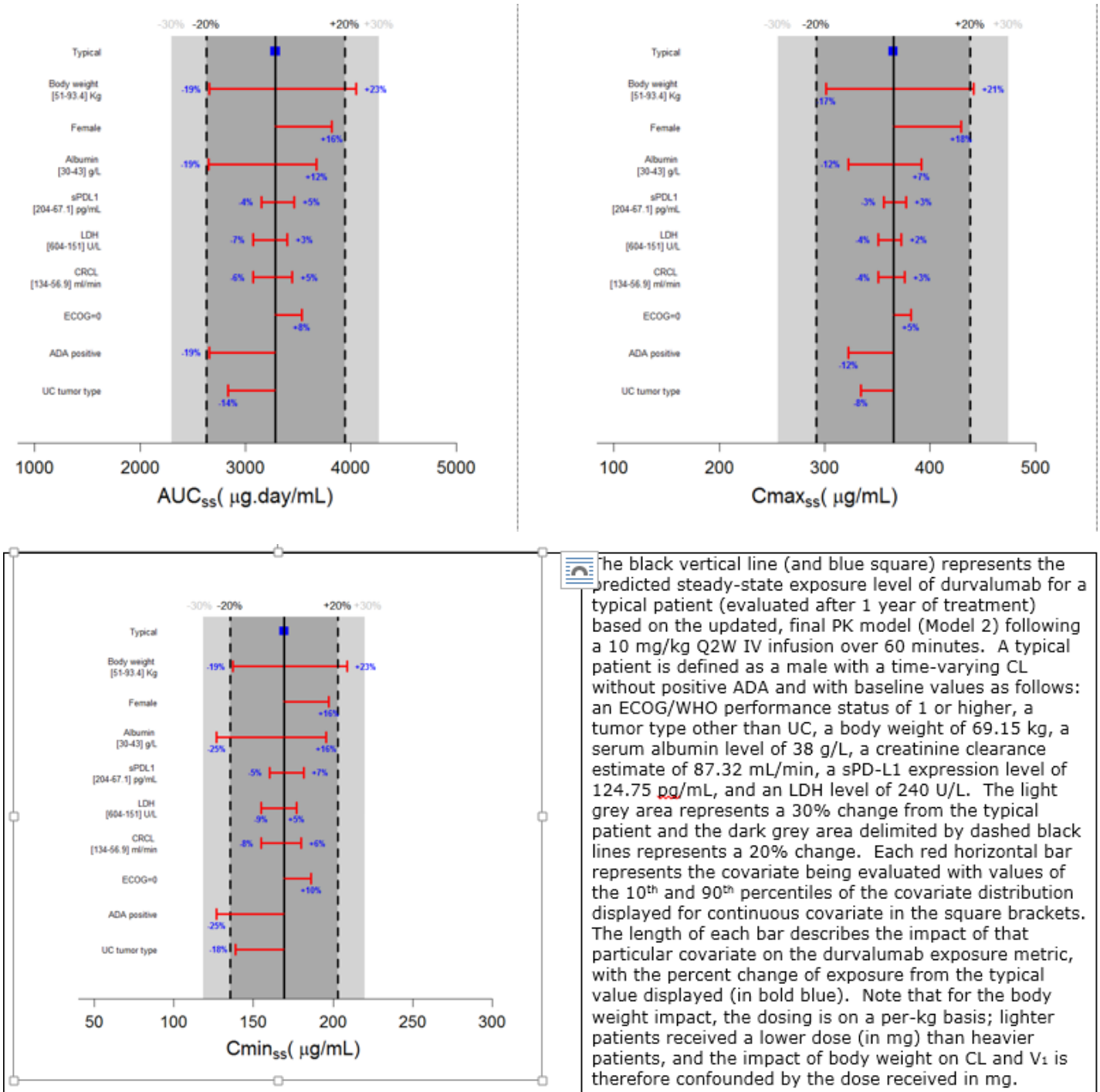
IV intravenous; LOQ limit of quantification; n number of patients; PK pharmacokinetics; Q2W every 2 weeks; Q3W every 3 weeks; Q4W every 4 weeks; SD standard deviation
Data are presented as arithmetic mean (±SD). Only the first 6 weeks are displayed for the dose-escalation phase of Study 1108. LOQ PK data were replaced by LOQ/2. The arithmetic mean (±SD) plot for the dose-escalation phase of Study 1108 (left panel) was produced by excluding any summary PK data with less than 2 individual points at each nominal time. Similarly, for the dose-exploration phase of Study 1108 (right panel 20 mg/kg IV Q4W), mean PK time-course was produced for summary PK data with at least 2 individual points at each nominal time. For the dose-expansion phase of Study 1108 at a dose level of 10 mg/kg Q2W (right panel), the mean PK time-course was produced for summary PK data with at least 10 individual points at each nominal time.
Source: Figure 6.1.6.1-1, Population PK Modeling and Simulation Report of Durvalumab in Urothelial Carcinoma, Module 5.3.3.5

Figure 6: Mean (SD) durvalumab serum concentration-time profile after IV administration

Special populations

The effect of intrinsic factors (i.e., race, age, renal impairment, hepatic impairment, sex, and body weight) on the PK of durvalumab has not been studied through specific dedicated studies.

The popPK analysis indicated that body weight, sex, post-baseline ADA, CLCR, ECOG/WHO performance status, LDH level, soluble PD L1 levels, tumour type, and ALB were statistically significant covariates, but no change in exposure parameters (AUC, C_{min}, C_{max}) was more than 30%. None were considered clinically relevant on key PK exposure metrics of durvalumab at steady state (AUCss, Cmax,ss, and Cmin,ss).



The black vertical line (and blue square) represents the predicted steady-state exposure level of durvalumab for a typical patient (evaluated after 1 year of treatment) based on the updated, final PK model (Model 2) following a 10 mg/kg Q2W IV infusion over 60 minutes. A typical patient is defined as a male with a time-varying CL without positive ADA and with baseline values as follows: an ECOG/WHO performance status of 1 or higher, a tumor type other than UC, a body weight of 69.15 kg, a serum albumin level of 38 g/L, a creatinine clearance estimate of 87.32 mL/min, a sPD-L1 expression level of 124.75 pg/mL, and an LDH level of 240 U/L. The light grey area represents a 30% change from the typical patient and the dark grey area delimited by dashed black lines represents a 20% change. Each red horizontal bar represents the covariate being evaluated with values of the 10th and 90th percentiles of the covariate distribution displayed for continuous covariate in the square brackets. The length of each bar describes the impact of that particular covariate on the durvalumab exposure metric, with the percent change of exposure from the typical value displayed (in bold blue). Note that for the body weight impact, the dosing is on a per-kg basis; lighter patients received a lower dose (in mg) than heavier patients, and the impact of body weight on CL and V_1 is therefore confounded by the dose received in mg.

ADA antidrug antibody; AUC_{ss} area under the serum concentration-time curve at steady-state; $C_{max,ss}$ maximum serum concentration at steady state; $C_{min,ss}$ minimum serum concentration at steady state; CRCL creatinine clearance; ECOG Eastern Cooperative Oncology Group; IV intravenous; LDH lactate dehydrogenase; PK pharmacokinetic; sPD-L1 soluble programmed cell death ligand-1; UC urothelial carcinoma; WHO World Health Organization.
Simulations were obtained in Berkeley Madonna software (version 8.3.18) based on the final population PK model estimates of NONMEM on Model 2 for each covariate separately. Steady-state readouts from the simulations were obtained at Week 16 after the first dose (since predicted concentration-time profiles suggested that steady-state was reached around that time after first dose.
Source: Figure 3.4.3-1, Addendum to the Population PK Modeling and Simulation Report of Durvalumab in Urothelial Carcinoma, Module 5.3.3.5.

Figure 7: **Effect of covariates on exposure parameters using the final model (Model 2): AUCss (top left panel), Cmax,ss (top right panel), and Cmin,ss (bottom right panel)**

The population PK indicates no need for dose adjustment based on these baseline patient characteristics:

Impaired renal function:

Mild and moderate renal impairment did not affect the PK of durvalumab. No patients with severe renal impairment were included. Based on the population PK analysis performed on patients with normal (n=609, 46.4%, CRCL ≥ 90 mL/min), mild (n=522, 39.8%, CRCL=60-89 mL/min), moderate (n=179, 13.6%, CRCL = 30-59 mL/min), and severe renal impairment (n=2, 0.2%, CRCL=30-59 mL/min), the effect of CRCL was not identified as having a clinically relevant impact on durvalumab PK since it did not change PK parameters and exposure parameters by more than 30% from a typical patient (defined with median CRCL of 87.32 mL/min). The updated, final population PK model confirmed that the impact of CL_{CR} on durvalumab PK was not clinically relevant, with an effect of no more than −6% to +5%, −4% to +3%, or −8% to +6% on AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, respectively.

Impaired hepatic function:

The majority of patients in the clinical studies had normal hepatic function. Mild hepatic impairment does not appear to affect clearance and no dose adjustment is required for this population. No effect of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (BIL) on durvalumab PK was observed in the population PK analysis in solid tumours.

Based on the population PK analysis performed on patients included all of the patients included in the final model development (Model 2) and in the external validation (n=1878) with normal hepatic function (n=1598 [85.1%], BIL ≤upper limit of normal [ULN] and AST ≤ULN), mild hepatic impairment (n=255 [13.6%], BIL ≤ ULN and AST >ULN, or BIL >1 to 1.5 × ULN and any AST), moderate hepatic impairment (n=3 [0.16%], BIL >1.5 to 3 × ULN and any AST), no clinically relevant effect of hepatic function was noticeable on the PK of durvalumab. This is supported by the covariate analysis of the PK model of durvalumab that showed no statistically significant impact of hepatic enzymes (AST, ALT, and BIL) on either CL, V1, or V2 of durvalumab.

Gender:

Sex was found to be a strong predictor of CL, V_1, and V_2 of durvalumab, with females having a 13.4% (95% CI: 10% – 17.5%) lower CL than males, a 16.4% (13.5% – 19.2%) lower V_1 than males, and a 23.4% (95% CI: 16.3% – 29.6%) lower V_2 than males. The updated, final population PK model (Model 2) confirmed the impact of sex on durvalumab PK. Females had +16%, +18%, and +16% higher AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, respectively, compared to males.

Weight:

Dosing of durvalumab is weight based, but no capping of dose has been suggested. For body weight, despite a combined effect of increased CL and V1 with increasing body weight, this did not translate into more than a 30% difference in AUC_{ss}, $C_{max,ss}$, or $C_{min,ss}$ with -17%, -17%, and -18%, respectively, for the 10th percentile patient (body weight = 51 kg) compared to a typical patient (body weight = 69.15 kg) and +21%, +21%, and +23% for the 90th percentile patient (body weight = 93.4 kg) compared to a typical patient (body weight = 69.15 kg) for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, respectively. The 2.5th and 97.5th percentile were 45 kg and 111 kg, respectively. Exposure in subjects with extreme body weight was assessed. Expected differences in exposure for obese patients (BMI>30) was compared to the typical patient. The observed/predicted exposure exceeds the 90% exposure range covered in the exposure-response analysis: Males: AUC_{ss} (NA), C_{maxss} (54%), C_{minss} (88.1%) and Females: AUC_{ss} (66.2%), C_{maxss} (73.6/78.6%%), C_{minss} (100/99.9%).

Age:

Age was not identified as a covariate influencing durvalumab PK based on the population PK analysis performed, which included all of the patients included in the final model development and in the external validation, with an age range from 19 to 96 years (n=1878), mean age of 61.6 years, and median age of 63 years.

Table 15: Number (%) of elderly patients in Study 1108, PACIFIC, and ATLANTIC – Population pharmacokinetics population

Study	PoP-PK patient population	Age 65 to 74 years	Age 75 to 84 years	Age 85 years and above
1108	984	311 (31.6%)	115 (11.7%)	6 (0.915%)
PACIFIC	462	176 (38.1%)	36 (7.79%)	0 (0%)
ATLANTIC	432	143 (33.1%)	31 (7.18%)	1 (0.231%)

No PK data are available in patients < 19 years of age.

Other parameters:

The change in the exposure parameters AUCss, Cmax,ss, or Cmin,ss were less than 30 % for ECOG status, high sPD-L1 level, race, LDH or albumin.

Patients tested positive for post-baseline ADAs had significant increased clearancehowever the prevalence was low.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with durvalumab, and the drug interaction potential of durvalumab is unknown.

Pharmacokinetics using human biomaterials

No in vitro permeability, in vitro metabolism, or in vitro metabolic drug-drug interaction studies that used human biomaterials were performed.

2.4.3. Pharmacodynamics

Mechanism of action

Durvalumab is a human monoclonal antibody (mAb) that binds to programmed cell death ligand 1 (PD L1) and blocks its interaction with programmed cell death 1 (PD-1) and cluster of differentiation (CD)80 (B7.1). The binding of durvalumab to PD-L1 inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumor immunity.

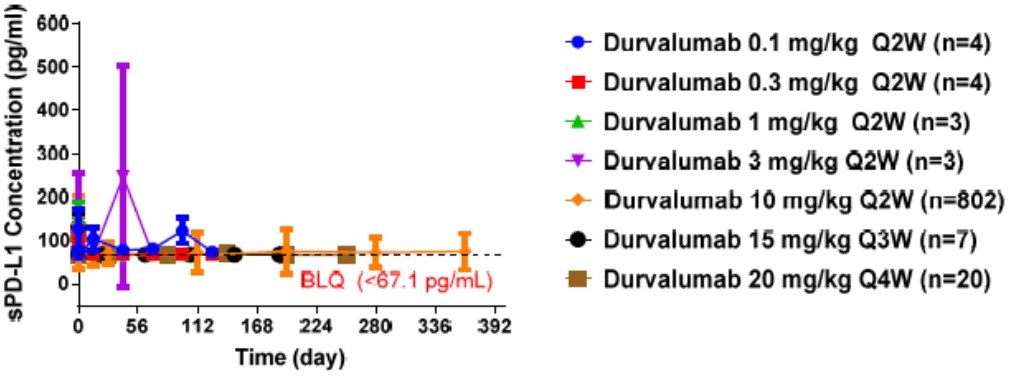
Durvalumab does not have ADCC or CDC activity due to the triple mutation in the Fc domain, confirmed in the cellular cytotoxicity studies. PD-L1 binding is completely saturated at therapeutic durvalumab concentrations and no increase in durvalumab concentration is therefore expected to cause cytokine release. Durvalumab at concentrations up to 300 µg/mL, did not induce cytokine release in a whole blood assay from

any healthy human donor. No cytokine release syndrome or ADCC/CDC induced cytotoxicity is therefore expected even at Cmax concentrations > 300 µg/mL.

Primary and Secondary pharmacology

IPD markers:

In study 1108, target engagement was assessed through measurement of reduction in levels of free soluble PD-L1 (sPDL1) in serum as a peripheral pharmacodynamics marker. Following administration of 0.1 to 20 mg/kg durvalumab, sPD-L1 concentrations were maximally suppressed at Day 14 (or after the first dose) for all doses except 0.1 mg/kg.



*The mean value of sPD-L1 concentration were taken from table 14.2_8.6

*sPD-L1 was highly variable at day 42 since SUBJID (3mg/kg Q2W) was ADA positive with high titer value of 4.96

ADA = antidrug antibody; BLQ = below limit of quantitation; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; sPD-L1 = soluble programmed cell death ligand-1; SUBJID = subject identification.

Figure 8: Mean (SD) sPD-L1 serum Concentration profiles measured at C_{trough} by cohort following IV administration of durvalumab

The extent and duration of the suppression was dose dependent. Following administration of durvalumab, complete sPD-L1 suppression was observed around the dose levels at ≥0.3 mg/kg. Following 10 mg/kg Q2W, approximately 97% of patients demonstrated complete sPD-L1 suppression throughout the dosing interval. Suppression of free sPD-L1 was similar among 10 mg/kg Q2W, 15 mg/kg Q3W, and 20 mg/kg Q4W cohorts.

An additional objective was to explore CD8+Ki67+ T cells as potential markers of the biological activity of PD-L1 blockade by durvalumab.

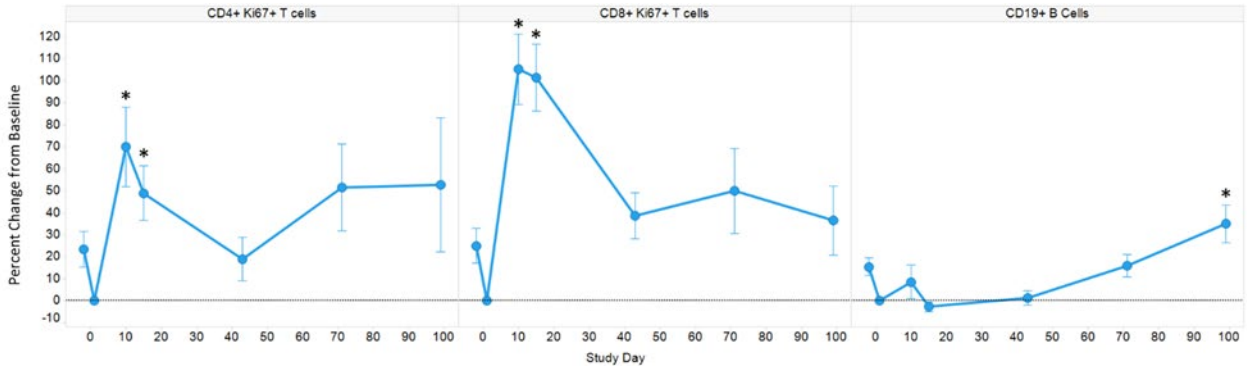


Figure 9: Mean (±SEM) percent change from baseline values for lymphocyte populations from NSCLC patients receiving 10 mg/kg Q2W durvalumab

In summary, flow cytometric analysis of quantities of circulating lymphocytes and proliferating T cells following durvalumab administration revealed:

- Significant elevations above baseline values for the below-listed population
  - CD8+Ki67+ T cells on Days 10 and 15
- Elevations above baseline values
  - CD4+Ki67+ T cells on Day 10
  - CD19+ B cells on Day 99
- No detectable changes outside of the RV in populations below
  - Total CD3+ T cells
  - CD4+ or CD8+ T cells
  - NK cells

The applicant has ongoing studies exploring biomarkers in NSCLC to further understand the prognostic and diagnostic value of biomarkers (Table 16).

The applicant is recommended to submit all data from the ongoing studies on biomarkers post-approval.

Table 16: Planned biomarker analyses in ongoing NSCLC studies

Study Name	Plan for biomarker analyses
Early stage NSCLC	
PACIFIC *EudraCT Number:* *2014-000336-42*	The exploratory biomarkers currently being explored include but not limited to PD-L1, TMB, ctDNA ; complete biomarker analyses will be
PACIFIC 2 *EudraCT number:* *2017-004397-34*	
Advanced/metastatic NSCLC	
MYSTIC *EudraCT Number:* *2015-001279-39*	
ARCTIC *EudraCT number:* *2014-000338-46*	
NEPTUNE	

EudraCT Number: 2015-002197-21	undertaken per protocol depending on the availability of tissue sample and on appropriate relevance for the respective study.
POSEIDON *EudraCT Number: 2017-000920-81*	

NSCLC Non-small cell lung cancer; PD-L1 Programmed cell death ligand-1; TC Tumor cell; TMB Tumor mutational burden.

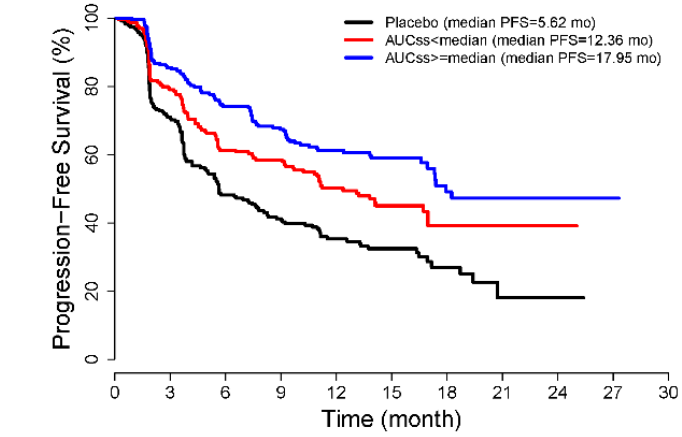
Inmunogenicity:

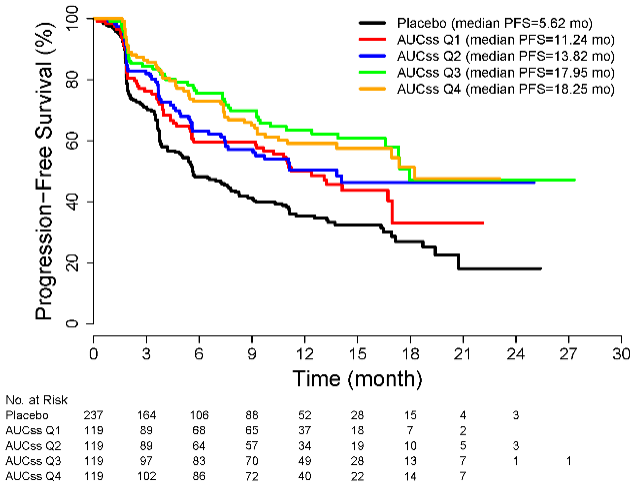
Across the 3 studies, durvalumab demonstrated a 2.9% (45 of 1570 patients; antidrug antibody [ADA] evaluable population) ADA incidence (treatment emergent ADAs [ie, treatment-induced ADA plus treatment-boosted ADA]) with no clinically significant effect on PK following 10 mg/kg Q2W IV dose across tumor types. There was no clear evidence that the presence of ADA or neutralizing antibodies (nAb) had any potential impact on safety but ADA increased durvalumab CL by 23.8% and decreased AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ by 19%, 12% and 25%, respectively, for a typical patient. The median titer of the treatment emergent ADA-positive patients was 4 %. nABs was detected in 8 of 1570 patients (0.5 %).

Exposure-efficacy relationship:

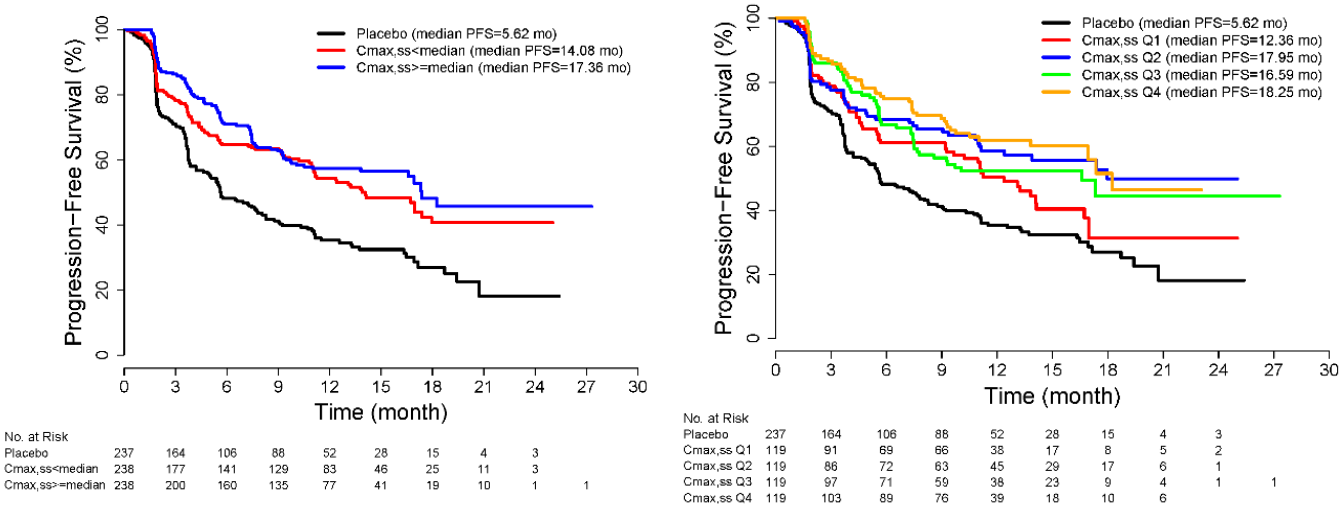
The PFS Kaplan-Meier curves in the durvalumab-treated patients stratified by model predicted exposures at steady state and overlaid with patients in the placebo group are presented in **Error! Reference source not found.**. Durvalumab treatment led to longer PFS compared to placebo. Patients with AUC_{ss} and $C_{min,ss}$ exposure above the median had slightly longer PFS compared to those with exposure below the median.

AUCss





Cmax



Cmin

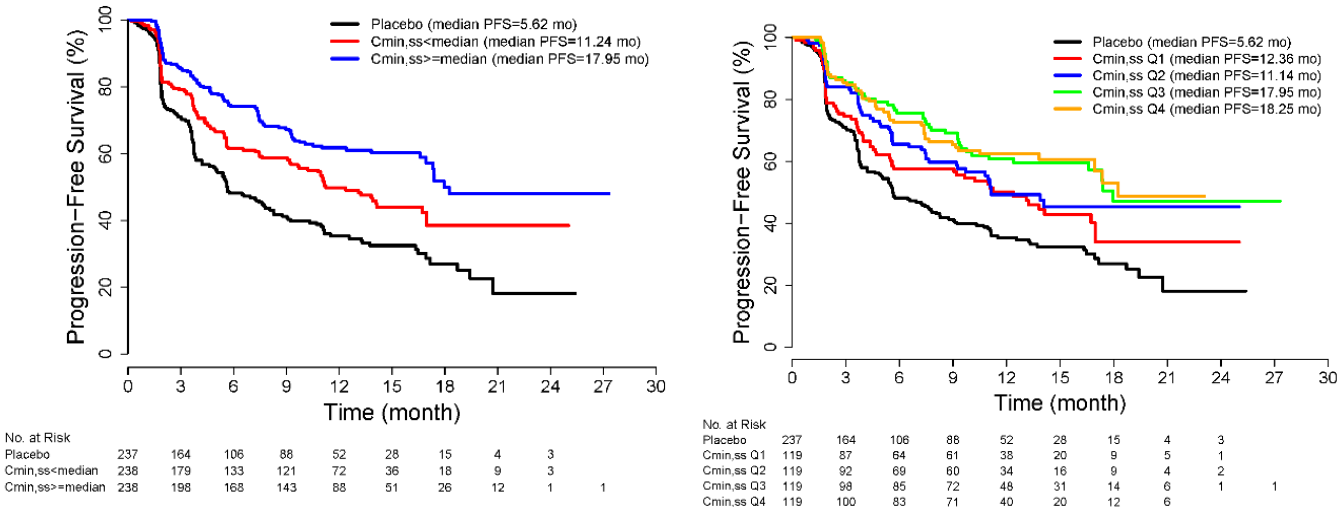


Figure 10: Progression-free survival profiles stratified by durvalumab exposure categories

In order to assess whether the time-varying CL is a confounding factor on the exposure response relationship, the relationship between PFS and AUC_{ss} with the change in CL over time was examined. The results suggest that larger percent reductions in time-varying CL were associated with longer PFS; however, greater percent reductions in durvalumab CL were also associated with higher AUC_{ss}. Therefore, the trend of longer PFS with higher AUC_{ss} is attributed to the PK being confounded by the decreased durvalumab CL in patients benefitting from the treatment.

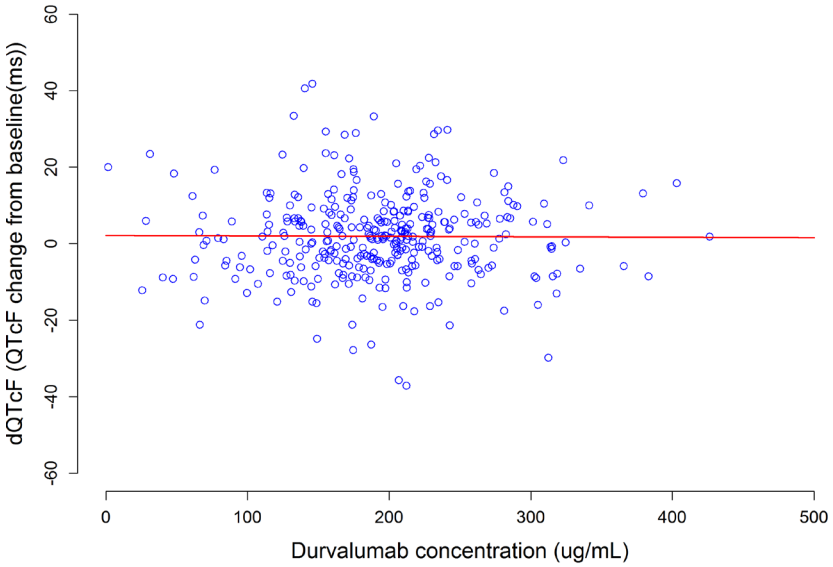
A small trend of a longer PFS with higher AUCss was found

Exposure-safety relationship:

Safety endpoints (Grade 3 or 4 drug-related AE, grade 3 or 4 drug-related AESI, AE leading to treatment discontinuation, and incidence of pneumonitis) were binary responses (yes/no). No exposure-response relationship was observed for the selected AEs based on the durvalumab-treated patients in PACIFIC.

An electrocardiography (ECG) study of patients enrolled in cohort 2 of ATLANTIC was conducted and included the study of ECG interval changes from baseline, categorical outlier values, and potential relationships between drug concentration and QTcF interval change. Modelling results did not identify a significant linear relationship between durvalumab concentrations and ΔQTcF. The mean change of QTcF from baseline was around 2 ms. These results indicate that durvalumab does not have an effect on QTcF and other ECG parameters in patients who have EGFR/ALK wild type NSCLC.

The PK-QT analysis supports that no QT prolongation or other ECG changes were seen for the proposed dosing regimen of 10 mg/kg QW, but cannot exclude QT prolongation at higher doses and concentrations.



CSR clinical study report; QTcF Fridericia's heart rate correction formula.
Note: Red line is the linear regression line.
Source: Figure 22, Appendix 12.1.13, ATLANTIC CSR, Module 5.3.5.2.

Figure 11: QTcF change from baseline versus durvalumab serum concentration

Table 17: ECG scheduled visit days per the study protocol

Period	Study week	ECG time point assessments[a]	PK time point assessments[b]
Screening	Day-28 to Day-1	ECG assessed	Not done
Day 1	Week 0	Pre-infusion (within 1 hr of start of the infusion) Within 30 mins post infusion 3 hours (±15 mins) post infusion	Pre-infusion End of infusion
On therapy	Week 4	Not done	Pre-infusion
On therapy Q8W	Week 8 (±7 days)	Pre-infusion	Not done
	Week 16 (±7 days)	Pre-infusion (within 1 hr of start of the infusion) Within 30 mins post infusion 3 hours (±15 mins) post infusion	Pre-infusion
	Week 24, 32 40, 48	Pre-infusion	Not done
On therapy Q12W	Week 28, 40, 52	Not done	Pre-infusion
Follow-up	30 days post last dose of study drug	ECG assessed	Not done
	90 days post last dose of study drug	Not done	PK assessed

ECG = electrocardiogram; hr = hour; mins = minutes; PK = pharmacokinetic; Q8W = every 8 weeks; Q12W = every 12 weeks.

[a] ECG assessments occurred every 8 weeks after the 8-week assessment (ie, at 16, 24, 32, 40, and 48 weeks).

[b] PK assessments occurred every 12 weeks following the 4-week assessment (ie, at 16, 28, 40, and 52 weeks).

Dose rationale

A durvalumab monotherapy dose of 10 mg/kg Q2W IV was used in Studies PACIFIC, 1108, and ATLANTIC and no other doses have been investigated in clinical trials. At the 10 mg/kg dose, no dose limiting toxicities were observed. In vitro studies have identified the target concentration, which is translated to human target exposure levels.

The 10 mg/kg dose was chosen to ensure a mean trough concentration of 50 µg/mL. The Km estimate from the Pop PK model was 0.533 mg/L (95% CI: 0.072 – 1.58 mg/L) and the target concentration of 53.3 µg/mL was based on 100 fold of the Km estimate. A target concentration of >53.3 µg/mL would in theory translate into >99 % target saturation in serum, and simulations of the proposed dose has indicated that 95.4 % of patients will have C_{trough} above 53.3 µg/mL and 78.6 % C_{trough} above >100 µg/mL.

2.4.4. Discussion on clinical pharmacology

Durvalumab is a human monoclonal antibody (mAb) that binds to programmed cell death ligand 1 (PD L1) and blocks its interaction with programmed cell death 1 (PD-1) and cluster of differentiation (CD)80 (B7.1).

The immunoassays used for durvalumab quantification were adequately specific and validated. Development of antibodies against durvalumab was measured throughout the clinical program.

The multiple-dose PK of durvalumab monotherapy has been investigated in three clinical studies. All studies included male and female patients ≥18 years of age with advanced solid tumours. The ATLANTIC and PACIFIC

studies were conducted in patients with NSCLC. No PK data are available in healthy volunteers. No single-dose PK studies with durvalumab have been conducted, which is acceptable for an anticancer product.

A Pop PK model has been developed with data from the clinical studies: Study 1108, and ATLANTIC. Linear distribution and elimination processes were assumed in the two-compartment model, including a time-varying effect on CL (using a sigmoid function) in order to characterize the decrease in CL over time. The final pop PK model included time varying clearance. The time dependent decrease in clearance of approximately 23 % is a result of change in disease state where the clearance of the immune inhibitor decreases over time as the patient's disease state improves due to less inflammation and lower protein catabolism. No safety concerns were identified related to the higher exposure.

The final population PK model of durvalumab adequately described the PK data and inter and intra individual variability of the patients in PACIFIC and Study 1108, suggesting the PK characteristics of durvalumab in NSCLC patients in PACIFIC was consistent with that in previous studies. Inter and intra- individual variability was moderate.

Several covariates were included in CL, Vc and Vp with the aim of partially explaining the inter-individual variability on durvalumab's PK. An external validation was performed including new individuals that were not used during model development. Bias and precision of model predictions were computed, showing no significant bias and 10% imprecision on model predictions. According to the results from pc-VPC, the population PK model developed is able to reproduce the observations after the administration of durvalumab. The population PK modelling was used to evaluate the need for dose adjustment in special populations based on patients' baseline characteristics. 1283 of the 1324 patients included in the pop PK analyses received the durvalumab 10 mg Q2W regimen. The final model was updated with exclusion of data <10 mg/kg given very low number of patients, removal of non-linear CL, and incorporation of time varying CL.

Non-compartmental analysis (NCA) was used to analyse the PK of multiple dose durvalumab in study 1108. Durvalumab exhibited nonlinear PK at doses <3 mg/kg Q2W, likely due to saturable target-mediated elimination of the antibody, and approached linearity at doses ≥3 mg/kg Q2W. The PK parameters estimated by popPK analysis were consistent with the non-compartmental analyses. The pharmacokinetic parameters are overall in agreement with what have previously been defined for other IgG medicinal products.

The Exposure-response evaluation was conducted with data from the PACIFIC study where all patients were treated with the same durvalumab dose of 10 mg/kg Q2W and PK sampling was sparse. The exposure parameters were simulated from the POP PK model.

Full comparability has been demonstrated between the formulation used in the clinical studies and the product to be commercialized, and no bioequivalence studies have been conducted (see section 2.2 Quality aspects).

The geometric mean steady state volume of distribution of durvalumab is 5.64 litres indicating that durvalumab is mostly confined to the blood compartment. Durvalumab, being an IgG antibody is not expected to bind to plasma proteins.

Durvalumab is a human monoclonal immunoglobulin and not subject to metabolism by P450 enzymes. No studies regarding durvalumab metabolism have been conducted and none are required in line with ICH SA6. No mass balance studies have been conducted. The primary elimination pathways of durvalumab are protein catabolism via RES or target-mediated disposition. Linear PK is seen at doses ≥ 3 mg/kg due to target-mediated drug disposition. Clearance is small (8.16 mL/h) as expected of an IgG antibody. Half-life is approximately 18 days. Steady state was achieved at approximately Week 16 after repeated dosing.

Dose proportionality is seen for durvalumab at doses ≥ 3 mg/kg. Lower doses had higher clearance likely due to target-mediated elimination. A dose above 3 mg/kg is supported.

The estimates of AUCss, Cmin,ss and Cmax,ss following durvalumab 10 mg/kg Q2W were predicted in the Pop PK analysis to be: AUCss (ug*day/mL):3816 [1562,17800], Cmax,ss (µg/mL) 364.1 [200.4,1221] and Cmin,ss (µg/mL) 160 [55.4,839.2].

Potential covariates of durvalumab pharmacokinetics were evaluated by popPK analysis. The popPK analysis indicated that body weight, sex, post-baseline ADA, CLCR, ECOG/WHO performance status, LDH level , soluble PD L1 levels, tumour type, and ALB were statistically significant covariates, but none had changed PK exposure parameters (AUC, C_{min}, C_{max}) by more than 30%. Several covariates (body weight, ADA status, albumin, UC type) modified exposure parameters around 20 %.

Durvalumab is a human monoclonal immunoglobulin and not subject to metabolism by P450 enzymes or excreted intact by the kidneys. No metabolism studies and no studies in hepatic and renal impaired patients have been conducted.

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) had no clinically significant effect on the PK of durvalumab. The effect of moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence durvalumab exposure. No dose adjustment of durvalumab is recommended for patients with hepatic impairment as no difference in exposure is expected (see sections 4.2 and 5.2 of the SmPC).

Mild (creatinine clearance (CrCL) 60 to 89 mL/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 mL/min) had no clinically significant effect on the PK of durvalumab.The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the PK of durvalumab is unknown. No dose adjustment of durvalumab is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see sections 4.2 and 5.2 of the SmPC).

Dosing of durvalumab is weight based, but no capping of dose has been suggested. The 97.5th percentile body weight was 111 kg, which is not representative of patients with extreme overweight or obesity. Individual simulation shows that dose adjustment may be necessary in these patients, and that the 8 mg/kg provide results are within the 90% range from the PopPK of the 10 mg/kg. However, the trial simulation show acceptable results, and it could be concluded that dose adjustment may not be necessary in obese patient. From a clinical perspective it is important that patients are not under-dosed. In case of over exposure in obese patients, there may be a higher risk of AEs. However, the treating physician can in such a case adjust the dose according to the guidance provided in the SmPC. Thus, it is endorsed that dose adjustment in obese patient is not necessary.

No clinical relevant effect of ECOG status, high sPD-L1 level, race or albumin on PK parameters was identified.

Patients tested positive for post-baseline ADAs had significant increased clearance, but as the prevalence was low, no obvious trend could be concluded in the Pop PK analyses. No safety issues are expected in patients and the reduction of PK exposure of less than 30% compared to a typical patient is not expected to be clinically relevant.

Durvalumab is a monoclonal antibody and is not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways. The use of systemic corticosteroids or immunosuppressants before starting durvalumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of durvalumab. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions (see Section 4.5 of the SmPC).

In study 1108, target engagement was assessed through measurement of reduction in levels of free soluble PD-L1 (sPDL1) in serum as a peripheral pharmacodynamics marker. No relationship between sPD-L1 suppression and clinical response has been demonstrated and sPD-L1 is not a useful biomarker for clinical efficacy. An additional objective was to explore CD8+Ki67+ T cells as potential markers of the biological activity of PD-L1 blockade by durvalumab. Biomarkers and translational research will be investigated further in durvalumab NSCLC development programmes.

Exposure-efficacy relationship has been evaluated against AUC_{ss}, C_{minss} and C_{maxss}. No trend was observed between C_{maxss} and PFS and this endpoint was discarded. AUC_{ss} and C_{minss} were slightly correlated to PFS.

A relevant change in exposure parameters (AUC_{ss}, C_{maxss} and C_{minss}) was observed for several covariates: body weight, ADA, UC tumour type and albumin. A 30% threshold was established in order to consider clinical relevance, but those covariates influenced nearly 20% AUC_{ss} and C_{minss} values. Considering those parameters (AUC_{ss} and C_{minss}) were established as significant exposure endpoints during exposure-efficacy analysis, model predictions in extreme individuals would be necessary in order to assess how the lack of clinical relevance would affect PFS prolongation.

No trend were observed between any exposure PK metric (AUCss, Cmaxss and Cminss) and the selected grade 3 and 4 adverse events.

No thorough QTc study has been conducted, but an ECG study was conducted in cohort 2 of the ATLANTIC study. In the ATLANTIC study all patients were treated with the same durvalumab dose 10 mg/kg Q2W, and PK was measured in one post-dose sample and a few predose trough samples. PK-QT relationship was assessed based on the common visits that both ECG and PK were measured, ie. Week 0 predose, Week 0 end of infusion, Week 16 predose and Week 40 predose. The PK-QT analysis supports that no QT prolongation is seen for the proposed dosing regimen of 10 mg/kg Q2W.

The proposed durvalumab monotherapy dose 10 mg/kg has been used in the clinical studies, but overall, uncertainties regarding the optimal dose have been identified. It is agreed that most patients will have an exposure that result in almost complete target saturation in serum, and it is also acknowledged that it is not feasible to show direct assessment of target saturation in tumour. However, the applicant has provided reasonable evidence that the target is expected to be saturated with the 10 mg/kg.

Durvalumab has a low immunogenic potential. The reduction in exposure observed in ADA positive patients is < 30 % and not expected to haveclinically relevant impact on efficacy.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of durvalumab has overall been adequately described, but few issues remain to be addressed.

No dose adjustments have been proposed to special populations, such as renal impaired, hepatic impaired, elderly and, extreme body weights according to the claimed clinical relevance threshold of 30%. Dose is

weight based with no capping.

Durvalumab has a low immunogenic potential, but data are yet limited. Durvalumab clearance is increased in ADA positive patients. No safety issues are expected in patients with ADAs but lack of efficacy for the individual patient could be a risk.

The pharmacodynamics of durvalumab is well understood. Durvalumab does not have ADCC or CDC activity due to the triple mutation in the Fc domain, and durvalumab is not expected to cause cytokine release.

The applicant is recommended to further investigate biomarkers to identify patients likely to respond to durvalumab treatment.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response study was conducted.

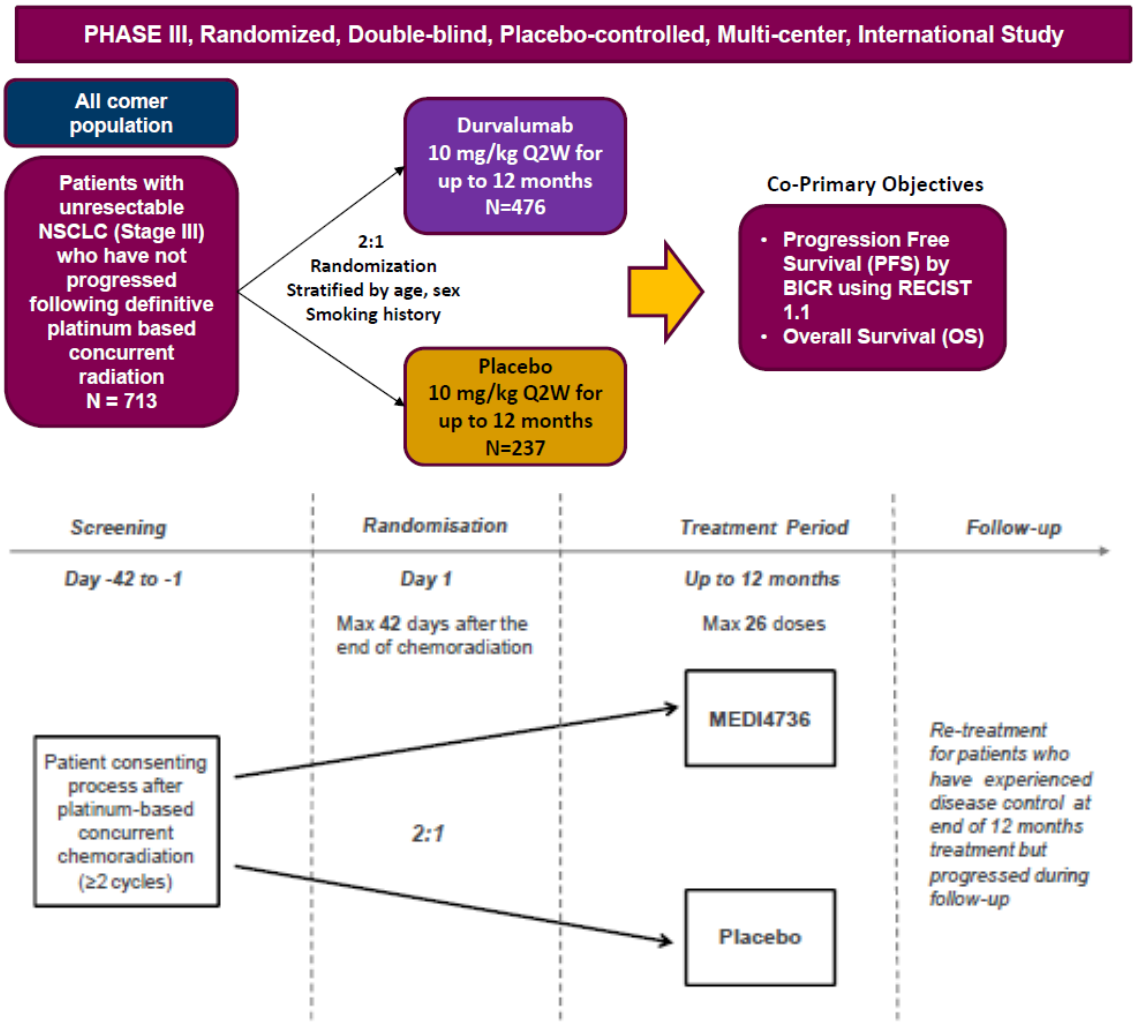
The recommended dosage of durvalumab is 10 mg/kg administered as an intravenous infusion over 60 minutes Q2W until disease progression or unacceptable toxicity. This dosing regimen is supported by a dataset from clinical and nonclinical trials. The key features are:

- Tolerability: no dose-limiting toxicity were observed up to a durvalumab dose of 10 mg/kg Q2W or 20 mg/kg Q4W (Study ID 302833, VMM0008, VMM0033: non clinical part)
- Achieves target exposure based on clinical PK/PD: durvalumab PK approached linearity at ≥3 mg/kg Q2W dose (trough concentration approximately 50 μg/mL), indicating complete target saturation. Population PK simulations indicated that following a durvalumab 10 mg/kg Q2W regimen, >99% of the patients will reach the target trough concentration of ≥50 μg/mL to achieve complete target saturation.
- Achieves target exposure based on nonclinical efficacy models: durvalumab 10 mg/kg Q2W achieves a median trough concentration of >100 μg/mL (identified as a target concentration of durvalumab that yielded maximum tumor growth inhibition in mouse models).
- The exposure-efficacy analysis based on PACIFIC indicated a longer PFS in durvalumab-treated patients (all exposure quartiles) compared to the placebo group. A slight trend suggesting longer PFS with higher durvalumab exposure at steady state is likely due to the PK being confounded by the slight decrease in durvalumab CL in patients benefitting from the treatment.
- No exposure-safety relationship was observed in the PACIFIC safety population following 10 mg/kg Q2W durvalumab.
- A 2.9% (45/1,570 patients) ADA incidence was observed following durvalumab 10 mg/kg Q2W. There is no clear evidence that the presence of ADAs or nAbs has any potential impact on safety and population PK analysis showed that the presence of ADA had no clinically relevant effect on durvalumab PK.

2.5.2. Main study(ies)

PACIFIC: 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.

Methods



Max maximum; MEDI4736 durvalumab

Study Participants

Inclusion criteria

For inclusion in the study, patients had to fulfill all of the following criteria:

1. Provision of signed, written, and dated informed consent prior to any study-specific procedures

2. Male or female aged 18 years or older

3. Patients must have histologically or cytologically documented locally advanced, unresectable Stage III NSCLC disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology).

4. Patients must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy, which must have been completed within 1 to 42 days prior to the first dose of study treatment in the study.

- The platinum-based chemotherapy regimen must have contained 1 of the following agents: etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed, according to the local standard-of-care regimens.
- The final chemotherapy cycle must have ended prior to or concurrently with the final dose of radiation. Consolidation chemotherapy after radiation was not permitted, but administration of chemotherapy prior to concurrent chemoradiation was acceptable.

5. Patients must have not progressed following definitive, platinum-based, cCRT.

6. Tumour sample requirements included the following:

- Provision of an archived tumour tissue block (or at least 10 newly cut unstained slides), where such samples existed in a quantity sufficient to allow for analysis (refer to Section 6.7.1 of the CSP and the Laboratory Manual for details).
- A recent (not more than 3 months) tumour biopsy (taken following completion of the most recent therapy) was an optional requirement, provided that a biopsy procedure was technically feasible and the procedure was not associated with unacceptable clinical risk.

7. Life expectancy at least 12 weeks at Day 1

8. World Health Organization (WHO) performance status of 0 or 1.

9. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women were considered postmenopausal if they were amenorrheic for 12 months without an alternative medical cause.

10. Adequate organ and marrow function.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Involvement in the planning and/or conduct of the study

2. Either of the following:

- Previous drug assignment in the present study

or

- Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment group assignment.

3. Participation in another clinical study with an investigational product during the last 4 weeks

4. Concurrent enrollment in another clinical study, unless it was an observational (non-interventional) clinical study or the follow-up period of an interventional study

5. Mixed small cell and NSCLC histology

6. Patients who received sequential chemoradiation therapy for locally advanced NSCLC

7. Patients with locally advanced NSCLC who had progressed following definitive platinum-based cCRT

8. Receipt of any immunotherapy or investigational drug within 4 weeks prior to the first dose of study treatment and, in the case of monoclonal antibodies, 6 weeks prior to the first dose of study treatment

9. Current or prior use of immunosuppressive medication within 28 days before the first dose of study treatment.

10. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody

11. Any unresolved toxicity Common Terminology Criteria for Adverse Event (CTCAE Version 4) greater than Grade 2 from the prior chemoradiation therapy.

12. Patients with at least Grade 2 pneumonitis from prior chemoradiation therapy

13. Any prior immune-related AE of Grade 3 or greater while receiving any previous immunotherapy agent or any unresolved immune-related AE greater than Grade 1

14. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment (see CSP Amendment 2)

15. Recent major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access) that would have prevented administration of study treatment

16. Active or prior documented autoimmune disease within the past 2 years.

17. Active or prior documented inflammatory bowel disease (eg, Crohn’s disease, ulcerative colitis)

18. History of primary immunodeficiency

19. History of allogeneic organ transplantation

20. History of hypersensitivity to durvalumab or any excipient

21. Mean QT interval corrected for heart rate at least 470 ms calculated from 3 electrocardiograms (ECGs) using Bazett’s Correction

22. Uncontrolled intercurrent illness

23. Active infection of tuberculosis, as determined by clinical signs and symptoms

24. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study treatment

25. History of another primary malignancy.

26. Female patients who were pregnant or breast-feeding or male or female patients of reproductive potential who were not employing an effective method of birth control.

Treatments

Table 18: Details of study treatments

Study Treatment	Dosage form and strength	Manufacturer	Batch number
Durvalumab	200 mg/vial, for intravenous infusion after dilution to 50 mg/mL	Sponsor	CC00004, BM0079, BT0026, CB0056, CF0171, CH0127, CJ0036, CJ0098, CK0194, CM0063
Placebo	Matching saline solution for intravenous infusion	To be sourced locally	N/A

N/A not applicable

The study treatment was to be discontinued prior to 12 months if there was confirmed progression of disease (PD), unacceptable toxicity, initiation of alternative cancer therapy, or withdrawal of consent. Patients who achieved and maintained disease control (i.e., CR, PR, or SD) through to the end of the 12-month study treatment period could re-start treatment with the study drug upon evidence of disease progression during follow-up.

Objectives

Primary objective

To assess the efficacy of Durvalumab treatment compared with placebo in terms of OS and PFS.

Secondary objectives

- To further assess the efficacy of durvalumab compared with placebo in terms of: OS24, ORR, DoR, APF12, APF18, and TTDM.
- To assess symptoms and health-related quality of life in patients treated with MEDI4736 compared with placebo using EORTC QLQ-C30 v3 and LC13.

Outcomes/endpoints

The pivotal PACIFIC study has 2 primary efficacy endpoints: progression free survival (PFS) and overall survival (OS).

Primary endpoints

PFS defined as the time from the date of randomization until the first date of objective progression (using BICR assessments according to RECIST 1.1) or death.

OS defined as the time from the date of randomization until death due to any cause.

Secondary endpoints

- Estimates of survival (24m) and PFS (12m and 24m) at different time points from randomisation.
- TTDM using BICR assessments according to RECIST 1.1 – defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis.
- ORR using BICR assessments according to RECIST 1.1– defined as the number (%) of patients with at least 1 visit response of CR or PR.

- DoR using BICR assessments according to RECIST 1.1 – defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression, whichever was earlier.
- PFS2 as defined by local standard clinical practice
- 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 PS Scores were also to be assessed.

PD-L1 expression in tumor tissue samples was assessed using a proprietary PD-L1 immunohistochemistry assay SP263; Ventana Medical Systems, Inc. (Midha et al 2016). Epidermal growth factor receptor (EGFR) mutations were assessed using a central laboratory (QIAGEN Therascreen) for those patients who did not have local laboratory results. The anaplastic lymphoma kinase (ALK) gene rearrangements were collected in this study.

Sample size

Three interim analyses (one for PFS and two for OS) were planned. In total, the sample size was estimated to be approximately 702 patients to obtain 491 death events in the ITT population (70% maturity). The primary PFS analysis data cut-off will occur when it is expected that 458 PFS events have occurred (65% maturity). If the true PFS HR is 0.67, the study will provide 95% power to demonstrate a statistically significant difference for PFS with a 2-sided significance level of 2.5% in the ITT population; this translates to a 5-month benefit in median PFS over 10 months on placebo if PFS is exponentially distributedThe smallest treatment difference that would be statistically significant is a HR of 0.80.

The primary OS analysis data cut-off will occur when it is expected that 491 OS events have occurred (70% maturity). If the true OS HR is 0.73, this number of death events will provide at least 85% power to demonstrate a statistically significant difference for OS, assuming a 2.5% 2-sided significance level in the ITT population; this translates to an 8-month benefit in median OS over 22 months on placebo if OS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.81.

Randomisation

Randomization is stratified by: age at randomisation (<65 vs ≥65 years of age), sex (male vs female), and smoking history (smoker vs non-smoker). Patients must not have progressed following definitive, platinum-based, concurrent chemoradiation therapy; radiation therapy must be completed within 1 to 42 days prior to randomisation in the study (the last dose of radiation therapy is defined as the day of the last radiation treatment session). For patients who were recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy.

The actual treatment given to patients was determined by the randomization scheme in the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). One randomization list was produced for each of the randomization strata, and all study centres used the same list in order to minimize any imbalance in the number of patients assigned to each treatment group. At Visit 2, patients who satisfied all entry criteria were randomized to either durvalumab (10 mg/kg) or placebo in a 2:1 ratio.

Blinding (masking)

This is a double-blinded study.

Statistical methods

The overall 5% type 1 error is split between the two primary endpoints OS and PFS. An alpha level of 2.5% is allocated to OS analysis and an alpha level of 2.5% is allocated to the PFS analysis. Several interim analyses were planned (see Figure xx below). The 2.5% alpha level allocated to PFS and to OS is controlled at the interim and primary time points by using the Lan DeMets (Lan and DeMets 1983) spending function. The family wise error rate (FWER) is controlled at 5% for PFS and OS according to Ye et al 2012. In this procedure, the testing will start from PFS, if the testing for PFS is significant at the alpha level specified in Figure xx at either interim or primary analysis the full 2.5% alpha level for PFS can be propagated to the testing of OS, which means that the OS will be tested at an overall alpha level of 5%. The alpha level for the interim analyses of OS will not be changed but the alpha level for the primary analysis of OS will be recalculated based on 5% alpha level overall with interim alpha levels as specified in Figure xx. OS24 and ORR will not be tested unless the null hypotheses for both PFS and OS are rejected. ORR will only be tested after the null hypothesis of PFS, OS, and OS24 are all rejected and ORR will be tested at a 5% level. The FWER for PFS, OS, and OS24 is also strongly controlled at 5% due to the fix-sequence testing nature and according to Glimm et al 2009. Finally, the FWER is still strongly controlled after adding the fix-sequence testing of ORR. So the FWER is strongly controlled at 5% for the testing of all four endpoints. In the presented analyses, the alpha level was derived based upon the exact number of PFS and OS events using the Lan and DeMets approach (PFS significance level = 1.1035 %; OS significance level =0.274%).

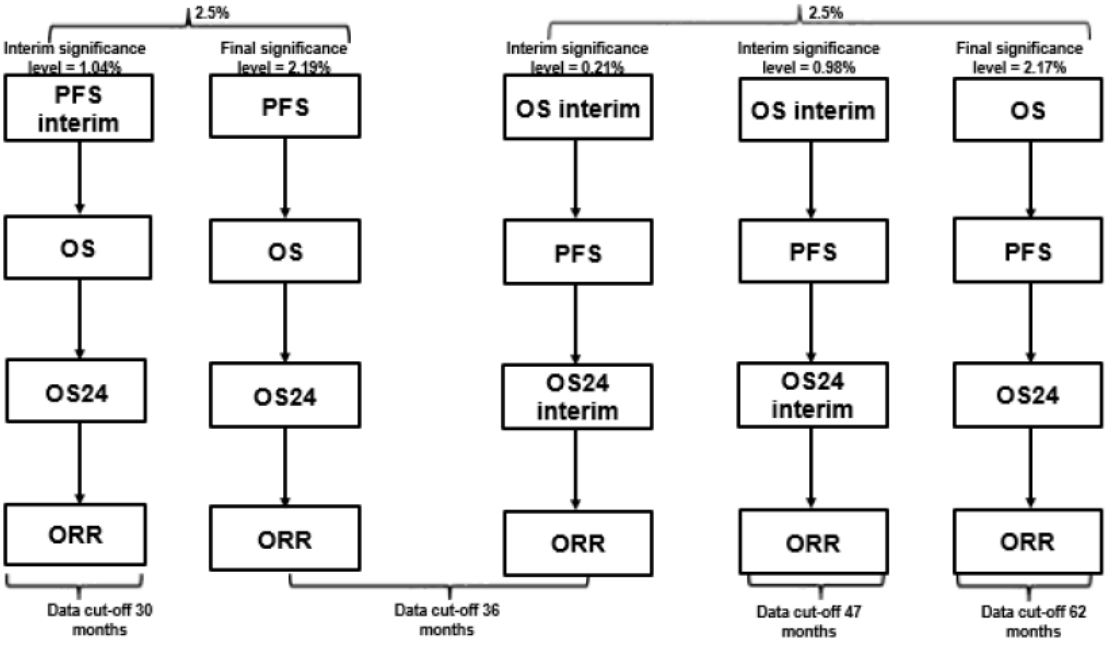
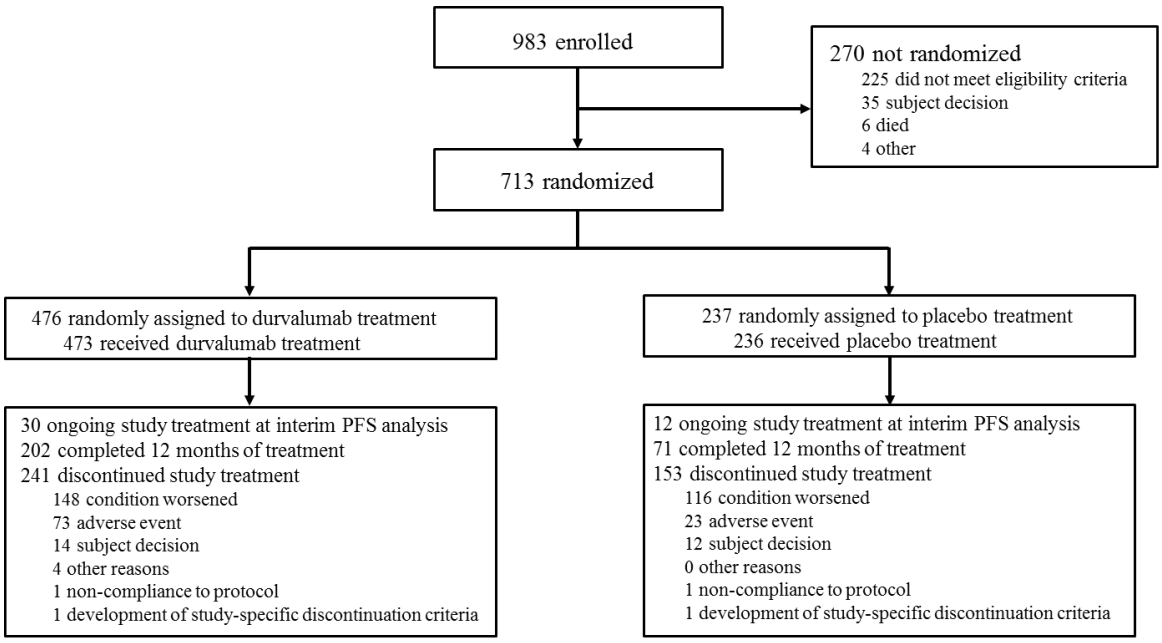


Figure 12:Multiple testing procedures for controlling the type 1 error rate

Results

Participant flow



PFS Progression-free survival.
Data source: Table 11.1.1, PACIFIC interim CSR, Module 5.3.5.1.
Figure 13: Patient disposition – All patients (PACIFIC) (Data cut-off: 13 February 2017)

Table 19: 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 ongoing study treatment at data cut-off date [c]	30 (6.3)	12 (5.1)	42 (5.9)
Patients who completed 12 months of treatment [c,d]	202 (42.7)	71 (30.1)	273 (38.5)
Patients who discontinued study treatment [c]	241 (51.0)	153 (64.8)	394 (55.6)
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)	116 (49.2)	264 (37.2)
Development of study specific discontinuation criteria	1 (0.2)	1 (0.4)	2 (0.3)
Other [f]	4 (0.8)	0	4 (0.6)
Patients ongoing study at data cut-off date [c]	346 (73.2)	144 (61.0)	490 (69.1)
Patients who completed study [c,e]	6 (1.3)	0	6 (0.8)
Patients who terminated study [c]	121 (25.6)	92 (39.0)	213 (30.0)

[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] The status of these 6 patients is ongoing in the study and they have been confirmed to be in the overall survival follow-up at the time of data cut-off date; however, they were incorrectly assigned as completed due to data entry issues on the study termination form.
[f] Other reasons for discontinuation included investigator decision due to the condition of the patient and general health deterioration, investigator decision due to excessive alcohol consumption, investigator decision due to patient hospitalisation, and death

Recruitment

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. The study is being conducted and managed by Quintiles, a contract research organization. Central laboratory facilities are being used in the study. First patient randomized: 09 May 2014. Last patient randomized: 22 April 2016. Data cut-off date: 13 February 2017 (study ongoing).

Conduct of the study

Protocol amendments:

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 were introduced by means of 4 protocol amendments. Main changes are summarized below:

- Amendment 1 (10 June 2014):

- Addition of text to indicate study treatment should be discontinued if there is confirmed progression of disease following a previous response (PR or CR) to study treatment.

- Amendment 2 (8 August 2014):

- Addition of an interim analysis for PFS

- Added secondary objectives and outcome measures for time to relapse and time to death or distant metastasis

- Amendment 3 (18 February 2015):

- The protocol was updated to allow patients who had completed radiation therapy from within 14 days from their last dose to within 42 days

- Amendment 4 (11 February 2016):

- Removal of time to relapse from study assessments.

- "Investigator site" assessments revised to "BICR" assessments

- Additional OS interim analysis added to determine if the results show superiority in OS

- The alpha allocation between PFS and OS has been changed to 2.5% and 2.5% from 0.5% and 4.5%, respectively, so that the statistical test can detect a smaller yet clinical meaningful treatment effect on PFS

- The timing of PFS interim analysis was changed to a later time point when more PFS events have occurred

- The Type I error was split between the 2 two primary endpoints, OS and PFS. The alpha level for OS and PFS was changed from 4.5% and 0.5%, respectively, to 2.5% equally. Additional adjustments were made with respect to this new approach in the multiple testing procedures for controlling the Type I error rate.

Protocol deviations

Table 20 Important protocol deviations (all patients)

	Number (%) of patients		
Important protocol deviations	**Durvalumab**	**Placebo**	**Total**
Number of patients with at least 1 important deviation	**13 (2.7)**	**8 (3.4)**	**21 (2.9)**
Eligibility and Entry Criteria[a]	**10 (2.1)**	**2 (0.8)**	**12 (1.7)**
Patients with Stage IV NSCLC at study entry (deviation from Inclusion #3)	4 (0.8)	0	4 (0.6)
Patients who progressed following definitive, platinum-based cCRT (deviation from Inclusion #5)	2 (0.4)	0	2 (0.3)
Patients who received a total dose of radiation <54 Gy or >66 Gy to be randomized as part of the chemoradiation therapy (Inclusion #4) [b]	3 (0.6)	1 (0.4)	4 (0.6)
Patients who receive sequential chemoradiation therapy for locally advanced NSCLC (deviation from Exclusion #6)	0	1 (0.4)	1 (0.1)
Did not receive platinum agent (deviation from Inclusion #4)	3 (0.6)	1 (0.4)	4 (0.6)
Efficacy Criteria	**0**	**3 (1.3)**	**3 (0.4)**
Baseline RECIST 1.1 scan >42 days before randomization	0	3 (1.3)	3 (0.4)
Study Treatment Compliance	**3 (0.6)**	**3 (1.3)**	**6 (0.8)**
Patients randomized but who did not receive durvalumab/matching placebo	3 (0.6)	1 (0.4)	4 (0.6)
Treatment received differs from the randomized treatment [c]	0	2 (0.8)	2 (0.3)

Baseline data

Table 21. Demographic characteristics and nicotine use (full analysis set)

Demographic characteristic and nicotine use	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Age (years)			
n	476	237	713
Mean	63.0	62.6	62.9
Standard deviation	8.66	9.64	8.99
Median	64.0	64.0	64.0
Min	31	23	23
Max	84	90	90
Age group (years), n (%)			
<50	30 (6.3)	22 (9.3)	52 (7.3)
≥50-<65	231 (48.5)	108 (45.6)	339 (47.5)
≥65-<75	178 (37.4)	88 (37.1)	266 (37.3)
≥75	37 (7.8)	19 (8.0)	56 (7.9)
Sex, n (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race, n (%)			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black or African American	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.4)	2 (0.3)
American Indian or Alaska Native	4 (0.8)	5 (2.1)	9 (1.3)
Other	1 (0.2)	0	1 (0.1)
Missing	1 (0.2)	0	1 (0.1)
Ethnic group, n (%)			
Hispanic or Latino	35 (7.4)	20 (8.4)	55 (7.7)
Not Hispanic or Latino	439 (92.2)	216 (91.1)	655 (91.9)
Missing	2 (0.4)	1 (0.4)	3 (0.4)
Smoking history, n (%)			
Non-smoker	43 (9.0)	21 (8.9)	64 (9.0)
Smoker [a]	433 (91.0)	216 (91.1)	649 (91.0)
Ex-smoker	354 (74.4)	178 (75.1)	532 (74.6)
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)

[a] Patients who checked options cigarettes, cigarillos, cigars, pipe tobacco, or tobacco for smoking are considered smokers.

Min minimum; Max maximum.

Source: Table 11.1.4 and Table 11.1.17

Table 22. Disease characteristics at baseline (full analysis set)

Disease Characteristic	Number (%) of patients MEDI4736 (N=476)	Placebo (N=237)	Total (N=713)
WHO performance status			
(0) Normal activity	234 (49.2)	114 (48.1)	348 (48.8)
(1) Restricted activity	240 (50.4)	122 (51.5)	362 (50.8)
(2) In bed <= 50% of the time	0	0	0
(3) In bed > 50% of the time	0	0	0
(4) 100% bedridden	0	0	0
Missing	2 (0.4)	1 (0.4)	3 (0.4)
Primary tumour location			
Lung	476 (100.0)	237 (100.0)	713 (100.0)
Histology type			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Squamous cell carcinoma (NOS)	221 (46.4)	101 (42.6)	322 (45.2)
Squamous cell carcinoma: Spindle cell	3 (0.6)	1 (0.4)	4 (0.6)
Non-squamous	252 (52.9)	135 (57.0)	387 (54.3)
Adenocarcinoma (NOS)	200 (42.0)	106 (44.7)	306 (42.9)
Adenocarcinoma: Acinar	5 (1.1)	3 (1.3)	8 (1.1)
Adenocarcinoma: Bronchiolo-Alveolar	6 (1.3)	1 (0.4)	7 (1.0)
Adenocarcinoma: Papillary	3 (0.6)	3 (1.3)	6 (0.8)
Adenocarcinoma: Solid With Mucous Formation	2 (0.4)	0	2 (0.3)
Adenosquamous carcinoma	3 (0.6)	6 (2.5)	9 (1.3)
Large cell carcinoma (NOS)	14 (2.9)	5 (2.1)	19 (2.7)
Other	19 (4.0)	11 (4.6)	30 (4.2)
AJCC Staging			
IA	1 (0.2)	0	1 (0.1)
IB	0	2 (0.8)	2 (0.3)
IIA	3 (0.6)	1 (0.4)	4 (0.6)
IIB	4 (0.8)	2 (0.8)	6 (0.8)
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
IV	4 (0.8)	0	4 (0.6)
Best response to previous therapy [a]			
Complete Response	9 (1.9)	7 (3.0)	16 (2.2)
Partial Response	232 (48.7)	111 (46.8)	343 (48.1)
Stable Disease	222 (46.6)	114 (48.1)	336 (47.1)
Progression	2 (0.4)	0	2 (0.3)
Non-Evaluable	9 (1.9)	4 (1.7)	13 (1.8)
Not Applicable	2 (0.4)	1 (0.4)	3 (0.4)
Overall disease classification			
Metastatic [b]	0	0	0
Locally advanced [c]	449 (94.3)	220 (92.8)	669 (93.8)
Missing	27 (5.7)	17 (7.2)	44 (6.2)
EGFR			
Negative	315 (66.2)	165 (69.6)	480 (67.3)
Positive	29 (6.1)	14 (5.9)	43 (6.0)
Unknown [d]	132 (27.7)	58 (24.5)	190 (26.6)
PD-L1			
<25%	187 (39.3)	105 (44.3)	292 (41.0)
>=25%	115 (24.2)	44 (18.6)	159 (22.3)
Unknown [d]	174 (36.6)	88 (37.1)	262 (36.7)

WHO = World Health Organization, AJCC = American Joint Committee on Cancer.
[a] Best response to prior therapy is based on the last therapy prior to entering the study.
[b] Metastatic disease - patient has any metastatic site of disease.
[c] Locally advanced - patient has only locally advanced sites of disease.
[d] Unknown = No sample collected or no valid test result

Table 23: Extent of disease at baseline (Full analysis set).

Extent of disease	Site of disease	Number(%) of patients [a] MEDI4736 (N=476)	Placebo (N=237)	Total (N=713)
Locally advanced	Total number of patients	449 (94.3)	220 (92.8)	669 (93.8)
	Cardiovascular	40 (8.9)	22 (10.0)	62 (9.3)
	Pleural Effusion	6 (1.3)	1 (0.5)	7 (1.0)
	Lymph Nodes	437 (97.3)	214 (97.3)	651 (97.3)
	Pericardial Effusion	2 (0.4)	0	2 (0.3)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Table 24: Primary tumour location and TNM classification at baseline (Full analysis set).

Extent of disease / Site	TNM class	Number (%) of patients MEDI4736 (N=476)	Placebo (N=237)	Total (N=713)
Primary tumour	T1	0	1 (0.4)	1 (0.1)
	T1a	33 (6.9)	13 (5.5)	46 (6.5)
	T1b	37 (7.8)	18 (7.6)	55 (7.7)
	T2	1 (0.2)	0	1 (0.1)
	T2a	103 (21.6)	52 (21.9)	155 (21.7)
	T2b	43 (9.0)	18 (7.6)	61 (8.6)
	T3	111 (23.3)	46 (19.4)	157 (22.0)
	T4	140 (29.4)	85 (35.9)	225 (31.6)
	TX	8 (1.7)	4 (1.7)	12 (1.7)
	Missing	0	0	0
Regional lymph nodes	N0	34 (7.1)	20 (8.4)	54 (7.6)
	N1	29 (6.1)	19 (8.0)	48 (6.7)
	N2	271 (56.9)	134 (56.5)	405 (56.8)
	N3	142 (29.8)	63 (26.6)	205 (28.8)
	NX	0	1 (0.4)	1 (0.1)
	Missing	0	0	0
Distant metastasis	M0	472 (99.2)	236 (99.6)	708 (99.3)
	M1a	3 (0.6)	0	3 (0.4)
	M1b	1 (0.2)	0	1 (0.1)
	Missing	0	1 (0.4)	1 (0.1)

Table 25 Prior anticancer therapy

Prior anticancer therapy	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Radiotherapy, n(%) [a]	**476 (100.0)**	**237 (100.0)**	**713 (100.0)**
Definitive	476 (100.0)	237 (100.0)	713 (100.0)
Total Radiation Dose (Gy) [b]			
n	475	236	711
Mean	62.5	63.0	62.7
Standard deviation	3.50	3.37	3.46
Median	61.2	63.0	61.5
Range	45.0 - 70.2	54.0 - 70.2	45.0 - 70.2
Total Radiation Dose (Gy) [b]			
<54	3 (0.6)	0	3 (0.4)
≥54 - ≤66	442 (92.9)	217 (91.6)	659 (92.4)
>66 - ≤74	30 (6.3)	19 (8.0)	49 (6.9)
>74	0	0	0
Missing [c]	1 (0.2)	1 (0.4)	2 (0.3)
Cytotoxic Chemotherapy [a]	**476 (100.0)**	**237 (100.0)**	**713 (100.0)**
Adjuvant	3 (0.6)	1 (0.4)	4 (0.6)
Neo-Adjuvant (Induction Chemotherapy)	123 (25.8)	68 (28.7)	191 (26.8)
Definitive	475 (99.8)	236 (99.6)	711 (99.7)
Not Applicable [d]	1 (0.2)	0	1 (0.1)

a Counts of the unique number of patients that received prior RT or cytotoxic chemotherapy.
b Total RT dose was calculated through medical review of the prior RT case report for, data.
c For the 2 patients in the missing row, the biological effective dose could not be calculated. This primarily occurred because we neither collected nor had access to their RT treatment planning data required to calculate a biological effective dose. One patient received a single 8Gy fraction to gross disease followed by a course of conventionally fractioned external beam RT (receiving 52Gy in 26 fractions). Whereas the other patient received a pre-operative course of RT comprising 50.6Gy delivered in 23 fractions followed post-operatively by a total dose of 40Gy, delivered in 8 fractions, to the residual tumor.
d Data entry error in the case report form. The data indicate the patient received neo-adjuvant (induction chemotherapy). Two patients also received high dose-rate brachytherapy before having gone on to receive a radical dose of conventionally fractionated external beam RT.

Numbers analysed

Table 26.Analysis sets

	Number of patients		
	Durvalumab	Placebo	Total
Patients randomized	476	237	713
Patients included in full analysis set	476	237	713
Patients included in safety analysis set [a]	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
Patients included in PK analysis set	473		473
Patients excluded from PK analysis set	3		3
Did not receive at least 1 dose of durvalumab	3		3

[a]Two patients 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 post-unblinding; the integrity of the blind remained intact.
Full analysis set - all randomized patients analyzed on an ITT basis.
Safety analysis set - all patients who received at least 1 dose of randomized study treatment, durvalumab or placebo.
PK analysis set - all patients who receive at least 1 dose of durvalumab per the protocol, for whom any post-dose data are available and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The 2 patients randomized to placebo group received 1 dose of durvalumab and were excluded from the PK analysis due to protocol violation.

ITT intent-to-treat; PK pharmacokinetic(s).

Outcomes and estimation

Primary endpoint: PFS by BICR

Table 27 Progression-free survival (BICR, RECIST 1.1) – Full analysis set

Progression status	Durvalumab (N=476)	Placebo (N=237)
Total events[a], n (%)	**214 (45.0)**	**157 (66.2)**
RECIST progression	189 (39.7)	140 (59.1)
Death in the absence of progression	25 (5.3)	17 (7.2)
Censored patients, n (%)	**262 (55.0)**	**80 (33.8)**
Median progression-free survival (months)[b]	**16.8**	**5.6**
95% CI for median progression-free survival	13.0, 18.1	4.6, 7.8
Progression-free survival rate at 12 months (%)[b]	**55.9**	**35.3**
95% CI for progression-free survival rate at 12 months	51.0, 60.4	29.0, 41.7
Progression-free survival rate at 18 months (%)[b]	**44.2**	**27.0**
95% CI for progression-free survival rate at 18 months	37.7, 50.5	19.9, 34.5
Hazard ratio[c]	0.52	
98.9% CI for hazard ratio[c, d]	0.39, 0.70	
95% CI for hazard ratio[c]	0.42, 0.65	
2-sided p-value[c]	<0.0001	

BICR Blinded Independent Central Review; CI Confidence interval; CSR clinical study report; RECIST Response Evaluation Criteria In Solid Tumors.

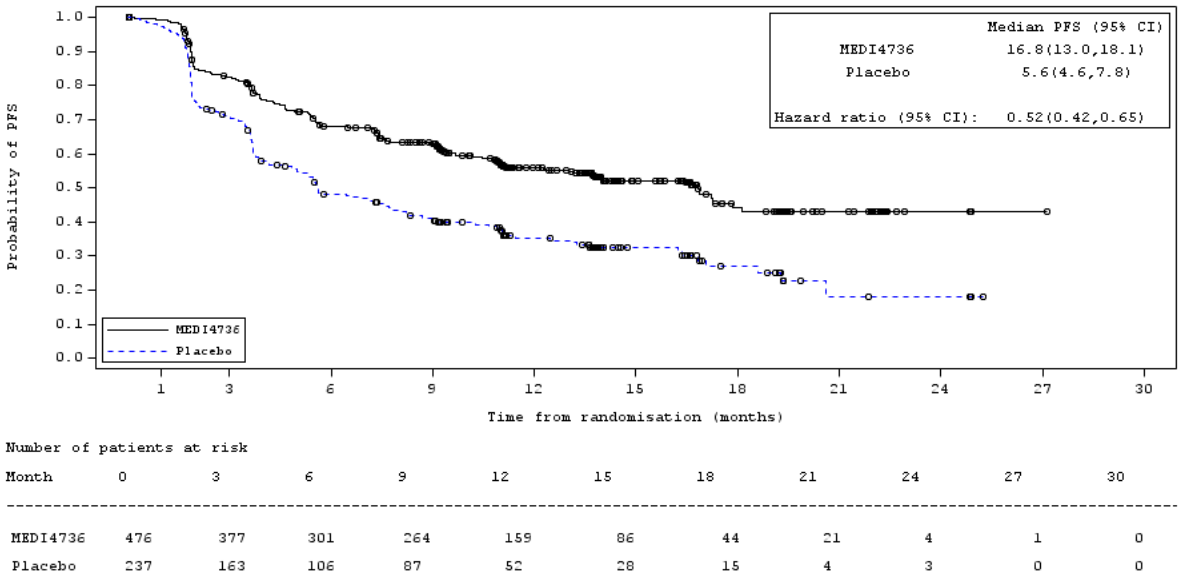
[a] Patients who have not progressed or died, or who progress or die after two or more missed visits, are censored at the latest non-missing RECIST assessment, or day 1 if there are no non-missing visits. Patients who have no non-missing visits or do not have baseline data will be censored at study day 1 unless they die within 2 visits of baseline.

[b] Calculated using Kaplan-Meier technique.

[c] The analysis was performed using a stratified log rank test adjusting for age at randomisation (<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 PFS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function.

Data source: Table 11.2.2.1, PACIFIC interim CSR, Module 5.3.5.1.



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30
MEDI4736	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

BICR Blinded Independent Central Review; CI Confidence interval; PFS Progression-free survival; RECIST

Figure 14 Progression-free survival (BICR, RECIST 1.1) Kaplan-Meier Plot – Full analysis set

Sensitivity analyses

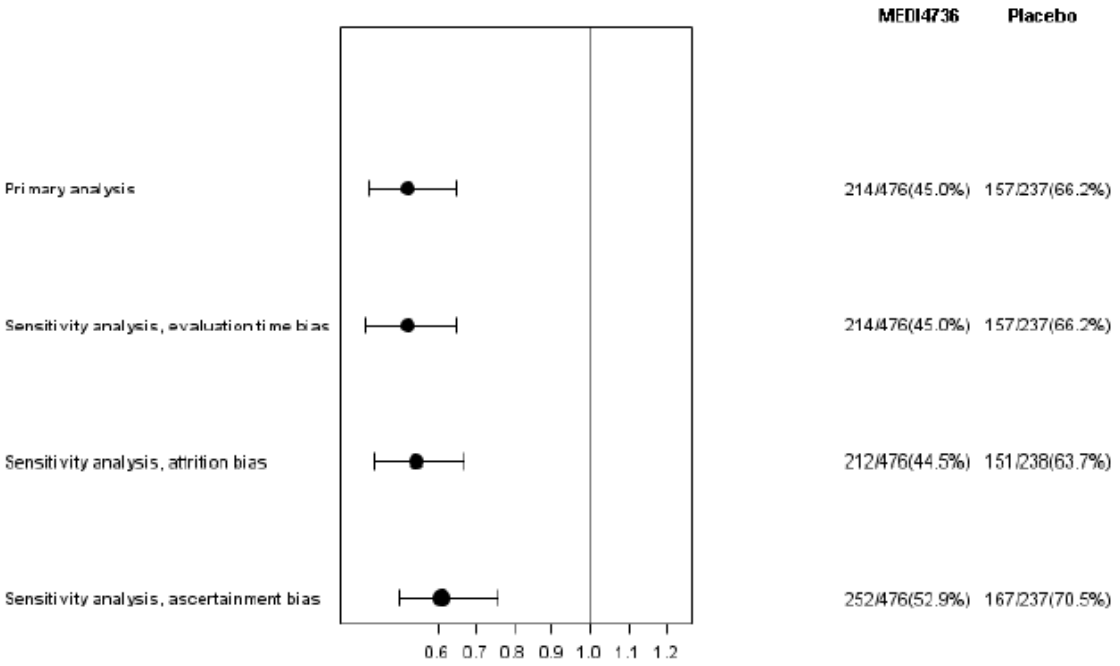
Analyses were conducted to assess the robustness of the PFS effect to the potential source biases in PFS.

An additional 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. 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 of these sensitivity analyses of PFS were consistent with those of the primary analyses.

Another sensitivity analysis assessing the impact of alternative censoring rule of censoring patients at the last evaluable RECIST 1.1 assessment (instead of the last RECIST 1.1 assessment) also showed consistent PFS effect (HR: 0.52; 95% CI: 0.41, 0.65) with the primary analysis where patients were censored at the last non-missing RECIST 1.1 assessment.



Hazard ratio (durvalumab: placebo) and 95% CI. HR <1 implies a lower risk of progression for durvalumab.
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.
Size of circle is proportional to the number of events.
CI confidence interval; HR hazard ratio; MEDI4736 durvalumab; PFS progression-free survival.
Source: Figure 11.2.1.8

Figure 15: Forest plot of PFS by primary and sensitivity analyses (full analysis set)

Table 28: PFS based on investigator assessments according to RECIST 1.1 (full analysis set)

Progression status	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n (%)	252 (52.9)	167 (70.5)
RECIST 1.1 progression	226 (47.5)	154 (65.0)
Death in the absence of progression	26 (5.5)	13 (5.5)
Censored patients, n (%)	224 (47.1)	70 (29.5)
Censored RECIST 1.1 progression [b]	0	0
Censored death [c]	3 (0.6)	1 (0.4)
Progression-free at time of analysis	203 (42.6)	64 (27.0)
Lost to follow-up	0	0
Withdrawn consent	11 (2.3)	3 (1.3)
Discontinued study	7 (1.5)	2 (0.8)
Median PFS (months) [d]	13.6	7.4
95% CI for median PFS [d]	11.0, 14.0	5.6, 9.0
PFS rate at 12 months (%) [d]	52.6	34.8
95% CI for PFS rate at 12 months [d]	47.8, 57.1	28.7, 41.1
PFS rate at 18 months (%) [d]	37.4	23.5
95% CI for PFS rate at 18 months [d]	31.7, 43.1	17.2, 30.3
Hazard ratio [e]	0.61	
95% CI for hazard ratio [e]	0.50, 0.76	
2-sided p-value [e]	<0.0001	

a Patients who have not progressed or died, or who progress or die after 2 or more missed visits, are censored at the latest non-missing RECIST 1.1 assessment, or Day 1 if there are 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.
b RECIST 1.1 progression event occurred after 2 or more missed visits or within 2 visits of baseline where the patient has no non-missing visits or does not have a baseline assessment.
c Death which occurred after 2 or more missed visits in the absence of RECIST 1.1 progression.
d Calculated using the Kaplan-Meier technique.

Concordance in PFS between the BICR and Investigator assessments

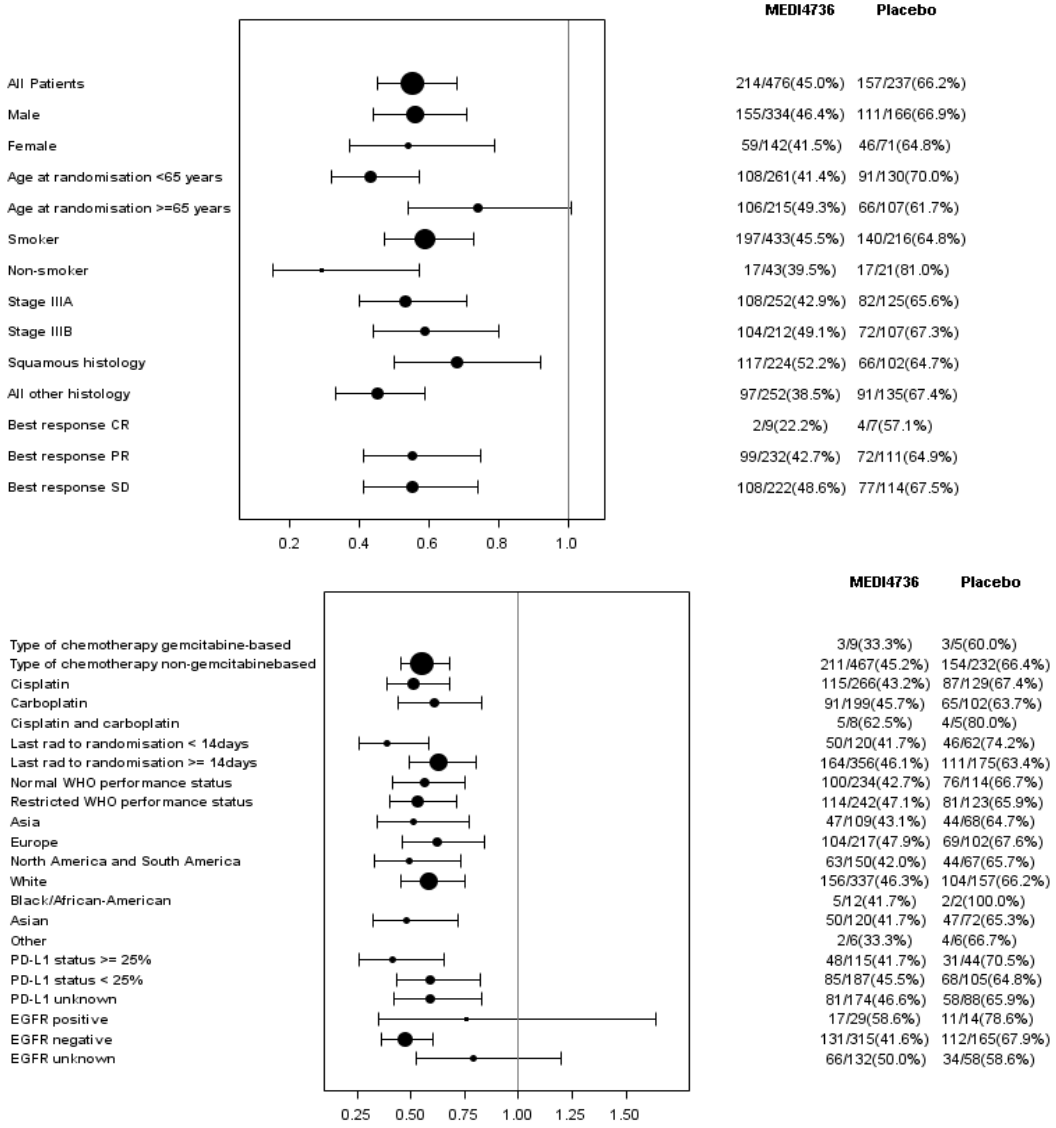
Table 29: Disagreements between investigator and central reviews of RECIST progression (full analysis set)

Progression	Number (%) of patients MEDI4736 (N=476)	Placebo (N=237)	Difference MEDI4736 - Placebo
RECIST progression [a] declared by:			
Investigator and central review	148 (31.1)	124 (52.3)	
Progression date agreement (within 2 weeks)	76 (16.0)	70 (29.5)	
Progression date >=2 weeks earlier by central review than by Investigator	60 (12.6)	48 (20.3)	
Progression date >=2 weeks earlier by Investigator than by central review	12 (2.5)	6 (2.5)	
Investigator but not central review	78 (16.4)	30 (12.7)	
Central review but not Investigator	41 (8.6)	16 (6.8)	
No Progression by both	209 (43.9)	67 (28.3)	
Early Discrepancy Rate (EDR) [b]	0.40	0.23	0.17
Late Discrepancy Rate (LDR) [c]	0.53	0.64	-0.11

[a] Progression events that do not occur within two visits of the last non-missing assessment (or randomisation) are censored.
[b] EDR is the frequency of Investigator declared progressions before central review as a proportion of all Investigator progressions.
[c] LDR is the frequency of Investigator declared progressions after central review as a proportion of all discrepancies.
RECIST version 1.1.

Subgroup analysis of progression free survival (PFS)

The Forest Plot of PFS (BICR, RECIST 1.1) by pre-specified subgroups is presented in Figure 18.



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.
Progression includes deaths in the absence of RECIST progression.
Patients who have not progressed or died, or who progress or die after two or more missed visits, are censored at the latest non-missing RECIST assessment, or Day 1 if there are 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; WHO World Health Organization; CR Complete response; PR Partial response; SD Stable disease; TFLD Time from last dose.

Figure 16: Progression free survival (BICR, RECIST 1.1), Forest Plot of pre-specified subgroups – Full analysis set

Primary endpoint: OS

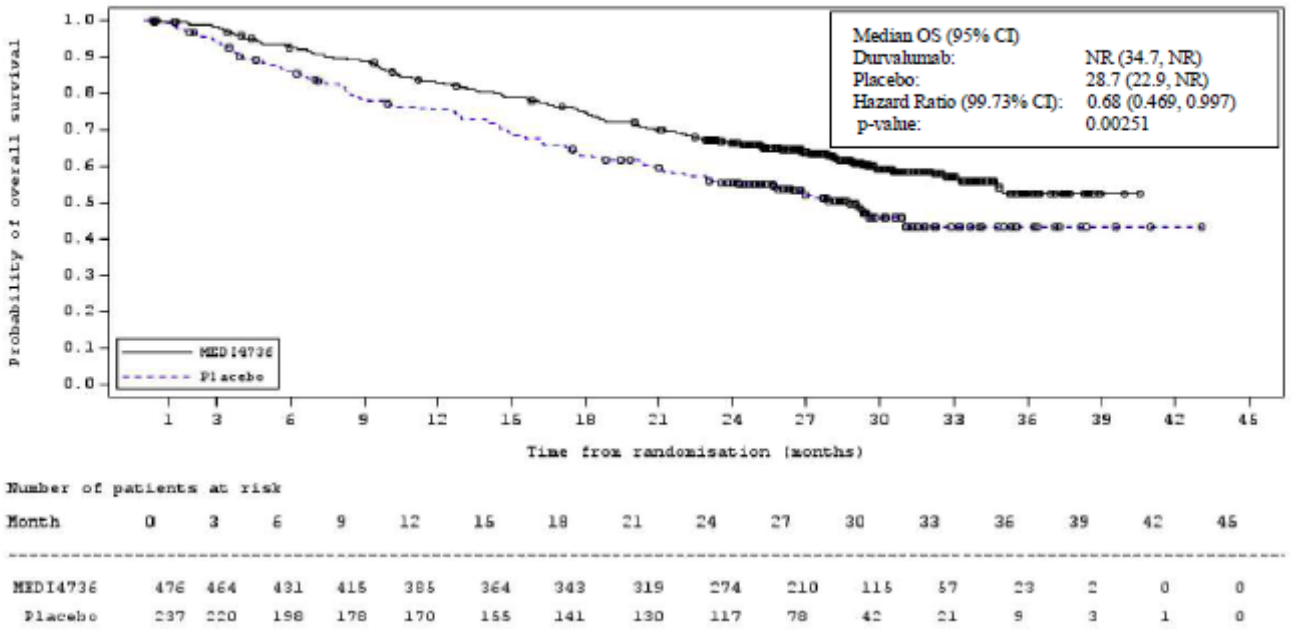
The data included in this report is from the first planned interim OS analysis from the DCO date of 22 March 2018. This analysis was planned after the occurrence of 285 deaths. At the time of this analysis, 299 deaths had occurred (61% of the final target 491 OS events).

Treatment with durvalumab resulted in a statistically significant improvement in OS compared to placebo (Table 30 and Figure 19).

Table 30: Overall survival, primary analysis (full analysis set)

Survival status	MEDI4736 (N=476)	Placebo (N=237)
Death, n(%)	183 (38.4)	116 (48.9)
Censored patients, n(%)	293 (61.6)	121 (51.1)
Still in survival follow-up [a]	273 (57.4)	108 (45.6)
Terminated prior to death [b]	20 (4.2)	13 (5.5)
Voluntary discontinuation by subject	19 (4.0)	13 (5.5)
Subject lost to follow-up	1 (0.2)	0
Other	0	0
Median overall survival (months) [c]	NR	28.7
95% CI for median overall survival [c]	34.7, NR	22.9, NR
Survival rate at 12 months (%) [c]	83.1	75.3
95% CI for survival rate at 12 months [c]	79.4, 86.2	69.2, 80.4
Survival rate at 24 months (%) [c]	66.3	55.6
95% CI for survival rate at 24 months [c]	61.7, 70.4	48.9, 61.8
2-sided p-value [d]	0.005	
Hazard ratio, comparing MEDI4736 vs. Placebo [e]	0.68	
99.73% CI for hazard ratio [e][f]	0.469, 0.997	
95% CI for hazard ratio [e]	0.534, 0.875	
2-sided p-value [e]	0.00251	

CI = Confidence interval, NR = Not reached.
[a] Includes patients known to be alive at data cut-off.
[b] Includes patients with unknown survival status or patients who were lost to follow-up.
[c] Calculated using the Kaplan-Meier technique.
[d] 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.
[e] The analysis was performed using stratified log-rank test adjusting for age at randomisation (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
[f] 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.



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

Figure 17: Overall survival, Kaplan-Meier plot (full analysis set)

Table 31: Overall survival, duration of follow-up and prematurely censored patients (full analysis set)

	MEDI4736 (N=476)	Placebo (N=237)	Total (N=713)
Duration of follow-up in all patients(months)			
n [a]	476	237	713
Min	0.2	0.3	0.2
Q1	16.4	9.2	14.1
Median	25.9	23.8	25.2
Q3	29.9	28.8	29.5
Max	40.5	43.1	43.1
Duration of follow-up in censored patients(months)			
n [b]	293	121	414
Min	0.4	0.5	0.4
Q1	25.8	25.1	25.6
Median	28.8	28.2	28.6
Q3	31.9	31.3	31.6
Max	40.5	43.1	43.1
Patients prematurely censored [c], n(%)	36 (7.6)	18 (7.6)	54 (7.6)
Censored patients			
Censored <= 8 weeks before DCO	267 (56.1)	106 (44.7)	373 (52.3)
Censored >8 weeks -<= 16 weeks before DCO	2 (0.4)	0	2 (0.3)
Censored >16 weeks -<= 24 weeks before DCO	3 (0.6)	0	3 (0.4)
Censored > 24 weeks before DCO	21 (4.4)	15 (6.3)	36 (5.0)

DCO = Data cut-off, Min = minimum, Max = maximum, Q1 = Lower Quartile, Q3 = Upper Quartile.
[a] n is the number of all patients.
[b] n is the number of censored patients.
[c] A patient would be defined as prematurely censored if their survival status was not defined at the DCO.

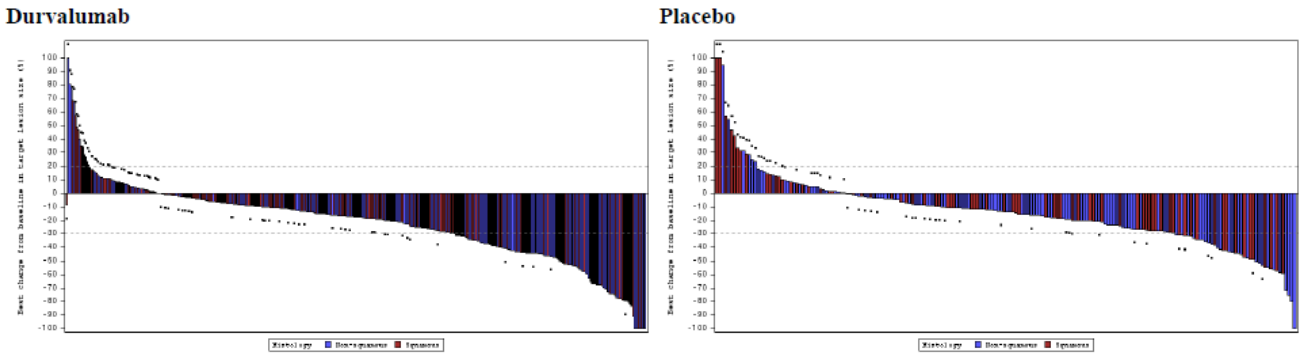
Secondary endpoint: ORR

Table 32. ORR based on BICR assessments according to RECIST 1.1 (full analysis set with measurable disease at baseline)

	Durvalumab (N=443)	**Placebo (N=213)**
Response, n (%)	**126 (28.4)**	**34 (16.0)**
Complete response [a]	6 (1.4)	1 (0.5)
Partial response [a]	120 (27.1)	33 (15.5)
Non-response, n (%)	**317 (71.6)**	**179 (84.0)**
Stable disease ≥8 weeks	233 (52.6)	119 (55.9)
Progression	73 (16.5)	59 (27.7)
RECIST 1.1 progression	66 (14.9)	55 (25.8)
Death	7 (1.6)	4 (1.9)
Not evaluable	10 (2.3)	1 (0.5)
Stable disease <8 weeks	0	0
Incomplete post-baseline assessments	10 (2.3)	1 (0.5)
ORR (%)	28.4	16.0
95% CI (%) [b]	24.28, 32.89	11.31, 21.59
p-value [c]	<0.001	

a Responses include unconfirmed responses.
b 95% CI 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.
BICR Blinded Independent Central Review; CI confidence interval; ORR objective response rate; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1.
Source: Table 11.2.6.1 and Table 11.2.6.5

For both treatment groups, the ORRs based on Investigator assessments were consistent with those based on BICR assessments (32.3% for the durvalumab group and 19.7% for the placebo group; p-value less than 0.001). The denominator included randomized patients with measurable disease at baseline as per BICR.



Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Dotted reference lines at -30% and 20% indicate thresholds for PR and Progressive Disease, respectively.
Values greater than 100% or less than -100% are displayed as 100% and -100%, respectively.
Patients with Progressive Disease as best overall response are marked with a dot.
BICR Blinded Independent Central Review; PR partial response; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 18: Waterfall plot of best percentage change in target lesion size based on BICR assessments according to RECIST 1.1 (full analysis set)

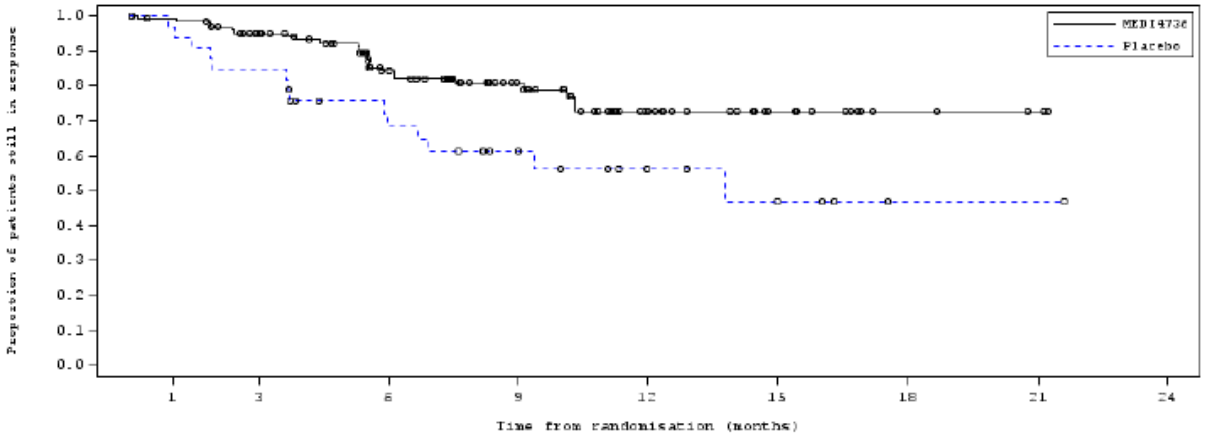
Secondary endpoint: Duration of response (DoR)

Duration of response seems to be longer in the durvalumab arm, but data are not yet mature. A formal comparison between the two treatment arms was not pre-planned, however, a post-hoc analysis for DOR shows a HR = 0.43 (95%CI: 0.22, 8.84).

Table 33: Duration of objective response based on BICR assessments according to RECIST 1.1 (full analysis set, patients with objective response)

Statistic	Durvalumab (N=126)	Placebo (N=34)
Number of responders who subsequently progressed or died, n (%)	**24 (19.0)**	**14 (41.2)**
DoR from onset of response (months) [a, b]		
- 25th percentile (95% CI)	10.3 (6.1, NR)	5.9 (1.4, 9.4)
- Median (95% CI)	NR (NR, NR)	13.8 (6.0, NR)
- 75th percentile (95% CI)	NR (NR, NR)	NR (13.8, NR)
Percentage remaining in response at [b]		
- 6 Months	84.3	68.4
- 12 Months	72.8	56.1
- 18 Months	72.8	46.8

a DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last non-missing RECIST 1.1 assessment for patients who do not progress or for patients who progress or die after 2 or more missed visits.
b Calculated using the Kaplan-Meier technique.
BICR Blinded Independent Central Review; CI confidence interval; CR complete response; DoR duration of response; NR not reached; PR partial response; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1.
Source: Table 11.2.7.1



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24
MEDI4736	126	109	77	49	24	12	4	2	0
Placebo	34	28	15	13	7	5	1	1	0

Circles indicate a censored observation.
BICR Blinded Independent Central Review; DoR duration of response; MEDI4736 durvalumab; RECIST 1.1 Response Evaluation Criteria In Solid Tumors version 1.1.

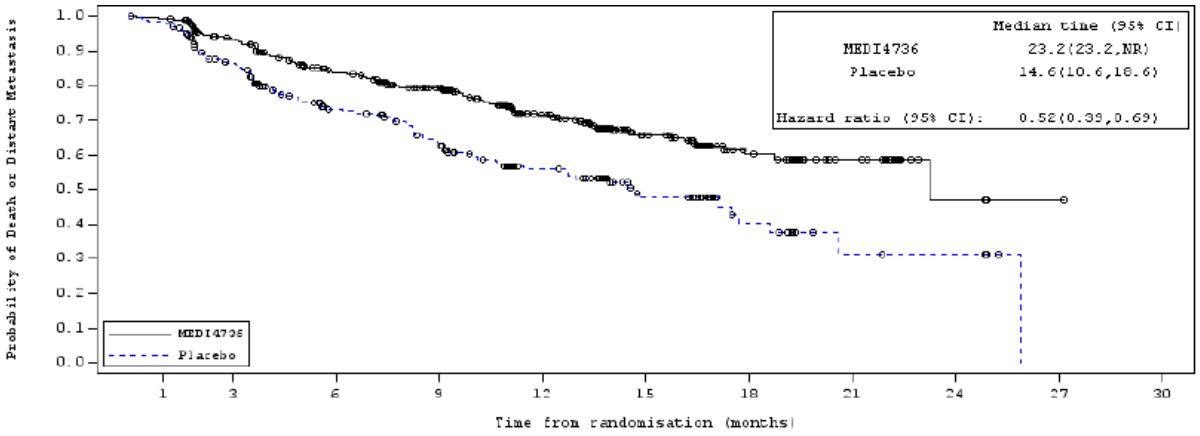
Figure 19: Kaplan-Meier plot of DoR based on BICR assessments according to RECIST 1.1 (full analysis set, patients with objective response)

Secondary endpoint: Time to death or distant metastasis (TTDM)

Table 34: 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 (%)	131 (27.5)	98 (41.4)
Distant metastasis [b]	67 (14.1)	56 (23.6)
Death in the absence of distant metastasis	64 (13.4)	42 (17.7)
Censored patients, n (%)	345 (72.5)	139 (58.6)
Censored distant metastasis [c]	2 (0.4)	0
Censored death [d]	10 (2.1)	1 (0.4)
Distant metastasis free at time of analysis	309 (64.9)	124 (52.3)
Lost to follow-up	1 (0.2)	0
Withdrawn consent	16 (3.4)	12 (5.1)
Discontinued study	7 (1.5)	2 (0.8)
Median time to death or distant metastasis (months) [e]	23.2	14.6
95% CI for time to death or distant metastasis [e]	23.2, NR	10.6, 18.6
Hazard ratio [f]	0.52	
95% CI for hazard ratio [f]	0.39, 0.69	
2-sided p-value [f]	<0.0001	

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 1.1 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 which 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.



Number of patients at risk

Month	0	3	6	9	12						
MEDI4736	476	407	336	288	173	91	46	22	4	1	0
Placebo	237	184	129	106	53	32	16	5	4	0	0

Circles indicate a censored observation.
CI confidence interval; MEDI4736 durvalumab; NR not recorded.Source: Figure 11.2.1.15

Figure 20 Kaplan-Meier plot of time to death or distant metastasis (full analysis set)

Updated data regarding time to death or distant metastasis were submitted during the procedure.

Table 35 Time to death or distant metastasis (BICR; RECIST 1.1) – Full analysis set (data cut-off 22 March 2018)

	Number (%) of patients	
	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)
Censored patients, n (%)	294 (61.8)	111 (46.8)
Median time to death or distant metastasis (months) [c]	28.3	16.2
95% CI for time to death or distant metastasis [c]	24.0, 34.9	12.5, 21.1
Hazard ratio [d]	0.53	
95% CI for hazard ratio [d]	0.41, 0.68	
2-sided p-value [d]	<.0001	

BICR Blinded Independent Central Review; CI Confidence interval; RECIST Response Evaluation Criteria in Solid Tumors.
[a] Patients who have not died or have distant metastasis, or who die or get distant metastasis after two 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] Calculated using the Kaplan-Meier technique.
[d] The analysis was performed using a stratified log rank test adjusting for age at randomisation (<65 vs ≥65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
Data source: Table 11.2.11.1, Appendix 1.

Secondary endpoint: Time to first subsequent therapy or death (TFST)

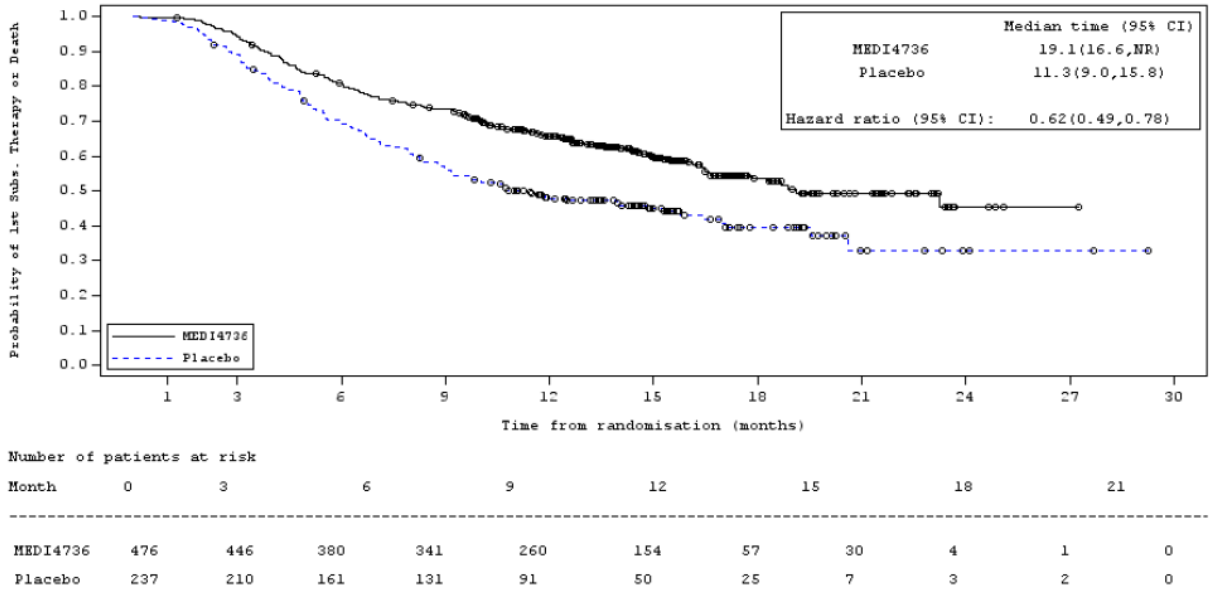
A total of 146 patients (30.7%) in the durvalumab group and 102 patients (43.0%) in the placebo group received subsequent disease-related, cancer therapy. Most patients in both treatment groups received cytotoxic chemotherapy (such as carboplatin and pemetrexed): 100 (21.0%) in the durvalumab group and 56 (23.6%) in the placebo group. A total of 52 patients (10.9%) in the durvalumab group and 45 patients (19.0%) in the placebo group received radiotherapy. More patients in the placebo group received immunotherapy (13.9% vs. 4.0% in the durvalumab group).

Table 36:Time to first subsequent therapy or death (full analysis set)

	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n (%)	194 (40.8)	132 (55.7)
Subsequent therapy [b]	146 (30.7)	102 (43.0)
Death	48 (10.1)	30 (12.7)
Censored patients, n (%)	282 (59.2)	105 (44.3)
Median time to first subsequent therapy or death (months) [c]	19.1	11.3
95% CI for Median time to first subsequent therapy or death [c]	16.6, NR	9.0, 15.8
Hazard ratio	0.62	
95% CI for hazard ratio	0.49, 0.78	
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] One patient in each treatment group received subsequent therapy, but the dates when these medication were taken were not recorded; thus, these patients were censored.



Circles indicate a censored observation.
CI confidence interval; MEDI4736 durvalumab; NR not reported.

Figure 21. Kaplan-Meier plot of time to first subsequent therapy or death (full analysis set)

The median time between RECIST 1.1-assessed progression and TFST was 71.0 days (range: 2 to 503 days) in the durvalumab group, compared to 58.0 days (range: 0 to 291 days) in the placebo group. The median time between onset of response and TFST was 171.0 days (range: 1 to 595 days) and 189.0 days (range: 37 to 472 days), respectively.

Updated data regarding time to first subsequent therapy or death were submitted during the procedure.

Table 37: Time to first subsequent therapy or death – Full analysis set (data cut-off 22 March 2018)

	Number (%) of patients	
	Durvalumab (N=476)	Placebo (N=237)
Total events [a], n (%)	267 (56.1)	169 (71.3)
Subsequent therapy	196 (41.2)	130 (54.9)
Death	71 (14.9)	39 (16.5)
Censored patients, n (%)	209 (43.9)	68 (28.7)
Median time to first subsequent therapy or death (months) [b]	21.0	10.4
95% CI for median time to first subsequent therapy or death [b]	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	<.0001	

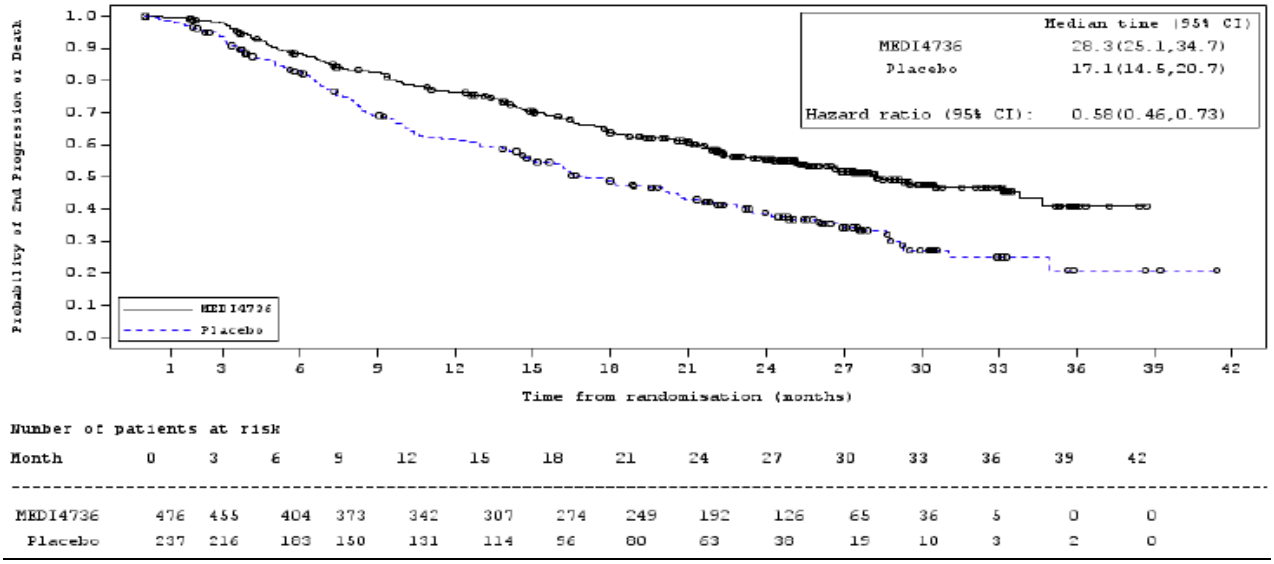
CI Confidence interval
[a] Patients with first subsequent therapy or death (TFST). TFST is defined as the time from randomisation to the start date of the first subsequent therapy after discontinuation of treatment, or death.
[b] Calculated using the Kaplan-Meier technique.
The analysis was performed using a stratified log rank test adjusting for age at randomisation (<65 vs >=65), sex (Male vs Female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.
Data source: Table 11.2.5.1, Appendix 1.

Secondary endpoint: PFS2

Table 38: Time from randomization to second progression or death, summary and stratified log-rank test (full analysis set)

	MEDI4736 (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)
Censored patients, n (%)	259 (54.4)	93 (39.2)
Alive & progression free	146 (30.7)	42 (17.7)
No second progression	96 (20.2)	39 (16.5)
Lost to follow-up	1 (0.2)	0
Withdrawn consent	16 (3.4)	12 (5.1)
Discontinued study	0	0
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]	<.0001	

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 randomisation (<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.



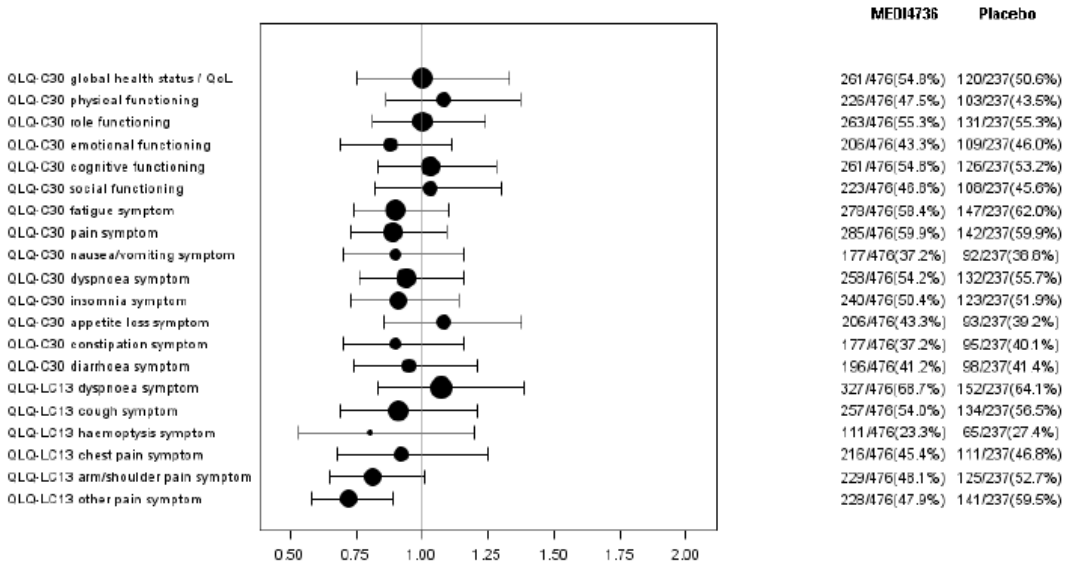
Number of patients at risk

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

Figure 22: Time to second progression or death, Kaplan-Meier plot (full analysis set)

<u>Secondary endpoint: QoL</u>

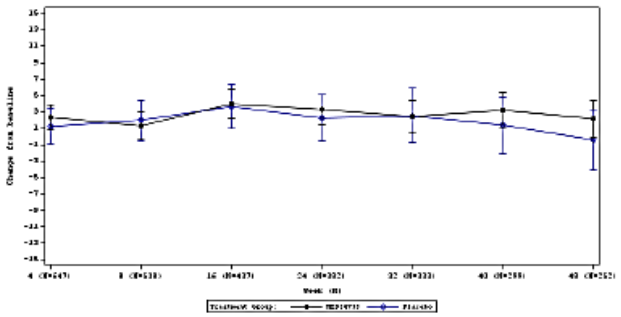
Compliance with completing the EORTC questionnaire was greater than 80% and very similar between the durvalumab and placebo groups up to Week 48, although compliance decreased to less than 65% at Week 60.



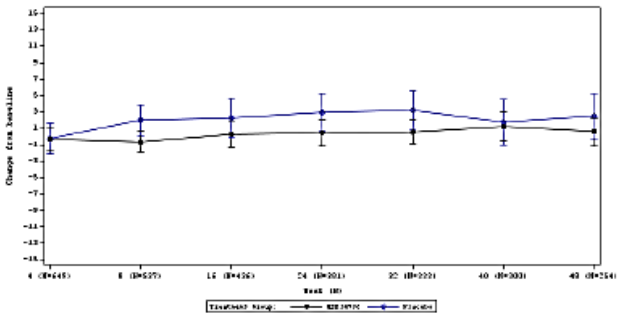
Hazard ratio (MEDI4736: Placebo); 99% CI for primary subscales and 95% for other subscales / items.
QLQ-C30 global health status / QoL and functional scales are based on patients with baseline scores >= 10.
QLQ-C30 and QLQ-LC13 symptom scales / items are based on patients with baseline scores <= 90.
A hazard ratio <1 implies a lower risk of deterioration on MEDI4736 study treatment.
The analysis is 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.
Size of circle is proportional to the number of events.
CI confidence interval; CSR clinical study report; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; QLQ-LC13 13-item self-administered questionnaire from the EORTC for lung cancer; MEDI4736 durvalumab; QoL quality of life.
Source: Figure 11.2.2.2, PACIFIC interim CSR, Module 5.3.5.1

Figure 23 Forest plot of Time to deterioration of EORTC QLQ-C30 and QLQ-LC13 subscales and items (full analysis set)

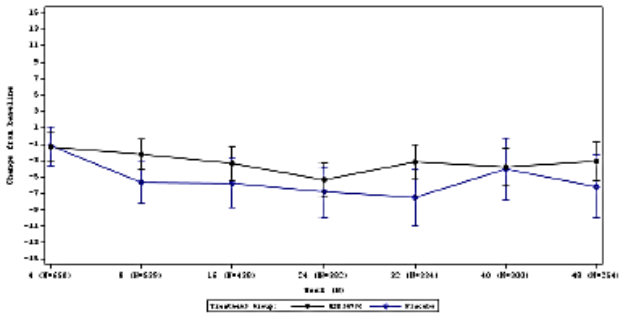
EORTC QLQ-C30 Global health status



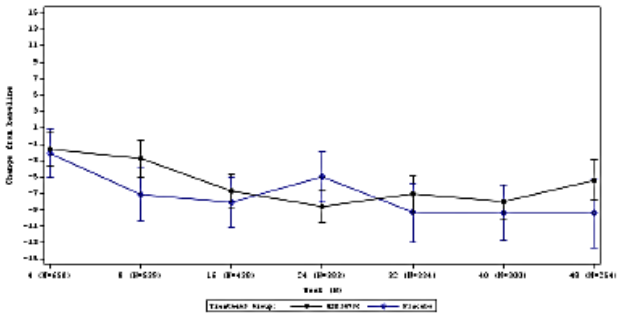
EORTC QLQ-C30 Physical functioning



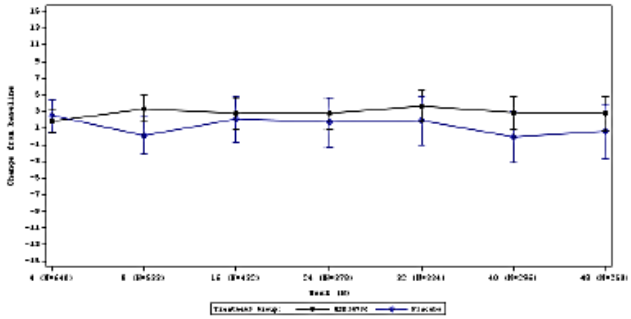
EORTC QLQ-C30 Fatigue



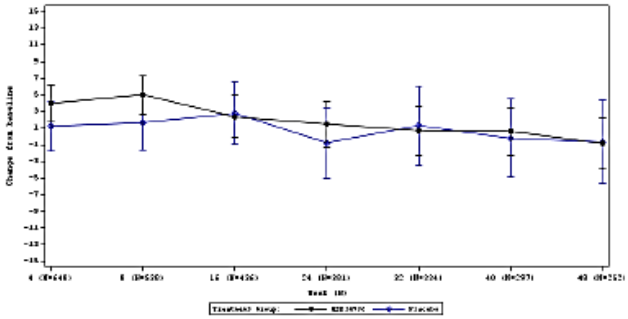
EORTC QLQ-C30 Appetite loss



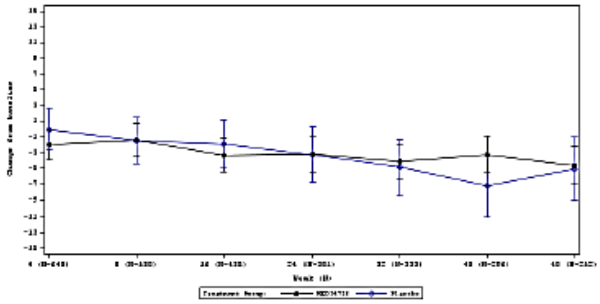
EORTC QLQ-LC13 Dyspnea



EORTC QLQ-LC13 Cough



EORTC QLQ-LC13 Chest pain



A negative change from baseline denotes an improvement in symptoms, whilst a positive change from baseline denotes worsening symptoms.

N is the number of patients which contribute to the change from baseline measurement at each visit, or any visit for the overall change from baseline estimates.

The LS mean estimates were determined using a mixed model repeated measures, which include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, age at randomization (<65 vs ≥65 years of age), sex (male vs female), smoking history (smoker vs non-smoker) as well as the continuous fixed covariate of baseline score and the baseline score-by-visit interaction.

CSR clinical study report; 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 Lung Cancer Module; 13-item self-administered questionnaire from the EORTC for lung cancer; LS least square.

Figure 24 Change from baseline in primary patient-reported outcome symptoms, mixed model repeated measures (full analysis set)

Secondary endpoint: Immunogenicity

Table 39: Summary of anti-drug antibody responses during the study (ADA-evaluable population)

Cohorts	Durvalumab 10 mg/kg Q2W (N=401)	Placebo Q2W (N=200)
ADA prevalence[a,f]	18 (4.5%)	10 (5.0%)
ADA incidence (treatment-emergent)[b,f]	7 (1.7%)	5 (2.5%)
ADA-positive at baseline and post-baseline[f]	2 (0.5%)	2 (1.0%)
ADA-positive post-baseline only[f]	7 (1.7%)	5 (2.5%)
ADA-positive at baseline only[f]	9 (2.2%)	3 (1.5%)
Treatment-boosted ADA[c,f]	0 (0.0%)	0 (0.0%)
ADA-persistently-positive[d,f]	6 (1.5%)	6 (3.0%)
ADA-transient-positive[e,f]	3 (0.7%)	1 (0.5%)
nAbs-positive at any visit[f]	3 (0.7%)	0 (0.0%)

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-positive 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

Ancillary analyses

- Outcomes in subgroups by PD-L1 expression:

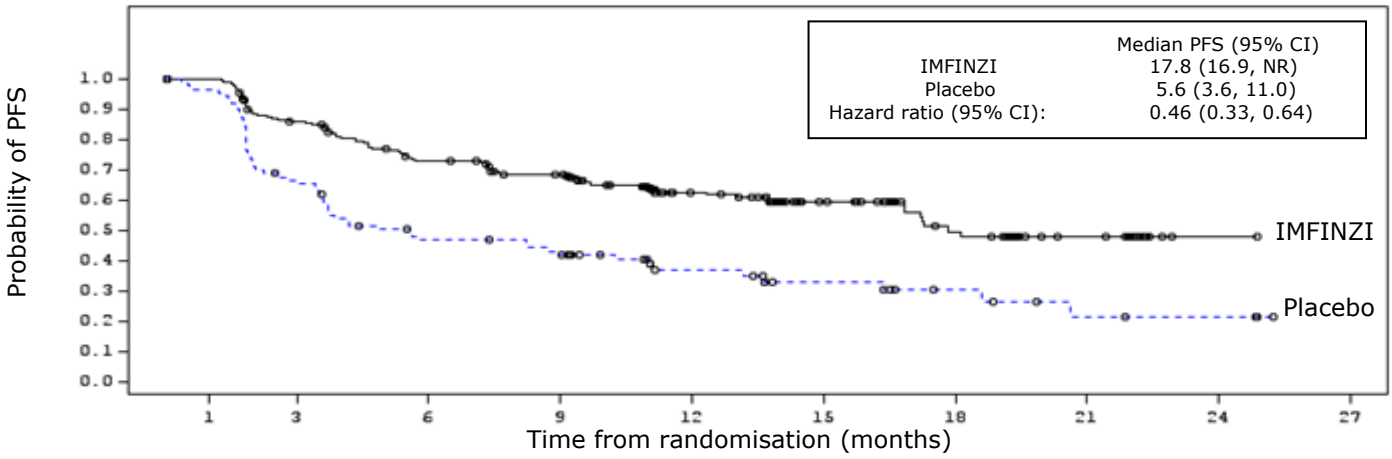
The Applicant conducted a retrospective analysis of PFS using a PD L1 TC 1% cut off. The SP263 stained tumour samples were therefore re-scored after completing validation of the PD L1 TC1% cut off, and were read by pathologists trained and certified specifically at this cut-off. Rescoring for the TC 1% cut off showed that of the 713 patients randomized, only 148 had TC expression <1% (90 in durvalumab group, 58 in the placebo group) and 303 had TC expression ≥1%. As previously noted, for 262 patients, PD L1 expression was unknown.

The results of this retrospective, exploratory analysis of PFS based on the PD L1 TC<1% and PD L1 TC≥1% cut offs, as well as PFS analysis in the PD-L1 unknown group, are summarized in Table 40.

Table 40: PFS (BICR, RECIST 1.1), exploratory subgroup analysis by PD-L1 status – Full analysis set

Subgroup	Group	N	Number(%) of patients with events	Median (Months) [a]	95% CI for Median [a]	Hazard Ratio [b]	95% CI for Hazard Ratio [b]
PD-L1 TC<1%	Durvalumab	90	49 (54.4)	10.7	7.3, NR	0.73	0.48, 1.11
	Placebo	58	40 (69.0)	5.6	3.7, 10.6		
PD-L1 TC≥1%	Durvalumab	212	84 (39.6)	17.8	16.9, NR	0.46	0.33, 0.64
	Placebo	91	59 (64.8)	5.6	3.6, 11.0		
PD-L1 Unknown [c]	Durvalumab	174	81 (46.6)	14.0	9.2, NR	0.59	0.42, 0.83
	Placebo	88	58 (65.9)	6.4	3.8, 9.0		

BICR Blinded Independent Central Review; CI Confidence interval; NR Not reached.
[a] Calculated using the Kaplan-Meier technique.
[b] 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.
[c] Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
PD-L1 subgroup <1%, ≥1% has been defined using the re-scored PD-L1 data.
Data source: Table 11.2.18.3.A, Appendix 1.



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27
Imfinzi	212	174	143	127	82	52	30	14	1	0
Placebo	91	59	39	34	20	13	8	4	3	0

Figure 25: Kaplan-Meier curve of PFS for PD-L1 TC ≥ 1%

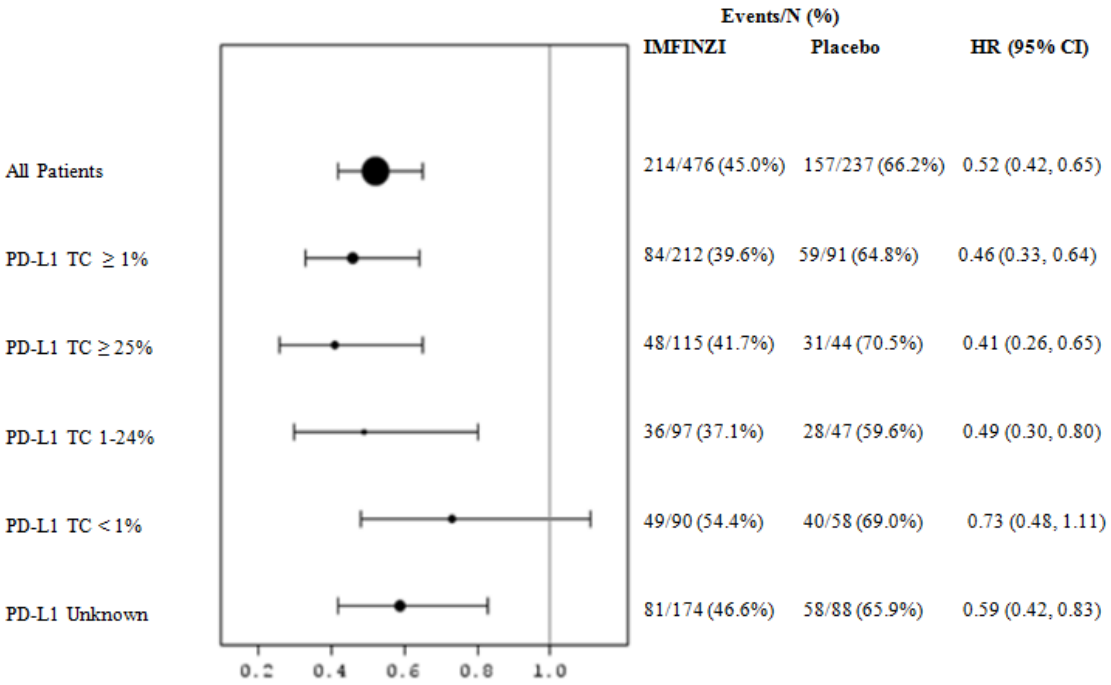
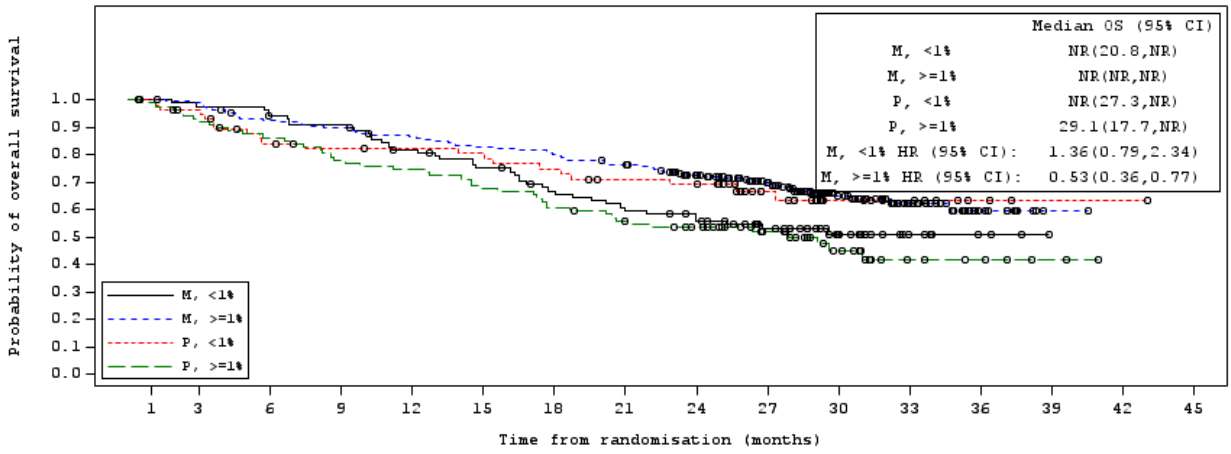


Figure 26: Forest plot of PFS by PD-L1 expression

Table 41: Overall survival, exploratory subgroup analysis by PD-L1 status – Full analysis set

Subgroup	Group	N	Number (%) of patients with events	Median (Months) [a]	95% CI for Median [a]	Hazard Ratio [b]	95% CI for Hazard Ratio [b]
PD-L1 TC<1%	Durvalumab	90	41 (45.6)	NR	20.8, NR	1.36	0.79, 2.34
	Placebo	58	19 (32.8)	NR	27.3, NR		
PD-L1 TC≥1%	Durvalumab	212	70 (33.0)	NR	NR, NR	0.53	0.36, 0.77
	Placebo	91	45 (49.5)	29.1	17.7, NR		
PD-L1 Unknown [c]	Durvalumab	174	72 (41.4)	33.2	29.3, NR	0.62	0.43, 0.89
	Placebo	88	52 (59.1)	23.5	16.2, 29.3		

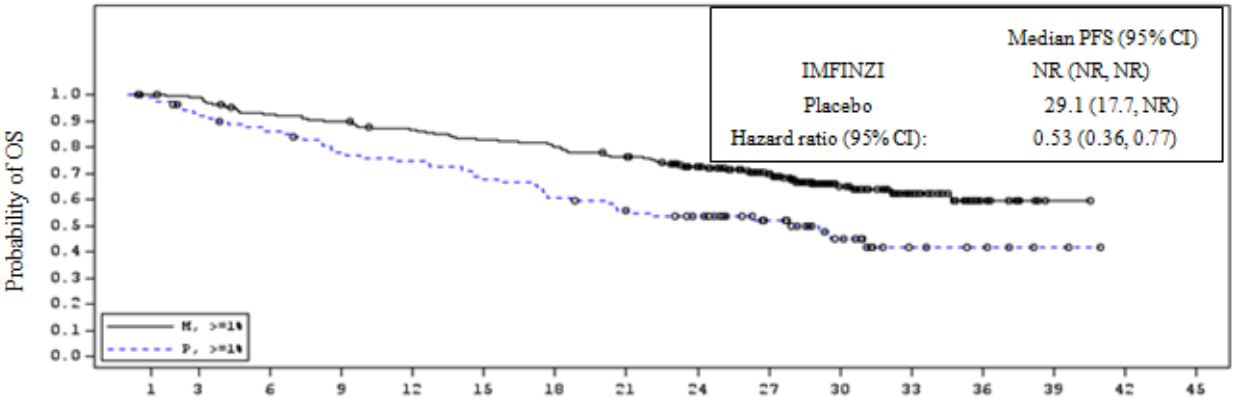
CI Confidence interval; NR Not reached.
[a] Calculated using the Kaplan-Meier technique.
[b] The hazard ratio and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
[c] Unknown is either insufficient tumour tissue, not able to be analysed or analysed but results were not interpretable.
PD-L1 subgroup <1%, ≥1% has been defined using the re-scored PD-L1 data.



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
M, <1%	90	88	84	81	72	65	56	50	45	35	20	7	3	0	0	0
M, >=1%	212	208	193	187	178	171	165	156	134	105	62	34	12	1	0	0
P, <1%	58	56	47	45	44	43	40	36	35	21	11	8	3	1	1	0
P, >=1%	91	81	75	67	64	58	52	46	41	29	17	7	5	2	0	0

Figure 27: Overall survival, Kaplan-Meier Plot by PD-L1 TC1% subgroups – Full analysis



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
IMFINZI	212	208	193	187	178	171	165	156	134	105	62	34	12	1	0
Placebo	91	81	95	67	64	58	52	46	41	29	17	7	5	2	0

Figure 28
Figure 29: Kaplan-Meier curve of OS for PD-L1 TC ≥ 1%

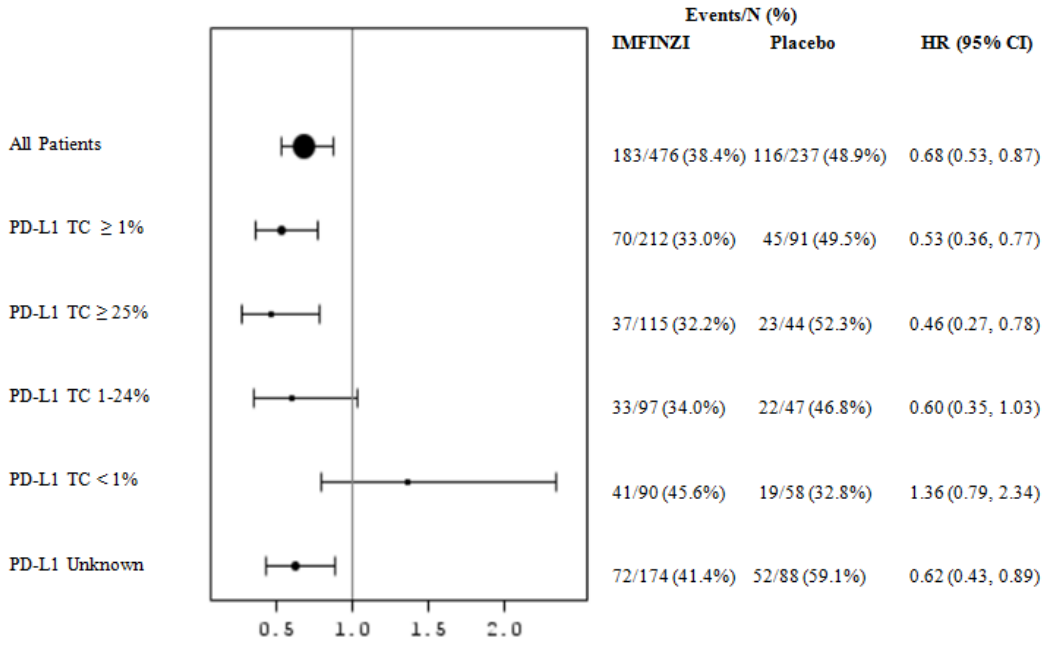


Figure 29: Forest plot of OS by PD-L1 expression

Outcomes in subgroups by histology (squamous vs. others)

Results of secondary endpoint in subgroups by histology (squamous vs. others).

Table 42: Objective response rate (BICR; RECIST 1.1) by histology – full analysis set with measurable disease at baseline

	Squamous		All other	
	Durvalumab (N=202)	Placebo (N=87)	Durvalumab (N=241)	Placebo (N=126)
Patients with objective response [a], n(%)	39 (19.3)	12 (13.8)	87 (36.1)	22 (17.5)
Objective response rate (%)	19.3	13.8	36.1	17.5
95% CI (%) [b]	14.10, 25.43	7.34, 22.85	30.03, 42.51	11.28, 25.23

BICR Blinded Independent Central Review; RECIST Response Evaluation Criteria in Solid Tumors.
[a] Responses include unconfirmed responses.
[b] 95% confidence intervals are calculated using the Clopper Pearson method.
RECIST Version 1.1.
Data Source: 11.2.17.1.A, Appendix 1.

Table 43: Time to death or distant metastasis (BICR; RECIST 1.1) by histology, Cox proportional hazards model- Full analysis set

Subgroup	Group	N	Number (%) of patients with events	Median, (Months) [a]	95% CI for Median [a]	Hazard Ratio [b]	95% CI for Hazard Ratio [b]
Squamous histology	Durvalumab	224	68 (30.4)	23.2	16.1, 23.2	0.64	0.44, 0.94
	Placebo	102	44 (43.1)	14.8	10.0, 25.9		
All other histology	Durvalumab	252	63 (25.0)	NR	NR, NR	0.49	0.34, 0.71
	Placebo	135	54 (40.0)	14.5	9.2, 18.6		

BICR Blinded Independent Central Review; RECIST Response Evaluation Criteria in Solid Tumors; NR = Not reached.
[a] Calculated using the Kaplan-Meier technique.
[b] 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.
Data Source: Table 11.2.17.2.A, Appendix 1.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for MEDI4736 (PACIFIC) trial

Title: 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 identifier	EudraCT Number 2014-000336-42		
Design	Randomised, double-blind, placebo-controlled		
	Duration of main phase:		First patient randomized: 09 May 2014 Last patient randomized: 22 April 2016 (study is ongoing)
Hypothesis	Superiority		
Treatments groups	Durvalumab		Durvalumab 10 mg/kg, up to 12 months, number randomized = 476
	Placebo		placebo, up to 12 months, number randomized = 237
Endpoints and definitions	Primary endpoint	PFS by BICR	Progression free survival by blinded independent central review
	Primary endpoint	OS	Overall survival
	Secondary endpoint	ORR	Overall response rate
	Secondary endpoint	DOR	Duration of response
	Secondary endpoint	PFS2	Progression free survival on next line of therapy
	Secondary endpoint	TTDM	Time to death or distant metastasis
Database lock	13 February 2017 and 22 March 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Durvalumab	Placebo
	Number of subject	N = 476	N = 237
	PFS by BICR in months	16.8	5.6
	95%CI	13.0, 18.1	4.6, 7.8
	OS in months	NR	28.7
	95%CI	34.7 NR	22.9, NR
	ORR , n/N (%) 95%CI	126/443 (28.4%) 24.28, 32.89	34/213 (16%) 11.31, 21.59
	DOR in months 95%CI	NR NR, NR	13.8 6.0, NR
	TTDM 95%CI	23.2 23.2, NR	14.6 10.6, 18.6
	PFS2 95%CI	28.3 25.1, 34.7	17.1 14.5, 20.7
Effect estimate per comparison	Primary endpoint – PFS by BICR	Comparison groups	Durvalumab vs placebo
		HR	0.52
		95%CI	0.42, 0.65
		P-value	<0.0001
	Primary endpoint – OS	HR	0.68
		95%CI	0.53, 0.87
		P-value	0.00251
	Secondary endpoint - ORR	Comparison groups	Durvalumab vs placebo
		Fisher's exact test	
		P-value	< 0.001
	Secondary endpoint – DOR	The applicant has not presented test statistics.	
	Secondary endpoint - TTDM	Comparison groups	Durvalumab vs placebo
		HR	0.52
		95%CI	0.39, 0.69
		p-value	<0.0001
	Secondary endpoint – PFS2	Comparison groups	Durvalumab vs placebo
		HR	0.58
		95%CI	0.46, 0.73
		p-value	<0.0001
Notes	PFS results come from the first pre-planned interim analysis that is considered final. OS results come from the first pre-planned interim analysis that is considered final.		

Analysis performed across trials (pooled analyses and meta-analysis)

No pooling was conducted for efficacy data, because available studies differed in patient populations, design, and primary endpoints.

Clinical studies in special populations

Table 44: Number of randomised patients in the PACIFIC MAA submission, by age category

	N	Age <65 years	Age 65 to 74 years	Age 75 to 84 years	Age 85 years and above
Controlled trial					
PACIFIC	713	391	266	54	2
Non-controlled trials	1414	808	454	145	7
Study 1108	970	543	307	114	6
ATLANTIC	444	265	147	31	1

For PACIFIC, the intention-to-treat (ITT) population was used, and for Non Controlled trials, the Safety Population was used.
Data Source: Table 1, Appendix 1.

Supportive study(ies)

The Applicant provides two supportive studies conducted in the metastatic setting: **The ATLANTIC study (d4191C00003) and the 1108 study (MEDI4736-1108)**

Table 45 Summary of clinical studies included in the submission package

Study Status DCO	Design	Population	Outcome measures	No. of patients
Supportive Phase I/II studies				
Study 1108 Ongoing 26 Oct 2016	FTIH, open-label, 3+3 dose-escalation, dose-expansion	Advanced solid tumors, including NSCLC, that are refractory to standard therapy and for which no standard therapy exists	Primary: MTD or OBD Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	1022 (total) 304 (NSCLC cohort)
ATLANTIC Ongoing 03 Jun 2016	Non-comparative, open-label, multicenter, international	Patients with locally advanced or metastatic (Stage IIIB – IV) NSCLC who have received at least 2 prior systemic treatment regimens	Primary efficacy: ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	444 (total) 111 (Cohort 1) 265 (Cohort 2) 68 (Cohort 3)

Efficacy results:

Objective response rate (ORR) and duration of response (DoR) in Study 1108 and ATLANTIC

	Study 1108			ATLANTIC (third line +)		
Parameter	**First-line**	**Second Line**	**Third Line +**	**Cohort 1 (EGFR/ALK+)**	**Cohort 2 (EGFR/ALK*wt*)**	**Cohort 3[a] (EGFR/ALK*wt*)** PD-L1 TC ≥90% only
PD-L1 TC ≥25%						
N	41	52	53	74	146	68
Objective response rate, n (%)	11 (26.8%)	12 (23.1%)	10 (18.9%)	9 (12.2%)	24 (16.4%)	21 (30.9%)
95% CI	(14.2% - 42.9%)	(12.5% - 36.8%)	(9.4%-32.0%)	(5.7%-21.8%)	(10.8%-23.5%)	(20.2%-43.3%)
Median DoR, months (95% CI)	19.35 (2.9-19.4)	NR (4.1-NE)	NR (2.8-NE)	7.4 (5.4-9.2)	12.3 (7.6-NE)	NR (7.4-NE)
PD-L1 TC <25%						
N	11	26	71	28	93	–
Objective response rate, n (%)	2 (18.2%)	0	3 (4.2%)	1 (3.6%)	7 (7.5%)	–
95% CI	(2.3% - 51.8%)	(0.0%-13.2%)	(0.9%-11.9%)	(0.1%-18.3%)	(3.1%-14.9%)	–
Median DoR, months (95% CI)	9.07 (6.0-12.1)	NA (NE-NE)	NR (3.0-NE)	NC[b]	NR (4.6-NE)	–

[a] Cohort 3 in ATLANTIC only contained patients with PD-L1 TC ≥90%.
[b] Median was not calculated for only 1 responder.
ALK anaplastic lymphoma kinase; CI confidence interval; EGFR epidermal growth factor receptor; PD-L1 programmed cell death ligand-1; N number of patients in group; n number of patients with response; NA not available; NC not calculable; NE not estimable; NR not recorded; TC tumor cells; wt wild type.

2.5.3. Discussion on clinical efficacy

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass that blocks the interaction of programmed cell death ligand-1 (PD-L1) with its receptors programmed cell death 1 (PD-1) on T cells and cluster of differentiation (CD) 80 (B7.1) on immune cells.

Design and conduct of clinical studies

The applicant has provided one pivotal study to support the claimed indication. The PACIFIC study is a double-blind, randomised, placebo-controlled study. The study design is acceptable in this patient population. The inclusion criteria clearly define the patient population as unresectable stage III NSCLC, who have received at least 2 cycles of platinum-based chemotherapy concurrent with radiotherapy. The PACIFIC study enrolled patients regardless of their programmed cell death ligand 1 (PD L1) expression. Tumour tissue collection was, not mandatory for inclusion, and testing was not conducted prospectively prior to randomization. However tumour PD L1 expression was tested retrospectively using, where available, tumour samples consisting of archival tissue obtained prior to chemoradiation with the VENTANA PD L1 (SP263) IHC assay. The study recruited all-comers with regard to PD-L1 expression, however, in the pre-defined subgroup analyses based on PD-L1 expression the applicant has applied a cut-off for PD-L1 expression at 25%. Patients

with prior exposure to any anti-PD-1 or anti-PD-L1 antibody are excluded. This is has been reflected in the SmPC, section 5.1**.**

The primary objectives of the study are clearly defined: to assess the efficacy of durvalumab compared with placebo in terms of PFS and OS. The Applicant has defined two primary endpoints; PFS by BICR and OS. Both endpoints are fully acceptable in this patient population. Several secondary endpoints are also defined; PFS2, OS24, ORR, DoR, AFP12 and AFP18 (proportion of patients alive and progression free at 12 months and 18 months from randomisation), and TTDM (time to death or distant metastasis).

Age is prognostic factor in this disease. Mean age at diagnosis has risen over the last decades from 60-65 to approximately 70-72 years in Caucasian patients. Most patients are above 65 years at the time of diagnosis (Postmus et al, 2017). However, patients in the study are younger, mean age is approximately 63 years. Furthermore, the majority of patients are ECOG/WHO PS 0 or 1. However, demographics and baseline characteristics are balanced and clearly reflected in the SmPC, section 5.1.

During the course of the study, several anti PD-1/PD-L1 agents were approved for treatment of NSCLC and, as such, a number of requests were made for patients to be unblinded in order to determine the best option for the subsequent treatment. A total of 86 patients were unblinded (47 in the durvalumab group and 39 in the placebo group). It was determined that these unblinding had no effect on the PFS analysis, as they occurred after progression

Efficacy data and additional analyses

The study met both of its pre-specified endpoints, PFS by BICR and OS. Median PFS was improved by 11.2 months in the durvalumab arm (16.8 vs 5.6 months in the durvalumab and placebo arm respectively). The HR is 0.52 (98.90%CI: 0.39, 0.70) , p<0.0001). This difference is statistically highly significant.

It is noted the median PFS in the placebo considerable shorter than what is observed in the clinical setting (Butts et al. 2014). However, there are several important differences between the findings in the PACIFIC study and the Butts paper. Most importantly PFS was assessed by BICR in the PACIFIC study, while PFS by investigator in the PACIFIC study seems to be more in line with the finding in the Butts paper, where PFS was assessed by investigator.

The Applicant presents OS interim data, which are 61% of the target number of final event. The results show an OS benefit in favour of durvalumab, the threshold for demonstrating superiority was crossed, and thus the Applicant considers the results as final. However, OS data are not fully mature yet, especially in the durvalumab arm. Thus, the Applicant is recommended to continue collecting OS data post-approval and provide yearly updates.

The Applicant has also provided PFS2 data during the procedure. These results are in line with PFS and OS data, confirming the benefit of early treatment with durvalumab in the proposed patient population. Overall, the totality of evidence clearly shows that early treatment with durvalumab not only improves PFS, but also PFS2 and OS. The results are considered clinically relevant in a patient population with high risk of relapse and a dismal prognosis.

The study is critically weakened by the fact that the Applicant did not stratify per PD-L1 expression. This may seem illogical considering the mode of action of the drug, i.e. selective blocking of the interaction of PD-L1 with PD-1 and CD80. The applicant was asked to provide evidence that efficacy was maintained for all patients irrespective of their expression of PD-L1 to provide subgroup analyses in patients with <1% and ≥ 1%, of tumour cells expressing PD-L1 (as well as other PD-L1 cut-off).

The Applicant presented a retrospective analysis of PFS by PD-L1 1% cut-off. This was done by BICR. In total, information on PD-L1 expression was available for 451 patients (63%). Of these, 148 patients had PD-L1 expression below 1%, and 303 patients had an expression over 1%. The results show that durvalumab is effective regardless of PD-L1 expression in terms of PFS, however, the size of the effect is considerable lower in patients with PD-L1 <1% (10.7 vs 5.6 months). Furthermore, OS data were provided during the procedure and do not show benefit of durvalumab in patients with PD-L1 <1%. Thus, it was concluded that efficacy had not been clearly established across all patients irrespective of their expression of PD-L1. In patients with PD-L1 expression below 1% efficacy could not be unequivocally established which is also supported by the mechanism of action of durvalumab.

The applicant provided efficacy data in various subgroups:

Smoking status: patients who never smoked derived a PFS benefit (HR: 0.29 [95% CI: 0.15, 0.57]) along with smokers (HR: 0.59 [0.47, 0.73]).

EGFR mutations: A PFS benefit was observed in the EGFR wild type subgroup (HR: 0.47, 95% CI: 0.36, 0.60). Additionally, the observed treatment effect was also in favour of durvalumab in the EGFR mutant subgroup (HR: 0.76; 95% CI: 0.35, 1.64). However, these results should be interpreted with caution due to the small number of patients who were EGFR mutant (29 in the durvalumab group and 14 in placebo) and the small number of events (17 in the durvalumab group and 11 in the placebo group).

Histology: Although the trial was not specifically designed to answer the question whether there could be relevant differences in efficacy across subgroups of NSCLC histology (squamous vs. non squamous), results in these subgroups in terms of PFS (squamous (HR: 0.68; 95% CI: 0.50, 0.92) vs. other (HR: 0.45; 95% CI: 0.33, 0.59) did not appear to show any clinically relevant difference according to histology. Additional data on subgroups according to histology remains consistent with results on PFS.

Age: There seems to be greater effect in younger patients (<65 years) compared to older patients (>=65 years).

The number of ADA positive patients is very limited (19 patients in the durvalumab arm vs. 10 patients in the placebo arm), and thus formal efficacy analyses for PFS and OS was not conducted. The applicant is recommended to further investigate efficacy in ADA positive patients post-authorisation.

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 were assessed at baseline, every 4 weeks for the first 8 weeks, followed by every 8 weeks until completion of the treatment period or discontinuation of durvalumab due to toxicity or disease progression. Compliance was similar between the Imfinzi and placebo treatment groups (83% vs 85.1% overall of evaluable forms completed).

At baseline, no differences in patient reported symptoms, function and HRQoL were observed between durvalumab and placebo groups. Throughout the duration of the study to Week 48, there was no clinically meaningful difference between durvalumab and placebo groups in symptoms, functioning and HRQoL (as assessed by a difference of greater than or equal to 10 points).

The applicant had planned several exploratory analyses. However, none of these were submitted in this application. It is recommended that the Applicant submits these analyses together with the final analysis (CSR) post-approval.

The Applicant provides two supportive studies. Overall, it is seen that efficacy is considerably smaller in the subgroup of patients with PD-L1 expression <25% compared to the subgroup of patients with a PD-L1

expression ≥ 25%. The results should be interpreted with caution. These studies are conducted in a different patient population, non-comparative and with different primary endpoints.

2.5.4. Conclusions on the clinical efficacy

Overall, the study met both of its primary endpoints. However, the study included all-comers, but the Applicant did not systematically collect data on different levels of PD-L1 expression. Considering the mode of action (i.e. the blocking of the interaction between PD-L1 and PD-1/CD80 receptors) the Applicant was asked to provide evidence of efficacy across all patients irrespective of PD-L1 expression. Efficacy in patients with PD-L1 expression below 1% could not be unequivocally established.

2.6. Clinical safety

An overview of durvalumab clinical studies that provide the safety and tolerability data in this application is presented in Table xx. The Pivotal Safety Analysis Set that provides evidence supporting the safety and tolerability claims in the proposed indication is based on the interim analysis of the ongoing pivotal D4191C00001 study (PACIFIC). This dataset includes 475 patients who received at least 1 infusion of durvalumab 10 mg/kg IV Q2W and 234 patients who received at least 1 infusion of placebo. A supportive assessment of the safety and tolerability is provided in the Supportive Safety Dataset (the Monotherapy Pool) that includes patients across the clinical program who received durvalumab 10 mg/kg Q2W. The Monotherapy Pool (1889 patients) includes data from 3 sponsored studies that have achieved a predefined interim data cut-off (DCO) date: 475 patients from the PACIFIC study, 444 patients from the ATLANTIC study, and 970 patients from Study 1108 (which enrolled patients with advanced solid tumours, including NSCLC). Patients with NSCLC were enrolled in all 3 studies, but the disease stage and prior therapy differed substantially across the 3 studies.

Table 46: Overview of durvalumab clinical studies providing safety and tolerability data in the application

Study number Name DCO date Status	Phase Study design	Patient population	Durvalumab dose, route of administration, and duration of treatment	Number of patients included in the safety analysis
Pivotal study				
D4191C00001 **PACIFIC** 13 February 2017 Ongoing	Phase III Randomized, double-blind, placebo-controlled, multicenter, international	Patients with locally advanced, unresectable, Stage III NSCLC that has not progressed after definitive platinum-based concurrent chemoradiation	10 mg/kg Q2W IV for a maximum of 12 months. Treatment was to be discontinued prior to 12 months if there was confirmed disease progression.	709 (total): 475 (durvalumab) 234 (placebo)
Supportive studies				
D4191C00003 **ATLANTIC** 03 June 2016 Ongoing	Phase II Non-comparative, open-label, multicenter, international	Patients with locally advanced or metastatic (Stage IIIB – Stage IV NSCLC) who have received at least 2 prior systemic treatments, including 1 platinum-based chemotherapy	10 mg/kg Q2W IV for a maximum of 12 months. Treatment was to be discontinued prior to 12 months if there was confirmed disease progression.	444
CD-ON-4736-1108 **Study 1108** 24 October 2016 Ongoing	Phase I/II, first-time-in-humans Open-label, 3+3 dose-escalation, dose-expansion, multicenter, international	Patients with advanced solid tumors, including NSCLC, that are refractory to standard therapy and for which no standard therapy exists	Dose-expansion phase: 10 mg/kg Q2W IV for a maximum of 12 months. Treatment was to be discontinued prior to 12 months if there was confirmed disease progression.	970 (from dose-expansion phase)

DCO = data cut-off; IV = intravenous; NSCLC = non-small cell lung cancer; Q2W = every 2 weeks
Source: PACIFIC interim CSR, Module 5.3.5.1; ATLANTIC CSR, Module 5.3.5.2; Study 1108 CSR, Module 5.3.5.2.

Patient exposure

Table 47 Duration of exposure (safety analysis set)

Treatment duration	Durvalumab (N=475)	Placebo (N=234)	Total (N=709)
Number of infusions			
n	475	234	709
Mean	16.5	14.8	16.0
Std Dev	9.01	8.83	8.98
Median	20.0	14.0	18.0
Min	1	1	1
Max	27	26	27
≥20 Infusions (% of population)	239 (50.3)	94 (40.2)	333 (47.0)
≥26 Infusions (% of population)	90 (18.9)	35 (15.0)	125 (17.6)
Total treatment duration (weeks) [a]			
n	475	234	709
Mean	35.1	31.0	33.7
Std Dev	18.66	18.29	18.63
Median	44.0	31.7	40.1
Min	1	1	1
Max	55	54	55
Total treatment duration (patient years)	319.8	138.8	458.6
Actual treatment duration (weeks) [b]			
n	475	234	709
Mean	33.0	29.6	31.8
Std Dev	18.01	17.66	17.95
Median	38.7	28.0	36.1
Min	1	1	1
Max	54	53	54
Total treatment duration (patient years)	300.0	132.7	432.7

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.
Max maximum; Min minimum; Std Dev standard deviation.
Source: Table 11.3.1.1

The duration of exposure at the 90-DSU DCO is summarized in Table 48.

Table 48: Duration of exposure- safety analysis set

	Durvalumab		Placebo	
Treatment duration	**DCO for sBLA**	**DCO for 90-DSU**	**DCO for sBLA**	**DCO for 90-DSU**
Number of infusions				
Mean (Standard deviation)	16.5 (9.01)	16.7 (9.12)	14.8 (8.83)	14.9 (8.93)
Median	20.0	20.0	14.0	14.0
Minimum, Maximum	1, 27	1, 27	1, 26	1, 26
≥20 infusions (% of population)	239 (50.3)	243 (51.2)	94 (40.2)	94 (40.2)
≥26 infusions (% of population)	90 (18.9)	101 (21.3)	35 (15.0)	43 (18.4)
Total treatment duration (weeks)				
Mean (Standard deviation)	35.1 (18.66)	35.5 (18.94)	31.0 (18.29)	31.2 (18.54)
Median	44.0	48.0	31.7	31.7
Minimum, Maximum	1, 55	1, 55	1, 54	1, 54
Total treatment duration (patient years)	319.8	323.3	138.8	140.0
Actual treatment duration (weeks)				
Mean (Standard deviation)	33.0 (18.01)	33.3 (18.27)	29.6 (17.66)	29.8 (17.91)
Median	38.7	40.1	28.0	28.0
Minimum, Maximum	1, 54	1, 54	1, 53	1, 53
Total treatment duration (patient years)	300.0	303.5	132.7	133.8

90-DSU 90-day safety update; DCO Data cut-off; sBLA Supplemental Biologic License Application.
Data source: Table 11.3.1.1.A, Appendix 1; and Table 11.3.1.1, PACIFIC interim CSR, Module 5.3.5.1.

Adverse events

Table 49: AES in any category (safety analysis set)

AE 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	152 (32.0)	65 (27.8)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	57 (12.0)	11 (4.7)
Any SAE (including events with outcome of death)	136 (28.6)	53 (22.6)
Any SAE (including events with outcome of death), causally related to treatment [b]	40 (8.4)	8 (3.4)
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)	14 (6.0)
Any AE with outcome of death, causally related to treatment[b]	7 (1.5)	3 (1.3)
Any AE leading to dose delay[c]	202 (42.5)	72 (30.8)
Any AESI	314 (66.1)	114 (48.7)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the Investigator. Missing responses are counted as related.
c 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 pre-treatment 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).
AE adverse event; AESI adverse event of special interest; CTCAE Common Terminology Criteria for Adverse Events; SAE serious adverse event.
Source: Table 11.3.2.1, Table 11.3.5.1

Most common AEs:

Table 50: Most common AEs (frecuency of >5% in either treatment group)(safety analysis set)

	Number (%) of patients[a]	
Preferred term	**Durvalumab (N=475)**	**Placebo (N=234)**
Patients with any AE	**460 (96.8)**	**222 (94.9)**
Cough	168 (35.4)	59 (25.2)
Fatigue	113 (23.8)	48 (20.5)
Dyspnoea	106 (22.3)	56 (23.9)
Radiation pneumonitis	96 (20.2)	36 (15.4)
Diarrhoea	87 (18.3)	44 (18.8)
Pyrexia	70 (14.7)	21 (9.0)
Decreased appetite	68 (14.3)	30 (12.8)
Nausea	66 (13.9)	31 (13.2)
Pneumonia	62 (13.1)	18 (7.7)
Pneumonitis	60 (12.6)	18 (7.7)
Arthralgia	59 (12.4)	26 (11.1)
Pruritus	58 (12.2)	11 (4.7)
Rash	58 (12.2)	17 (7.3)
Upper respiratory tract infection	58 (12.2)	23 (9.8)
Constipation	56 (11.8)	20 (8.5)
Hypothyroidism	55 (11.6)	4 (1.7)
Headache	52 (10.9)	21 (9.0)
Asthenia	51 (10.7)	31 (13.2)
Back pain	50 (10.5)	27 (11.5)
Insomnia	45 (9.5)	16 (6.8)
Productive cough	45 (9.5)	16 (6.8)
Nasopharyngitis	41 (8.6)	14 (6.0)
Musculoskeletal pain	39 (8.2)	24 (10.3)
Myalgia	38 (8.0)	10 (4.3)
Dry skin	37 (7.8)	12 (5.1)
Oedema peripheral	37 (7.8)	9 (3.8)
Vomiting	37 (7.8)	19 (8.1)
Anaemia	36 (7.6)	25 (10.7)
Hyperthyroidism	35 (7.4)	4 (1.7)
Non-cardiac chest pain	35 (7.4)	22 (9.4)
Bronchitis	33 (6.9)	19 (8.1)
Dizziness	33 (6.9)	21 (9.0)
Pain in extremity	32 (6.7)	12 (5.1)
Urinary tract infection	28 (5.9)	13 (5.6)
Hypertension	27 (5.7)	8 (3.4)
Musculoskeletal chest pain	25 (5.3)	18 (7.7)
Hypokalaemia	24 (5.1)	12 (5.1)
Paraesthesia	20 (4.2)	12 (5.1)

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 pre-treatment 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.
MedDRA version 19.1.
AE adverse event; MedDRA Medical Dictionary for Regulatory Activities.
Source: Table 11.3.2.2

Table 51: Most common CTCAE Grade 3 or 4 AEs (frecuency of >1%)(safety analysis set)

	Number (%) of patients[a]	
Preferred term	**Durvalumab (N=475)**	**Placebo (N=234)**
Patients with any AE of CTCAE Grade 3 or 4	152 (32.0)	65 (27.8)
Pneumonia	21 (4.4)	10 (4.3)
Anaemia	14 (2.9)	8 (3.4)
Hypertension	10 (2.1)	2 (0.9)
Pneumonitis	8 (1.7)	5 (2.1)
Dyspnoea	7 (1.5)	6 (2.6)
Radiation pneumonitis	7 (1.5)	1 (0.4)
Aspartate aminotransferase increased	6 (1.3)	0
Lung infection	6 (1.3)	2 (0.9)
Hyperglycaemia	5 (1.1)	1 (0.4)
Hypokalaemia	5 (1.1)	5 (2.1)
Sepsis	4 (0.8)	3 (1.3)
Diarrhoea	3 (0.6)	3 (1.3)
Fatigue	1 (0.2)	3 (1.3)

a Patients with multiple AEs of CTCAE Grade 3 or 4 are counted once for each preferred term.
Number (%) of patients with AEs of CTCAE Grade 3 or 4 with a total frequency of >1%, sorted in decreasing frequency of preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).
MedDRA version 19.1.
AE adverse event; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities.
Source: Table 11.3.2.5

Adverse events of special interest (AESI)

The Applicant also defined a category of "immune-mediated AEs", which were AEs that medical review determined to be consistent with an immune-mediated mechanism of action, required the use of systemic steroids or other immunosuppressant, or endocrine therapy, and for which there was no clear alternate etiology.

Table 52: AESIs and immune-mediated AEs categories (safety analysis set)

	Number (%) of patients[a]			
	Durvalumab (N=475)		Placebo (N=234)	
AE category	AESI	imAE [c]	AESI	imAE [c]
Any AE	311 (65.5)	115 (24.2)	114 (48.7)	19 (8.1)
Any AE causally related to treatment [b]	228 (48.0)	99 (20.8)	61 (26.1)	10 (4.3)
Any AE of CTCAE Grade 3 or 4	39 (8.2)	16 (3.4)	9 (3.8)	6 (2.6)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	28 (5.9)	14 (2.9)	6 (2.6)	4 (1.7)
Any SAE (including events with outcome of death)	24 (5.1)	20 (4.2)	12 (5.1)	9 (3.8)
Any SAE (including events with outcome of death), causally related to treatment [b]	23 (4.8)	20 (4.2)	6 (2.6)	5 (2.1)
Any AE leading to discontinuation of study treatment	35 (7.4)	28 (5.9)	9 (3.8)	7 (3.0)
Any AE with outcome of death	4 (0.8)	4 (0.8)	4 (1.7)	3 (1.3)
Any AE with outcome of death, causally related to treatment [b]	4 (0.8)	4 (0.8)	2 (0.9)	2 (0.9)
Received systemic corticosteroids	72 (15.2)	68 (14.3)	16 (6.8)	13 (5.6)
Received high dose steroids	42 (8.8)	39 (8.2)	12 (5.1)	10 (4.3)
Received endocrine therapy	55 (11.6)	51 (10.7)	3 (1.3)	3 (1.3)
Received other immunosuppressants	2 (0.4)	2 (0.4)	1 (0.4)	1 (0.4)
Event outcome resolved	185 (38.9)	50 (10.5)	74 (31.6)	8 (3.4)
Event outcome not resolved	122 (25.7)	61 (12.8)	36 (15.4)	8 (3.4)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the Investigator. Missing responses are counted as related.
c Immune-mediated AEs were adjudicated by the Sponsor.
Includes AEs with an onset date on or after the date of first dose and up to and including 90 days following the date of last dose of study medication or date of subsequent therapy, whichever occurs first.
AESI terms of Infusion related/Hypersensitivity/Anaphylactic reactions and Radiation pneumonitis are not included in this table.
Reasons of NOT RECOVERED/NOT RESOLVED, and RECOVERING/RESOLVING map to an outcome of Not Resolved.
Reasons of RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE map to an outcome of Resolved.

Table 53: AESIs and imAEs for durvalumab (safety analysis set)

AESI Category	Any AE	Any SAE	CTCAE Grade 3-4	Received Intervention: Systemic Cortico-steroid	Received Intervention: High Dose Steroid	Received Intervention: Other Immuno-suppressants	Received Intervention: Requires Endocrine Therapy	Leading to Discontinuation of Study Treatment	Resulted in Death	Event Outcome: Not Resolved	Event Outcome: Resolved
Adrenal insufficiency											
AESI	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	1
imAE	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	1
Colitis											
AESI	5 (1.1)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1	0	0	5
imAE	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1	0	0	1
Dermatitis											
AESI	85 (17.9)	0 (0.0)	0 (0.0)	5 (1.1)	2 (0.4)	0 (0.0)	0 (0.0)	1	0	28	57
imAE	5 (1.1)	0 (0.0)	0 (0.0)	5 (1.1)	2 (0.4)	0 (0.0)	0 (0.0)	1	0	2	3
Dermatitis or Rash											
AESI	155 (32.6)	0 (0.0)	4 (0.8)	9 (1.9)	5 (1.1)	0 (0.0)	0 (0.0)	2	0	47	108
imAE	9 (1.9)	0 (0.0)	2 (0.4)	9 (1.9)	5 (1.1)	0 (0.0)	0 (0.0)	2	0	4	5
Diabetes Mellitus Type 1											
AESI	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1	0	0	1
imAE	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1	0	0	1
Diarrhoea											
AESI	87 (18.3)	1 (0.2)	3 (0.6)	4 (0.8)	2 (0.4)	0 (0.0)	0 (0.0)	1	0	13	74
imAE	4 (0.8)	1 (0.2)	1 (0.2)	4 (0.8)	2 (0.4)	0 (0.0)	0 (0.0)	1	0	0	4
Diarrhoea or Colitis											
AESI	90 (18.9)	2 (0.4)	4 (0.8)	5 (1.1)	3 (0.6)	0 (0.0)	0 (0.0)	2	0	12	78
imAE	5 (1.1)	2 (0.4)	2 (0.4)	5 (1.1)	3 (0.6)	0 (0.0)	0 (0.0)	2	0	0	5
Hyperthyroidism											
AESI	48 (10.1)	0 (0.0)	0 (0.0)	5 (1.1)	1 (0.2)	0 (0.0)	12 (2.5)	0	0	11	37
imAE	13 (2.7)	0 (0.0)	0 (0.0)	5 (1.1)	1 (0.2)	0 (0.0)	10 (2.1)	0	0	5	8
Hypothyroidism											
AESI	63 (13.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	46 (9.7)	0	0	44	19
imAE	44 (9.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	44 (9.3)	0	0	35	9
Other rare/miscellaneous											
AESI	7 (1.5)	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	2	0	4	3
imAE	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	1	0	0	2
Pneumonitis											
AESI	65 (13.7)	17 (3.6)	9 (1.9)	48 (10.1)	31 (6.5)	2 (0.4)	0 (0.0)	24	4	27	34
imAE	51 (10.7)	14 (2.9)	8 (1.7)	44 (9.3)	28 (5.9)	2 (0.4)	0 (0.0)	21	4	20	27
Rash											
AESI	96 (20.2)	0 (0.0)	4 (0.8)	5 (1.1)	3 (0.6)	0 (0.0)	0 (0.0)	1	0	24	72
imAE	5 (1.1)	0 (0.0)	2 (0.4)	5 (1.1)	3 (0.6)	0 (0.0)	0 (0.0)	1	0	2	3
Select hepatic events											
AESI	35 (7.4)	0 (0.0)	9 (1.9)	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	2	0	10	25
imAE	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0	0	1	2
Select pancreatic events											
AESI	8 (1.7)	0 (0.0)	7 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1	0	1	7
imAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0
Select renal events											
AESI	30 (6.3)	3 (0.6)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1	0	11	19
imAE	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1	0	1	0

Includes AEs with an onset date on or after the date of first dose and up to and including 90 days following the date of last dose of study medication or date of subsequent therapy, whichever occurs first.
AESI terms of infusion-related/hypersensitivity/anaphylactic reactions and radiation pneumonitis are not included in this table.
Patients with multiple AEs are counted for each grade they report an AE for each category.
Reasons of not recovered/not resolved and recovering/resolving map to an outcome of not resolved.
Reasons of recovered/resolved, recovered/resolved with sequelae map to an outcome of resolved.

Immune mediated pneumonitis:

Table 54: Adverse events of special interest and immune mediated adverse events of pneumonitis, radiation pneumonitis, and pneumonitis or radiation pneumonitis by category in PACIFIC

					Treatment administered						
Event	Treatment	Category	Any AE	Grade 3-4	Systemic cortico-steroid	High-dose steroid	Other immune-suppressant	Led to discontin-uation	Resulted in death	Not resolved[b]	Resolved[b]
Pneumonitis or radiation pneumonitis	Durvalumab	AE	161 (33.9)	16 (3.4)	100 (21.1)	56 (11.8)	2 (0.4)	30	5	80 (49.7)	76 (47.2)
		imAE	79 (16.6)	12 (2.5)	60 (12.6)	37 (7.8)	2 (0.4)	24	5	31 (39.2)	43 (54.4)
	Placebo	AE	58 (24.8)	7 (3.0)	30 (12.8)	23 (9.8)	1 (0.4)	10	4	33 (56.9)	21 (36.2)
		imAE	31 (13.2)	7 (3.0)	22 (9.4)	17 (7.3)	1 (0.4)	9	4	14 (45.2)	13 (41.9)
Pneumonitis	Durvalumab	AESI	65 (13.7)	9 (1.9)	48 (10.1)	31 (6.5)	2 (0.4)	24	4	27 (41.5)	34 (52.3)
		imAE	51 (10.7)	8 (1.7)	44 (9.3)	28 (5.9)	2 (0.4)	21	4	20 (39.2)	27 (52.9)
	Placebo	AESI	22 (9.4)	6 (2.6)	13 (5.6)	11 (4.7)	1 (0.4)	7	3	11 (50.0)	8 (36.4)
		imAE	16 (6.8)	6 (2.6)	11 (4.7)	9 (3.8)	1 (0.4)	7	3	7 (43.8)	6 (37.5)
Radiation pneumonitis	Durvalumab	AE	96 (20.2)	7 (1.5)	52 (10.9)	25 (5.3)	0	6	1	53 (55.2)	42 (43.8)
		imAE	28 (5.9)	4 (0.8)	16 (3.4)	9 (1.9)	0	3	1	11 (39.3)	16 (57.1)
	Placebo	AE	36 (15.4)	1 (0.4)	17 (7.3)	12 (5.1)	0	3	1	22 (61.1)	13 (36.1)
		imAE	15 (6.4)	1 (0.4)	11 (4.7)	8 (3.4)	0	2	1	7 (46.7)	7 (46.7)

a As assessed by the investigator.
b Percentages for each outcome category are calculated using the number of patients who had the event (shown in the "Any AE" column) as the denominator.
Includes adverse events with an onset date on or after the date of first dose and up to and including 90 days following the date of last dose of study medication or date of subsequent therapy, whichever occurs first. Reasons of NOT RECOVERED/NOT RESOLVED, and RECOVERING/RESOLVING map to an outcome of Not Resolved. Reasons of RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE map to an outcome of Resolved.
AE = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events v4.03; imAE = immune-mediated adverse event
Source: Tables 11.3.8.7 and 11.3.8.8, PACIFIC interim CSR, Module 5.3.5.1

Table 55: Immune-Mediated Adverse Events by Preferred Terms in the Monoterapy Pool (n=1889)

					Treatment Related(a)			
AESI Category	Any AE	CTCAE Grade 3	CTCAE Grade 4	CTCAE Grade 5	Any AE	CTCAE Grade 3	CTCAE Grade 4	CTCAE Grade 5
Pneumonitis								
INTERSTITIAL LUNG DISEASE	7(0.4)	0(0.0)	0(0.0)	0(0.0)	6(0.3)	0(0.0)	0(0.0)	0(0.0)
PNEUMONITIS	70(3.7)	12(0.6)	1(0.1)	5(0.3)	53(2.8)	9(0.5)	1(0.1)	5(0.3)
PULMONARY FIBROSIS	2(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

[a] As assessed by the investigator.
Includes adverse events with an onset date on or after the date of first dose and up to and including 90 days following the date of last dose of study medication or date of subsequent therapy, whichever occurs first.
AESI terms of Infusion related/Hypersensitivity/Anaphylactic reactions and Radiation pneumonitis are not included in this table.
Patients with multiple AEs are counted for each grade they report an AE for each category / preferred term.
imAE = Immune Mediated Adverse Event.
MedDRA version 19.1.
CTCAE = Common Terminology Criteria for Adverse Events (version 4.0).

In the combined safety database 45 of the 79 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. Durvalumab was discontinued in 26 patients. Resolution occurred in 42 patients.

In the PACIFIC Study, immune-mediated pneumonitis occurred more frequently in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (10.7%), than in the other patients in the combined safety database (2.0%).

In the PACIFIC Study, the median time to onset in the durvalumab -treated group was 53 days (range: 1-341 days) vs. 55.5 days (range: 0-231 days) in the placebo group. In the durvalumab -treated group, 44 of the 51 patients received systemic corticosteroids, including 28 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group, 11 of the 16 patients received systemic corticosteroids, including 9 patients who received

high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred for 27 patients in the durvalumab treated group vs 6 in placebo.

Immune-mediated hepatitis

In the combined safety database with durvalumab monotherapy, immune-mediated hepatitis occurred in 19 (1.0%) patients, including Grade 3 in 11 (0.6%) patients and Grade 5 (fatal) in 1 (< 0.1%) patient. The median time to onset was 70 days (range: 15-312 days). Thirteen of the 19 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received mycophenolate treatment. Durvalumab was discontinued in 4 patients. Resolution occurred in 13 patients.

Immune-mediated colitis

In the combined safety database with durvalumab monotherapy, immune-mediated colitis or diarrhoea occurred in 31 (1.6%) patients, including Grade 3 in 6 (0.3%) patients and Grade 4 in 1 (<0.1%) patient. The median time to onset was 74 days (range: 1-365 days). Sixteen of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment. Durvalumab was discontinued in 8 patients. Resolution occurred in 23 patients.

Immune-mediated endocrinopathies

Hypothyroidism

In the combined safety database with durvalumab monotherapy, immune-mediated hypothyroidism occurred in 137 (7.3%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 85 days (range: 9-378 days). Of the 137 patients, 134 patients received hormone replacement therapy and two patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for hypothyroidism followed by hormone replacement. Durvalumab was not discontinued in any patient due to hypothyroidism.

Hyperthyroidism

In the combined safety database with durvalumab monotherapy, immune-mediated hyperthyroidism occurred in 34 (1.8%) patients, there were no Grade 3 or 4 cases. The median time to onset was 41 days (range: 14-195 days). Twenty-six of the 34 patients received medical therapy (thiamazole, carbimazole, propylthiouracil or beta-blocker), 12 patients received thyroxine when hyperthyroidism transitioned to hypothyroidism, 12 patients received systemic corticosteroids and 3 of the 12 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Durvalumab was not discontinued in any patient due to hyperthyroidism. Eight patients experienced hypothyroidism following hyperthyroidism.

Adrenal insufficiency

In the combined safety database with durvalumab monotherapy, immune-mediated adrenal insufficiency occurred in 7 (0.4%) patients, including Grade 3 in 1 (<0.1%) patient. The median time to onset was 141 days (range: 70-265 days). All 7 patients received systemic corticosteroids; 2 of the 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Durvalumab was not discontinued in any patient due to adrenal insufficiency. Resolution occurred in 1 patient.

Type 1 diabetes mellitus

In the combined safety database with durvalumab monotherapy, immune-mediated type 1 diabetes mellitus occurred in 1 (< 0.1%) patient (Grade 3). Durvalumab was discontinued due to type 1 diabetes mellitus. The time to onset was 42 days. This 1 patient received insulin.

Hypophysitis/Hypopituitarism

In the combined safety database with durvalumab monotherapy, immune-mediated hypopituitarism occurred in 1 (< 0.1%) patient (Grade 3). This 1 patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and durvalumab was not discontinued.

Immune-mediated nephritis

In the combined safety database with durvalumab monotherapy, immune-mediated nephritis occurred in 3 (0.2%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 95 days (range: 28-239 days). Two (0.1%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Durvalumab was discontinued in all 3 patients. Resolution occurred in 2 patients.

Immune-mediated rash

In the combined safety database with durvalumab monotherapy, immune-mediated rash or dermatitis occurred in 30 (1.6%) patients, including Grade 3 in 7 (0.4%) patients. The median time to onset was 74 days (range: 1-365 days). Eleven of the 30 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Durvalumab was discontinued in 2 patients. Resolution occurred in 18 patients.

Infection:

Table 56: Infection adverse events by category (PACIFIC - safety analysis set)

Adverse event category	Number (%) of patients[a]	
	Durvalumab (N=475)	Placebo (N=234)
Any adverse event	266 (56.0)	109 (46.6)
Any AE causally related to treatment [b]	26 (5.5)	10 (4.3)
Any AE of CTCAE grade 3 or 4	43 (9.1)	18 (7.7)
Any AE of CTCAE grade 3 or 4, causally related to treatment [b]	6 (1.3)	1 (0.4)
Any SAE (including events with outcome = death)	52 (10.9)	21 (9.0)
Any SAE (including events with outcome = death), causally related to treatment [b]	8 (1.7)	1 (0.4)
Any AE leading to discontinuation of study treatment[c]	11 (2.3)	6 (2.6)
Any AE leading to discontinuation of study treatment, causally related to treatment [b]	5 (1.1)	1 (0.4)
Any AE with outcome = death	5 (1.1)	5 (2.1)
Any AE with outcome = death, causally related to treatment[b]	0	0
Any AE leading to dose delay[d]	65 (13.7)	25 (10.7)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the investigator. Missing responses are counted as related.
c Action taken = study treatment permanently stopped
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 pre-treatment 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).
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); SAE = serious adverse event
Source: Table 11.3.2.4, Table 11.3.2.4.1, Table 11.3.2.8, Table 11.3.3.1.3, Table 11.3.3.1.3.1, Table 11.3.4.1.1, Table 11.3.4.1.2, Table 11.3.4.2.1, and Table 11.3.4.2.2, PACIFIC interim CSR, Module 5.3.5.1

The incidence of the specific infection AEs was generally similar in the durvalumab and placebo group:

- Pneumonia (grouped term): 17.1% durvalumab, 11.5% placebo
- Upper respiratory tract infection (grouped term): 26.1% durvalumab, 19.2% placebo.
- Dental/oral soft tissue infection (grouped term): 3.6% durvalumab, 0.4% placebo.
- Oral candidiasis (preferred term): 3.2% durvalumab, 0.9% placebo
- Influenza (preferred term): 2.5% durvalumab, 0.9% placebo.

Adverse drug reactions

The frequency of ADRs in the target population is estimated based on the AE frequency in PACIFIC, regardless of causality. All identified ADRs are included in the Table 57.

Table 57: Adverse drug reactions in patients with Stage III unresectable NSCLC treated with Imfinzi at 10 mg/kg

	Any Grade (%)		Grade 3-4 (%)
Infections and infestations			
Upper respiratory tract infections[a]	Very common	26.1	0.4
Pneumonia[b,c]	Very common	17.1	6.5
Dental and oral soft tissue infections[d]	Common	3.6	0
Oral candidiasis	Common	3.2	0
Influenza	Common	2.5	0
Endocrine disorders			
Hypothyroidism[e]	Very common	11.6	0.2
Hyperthyroidism[f]	Common	8.2	0

Adrenal insufficiency	Uncommon	0.2	0
Type 1 diabetes mellitus	Uncommon	0.2	0.2
Hypophysitis/ Hypopituitarism	Rare[g]	<0.1	<0.1
Diabetes insipidus	Rare[g]	<0.1	<0.1
Cardiac disorders			
Myocarditis	Rare[g]	<0.1	<0.1
Respiratory, thoracic and mediastinal disorders			
Cough/Productive Cough[h]	Very common	40.2	0.6
Pneumonitis[b]	Very common	12.6	1.7
Dysphonia	Common	3.8	0
Interstitial lung disease	Uncommon	0.6	0
Gastrointestinal disorders			
Diarrhoea	Very common	18.3	0.6
Abdominal pain[i]	Very common	10.1	0.4
Colitis[j]	Common	1.1	0.2
Hepatobiliary disorders			
Aspartate aminotransferase increased or Alanine aminotransferase increased[g]	Common	6.1	1.9
Hepatitis[b,k]	Uncommon	0.6	0
Skin and subcutaneous tissue disorders			
Rash[l]	Very common	21.7	0.6
Pruritus[n]	Very common	12.4	0
Dermatitis	Common	1.5	0
Night sweats	Common	2.3	0
Musculoskeletal and connective tissue disorders			
Myalgia	Common	8.0	0.2
Myositis	Uncommon	0.4	0
Polymyositis[h]	Rare[f]	<0.1	<0.1
Renal and urinary disorders			
Blood creatinine increased	Common	4.6	0.2
Dysuria	Common	2.3	0
Nephritis[o]	Uncommon	0.4	0
General disorders and administration site conditions			
Pyrexia	Very common	14.7	0.2
Peripheral oedema	Common	7.8	0
Injury, poisoning and procedural complications			
Infusion related reaction[po]	Common	1.9	0

- [a] includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.
- [b] includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal and pneumonia streptococcal.
- [c] fatal pneumonitis and fatal pneumonia were reported at similar rate between the Imfinzi-treated group and placebo group in the PACIFIC Study; fatal hepatitis and fatal polymyositis were reported in other clinical trials.
- [d] includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.
- [e] includes autoimmune hypothyroidism and hypothyroidism.
- [f] includes hyperthyroidism, autoimmune thyroiditis, thyroiditis, thyroiditis subacute and Basedow's disease.
- [g] frequency is based on events not observed in the PACIFIC Study but observed in other clinical trials (n=1889).
- [h] includes cough and productive cough.
- [i] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
- [j] includes colitis, enteritis, enterocolitis, and proctitis.
- [k] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, and hepatotoxicity.
- [l] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
- [m] includes pruritus generalised and pruritus.
- [n] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
- [o] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.

[p] includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 58: Most common SAEs (frequency of >1%) (safety analysis set).

System organ class/ Preferred term	Number (%) of patients [a] Durvalumab (N=475)	Placebo (N=234)
Patients with any SAE	**136 (28.6)**	**53 (22.6)**
Pneumonia	27 (5.7)	12 (5.1)
Pneumonitis	16 (3.4)	7 (3.0)
Radiation pneumonitis	17 (3.6)	3 (1.3)
Lung infection	6 (1.3)	2 (0.9)
Chronic obstructive pulmonary disease	5 (1.1)	0 (0.0)

a Number (%) of patients with an SAE, sorted by international order for SOC and alphabetically for PT.
Patients with multiple SAEs are counted once for each system organ class / preferred term.
Includes SAEs with an onset date on or after the date of first dose or pre-treatment 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).
MedDRA version 19.1.
AE adverse event; MedDRA Medical Dictionary for Regulatory Activities; PT preferred term; SAE serious adverse event; SOC system organ class.
Source: Derived from Table 11.3.4.1.1

Table 59: Serious adverse events, casually related to study treatment, by system organ class and preferred term (PACIFIC - Safety analysis set)

System organ class/ Preferred term	Number (%) of patients [a] MEDI4736 (N=475)	Placebo (N=234)
Patients with a causally related SAE [b]	40 (8.4)	8 (3.4)
Infections and infestations	8 (1.7)	1 (0.4)
Herpes zoster	2 (0.4)	0
Lung infection	2 (0.4)	1 (0.4)
Pneumocystis jirovecii pneumonia	1 (0.2)	0
Pneumonia	3 (0.6)	0
Blood and lymphatic system disorders	1 (0.2)	0
Thrombocytopenia	1 (0.2)	0
Immune system disorders	1 (0.2)	0
Sarcoidosis	1 (0.2)	0
Metabolism and nutrition disorders	2 (0.4)	0
Iron overload	1 (0.2)	0
Type 1 diabetes mellitus	1 (0.2)	0
Cardiac disorders	3 (0.6)	0
Cardiomyopathy	1 (0.2)	0
Pericardial effusion	1 (0.2)	0
Right ventricular failure	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	18 (3.8)	5 (2.1)
Acute interstitial pneumonitis	1 (0.2)	0
Dyspnoea	1 (0.2)	0
Interstitial lung disease	0	1 (0.4)
Pneumonitis	16 (3.4)	4 (1.7)
Respiratory distress	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Gastrointestinal disorders	2 (0.4)	1 (0.4)
Diarrhoea	1 (0.2)	1 (0.4)
Enteritis	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.2)	0
Polymyalgia rheumatica	1 (0.2)	0
Renal and urinary disorders	2 (0.4)	0
Glomerulonephritis membranous	1 (0.2)	0
Renal tubular acidosis	1 (0.2)	0
General disorders and administration site conditions	0	1 (0.4)
Death	0	1 (0.4)
Investigations	2 (0.4)	0
Brain natriuretic peptide increased	1 (0.2)	0
Myocardial necrosis marker increased	1 (0.2)	0
Injury, poisoning and procedural complications	5 (1.1)	0
Infusion related reaction	1 (0.2)	0
Radiation pneumonitis	4 (0.8)	0

SAE = Serious AE.
[a] Number (%) of patients with a causally related SAE, sorted by international order for system organ class and alphabetically for preferred term.
[b] Causally related to treatment, as assessed by the investigator. Missing responses are counted as related.
Patients with multiple causally related SAEs are counted once for each system organ class / preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).
MedDRA version 19.1.

Deaths

Table 60: Adverse events with outcome of death by SOC and PT (safety analysis set)

System organ class/ Preferred term	Number (%) of patients[a] Durvalumab (N=475)	Placebo (N=234)
Patients with any AE with outcome of death	**21 (4.4)**	**14 (6.0)**
Infections and infestations	**5 (1.1)**	**5 (2.1)**
Pneumonia	1 (0.2)	3 (1.3)
Pneumonia bacterial	1 (0.2)	0
Pneumonia pneumococcal	1 (0.2)	0
Pneumonia streptococcal	0	1 (0.4)
Sepsis	1 (0.2)	0
Septic shock	1 (0.2)	0
West Nile viral infection	0	1 (0.4)
Cardiac disorders	**5 (1.1)**	**2 (0.9)**
Cardiac arrest	2 (0.4)	1 (0.4)
Cardiomyopathy	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0
Eosinophilic myocarditis	0	1 (0.4)
Myocardial infarction	1 (0.2)	0
Vascular disorders	**1 (0.2)**	**0**
Aortic dissection	1 (0.2)	0
Respiratory, thoracic, and mediastinal disorders	**8 (1.7)**	**4 (1.7)**
Dyspnoea	1 (0.2)	0
Emphysema	1 (0.2)	0
Haemoptysis	1 (0.2)	1 (0.4)
Pneumonitis	4 (0.8)	3 (1.3)
Respiratory distress	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Gastrointestinal disorders	**0**	**1 (0.4)**
Intestinal obstruction	0	1 (0.4)
General disorders and administration site conditions	**1 (0.2)**	**1 (0.4)**
Death	1 (0.2)	1 (0.4)
Injury, poisoning, and procedural complications	**1 (0.2)**	**2 (0.9)**
Post procedural fistula	0	1 (0.4)
Radiation pneumonitis	1 (0.2)	1 (0.4)

a Number (%) of patients with an AE with outcome of death, sorted by international order for system organ class and alphabetically for preferred term.
Patients with multiple AEs with outcome of death are counted once for each system organ class / preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).

Table 61: Adverse events with outcome of death, casually related to study treatment, by system organ class and preferred term (PACIFIC - Safety analysis set)

System organ class/ Preferred term	Number (%) of patients [a] MEDI4736 (N=475)	Placebo (N=234)
Patients with a causally-related AE with outcome of death [b]	7 (1.5)	3 (1.3)
Cardiac disorders	1 (0.2)	0
Cardiomyopathy	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	5 (1.1)	2 (0.9)
Pneumonitis	4 (0.8)	2 (0.9)
Respiratory distress	1 (0.2)	0
Respiratory failure	1 (0.2)	0
General disorders and administration site conditions	0	1 (0.4)
Death	0	1 (0.4)
Injury, poisoning and procedural complications	1 (0.2)	0
Radiation pneumonitis	1 (0.2)	0

[a] Number (%) of patients with AE with outcome of death, sorted by international order for system organ class and alphabetically for preferred term.
[b] Causally related to treatment, as assessed by the investigator. Missing responses are counted as related.
Patients with multiple AEs with outcome of death are counted once for each system organ class / preferred term.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).
MedDRA version 19.1.

Laboratory findings

In patients treated with durvalumab in the PACIFIC Study, the proportion of patients who experienced a laboratory abnormality worsening from baseline was as follows: 38.5% (all Grades), 2.3% (Grades 3-4) for alanine aminotransferase increased, 36.0% (all Grades), 2.8% (Grade 3-4) for aspartate aminotransferase increased, 16.3% (all Grades) for creatinine increased, 26.5% (all Grades) for TSH elevated > ULN and above baseline, 31.9% (all Grades) for TSH decreased < LLN and below baseline.

Haematology laboratory parameters

Table 62: Clinically important changes in hematology parameters (safety analysis set)

	n/N (%) of patients					
	Durvalumab (N=475)			Placebo (N=234)		
Hematology parameter	≥1 CTCAE Grade changes	≥2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
Hemoglobin	73/471 (15.5)	6/471 (1.3)	9/471 (1.9)	37/229 (16.2)	5/229 (2.2)	9/229 (3.9)
Leukocytes	86/471 (18.3)	6/471 (1.3)	1/471 (0.2)	46/229 (20.1)	5/229 (2.2)	0/229
Lymphocytes	200/466 (42.9)	56/466 (12.0)	78/466 (16.7)	89/227 (39.2)	32/227 (14.1)	41/227 (18.1)
Neutrophils	35/466 (7.5)	15/466 (3.2)	2/466 (0.4)	14/227 (6.2)	4/227 (1.8)	0/227
Platelets	53/471 (11.3)	5/471 (1.1)	2/471 (0.4)	30/229 (13.1)	0/229	0/229

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.
Hematology parameters are all low unless stated otherwise.
CTCAE Common Terminology Criteria for Adverse Events.
Source: Table 11.3.10.4.1

Blood chemistry laboratory parameters

Table 63: Clinically important changes in clinical chemistry parameters (safety analysis set)

	n/N (%) of patients					
	Durvalumab (N=475)			Placebo (N=234)		
Clinical chemistry parameter	≥1 CTCAE Grade changes	≥2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
ALT	181/470 (38.5)	24/470 (5.1)	11/470 (2.3)	49/228 (21.5)	2/228 (0.9)	1/228 (0.4)
Albumin	80/469 (17.1)	33/469 (7.0)	2/469 (0.4)	43/228 (18.9)	26/228 (11.4)	4/228 (1.8)
Alkaline Phosphatase	87/471 (18.5)	7/471 (1.5)	5/471 (1.1)	31/228 (13.6)	1/228 (0.4)	1/228 (0.4)
AST	169/469 (36.0)	17/469 (3.6)	13/469 (2.8)	48/228 (21.1)	4/228 (1.8)	1/228 (0.4)
Bicarbonate	51/332 (15.4)	3/332 (0.9)	0/332	20/159 (12.6)	3/159 (1.9)	0/159
Corrected Calcium	225/468 (48.1)	8/468 (1.7)	2/468 (0.4)	95/226 (42.0)	1/226 (0.4)	1/226 (0.4)
Low	217/468 (46.4)	4/468 (0.9)	1/468 (0.2)	92/226 (40.7)	0/226	0/226
High	9/468 (1.9)	4/468 (0.9)	1/468 (0.2)	3/226 (1.3)	1/226 (0.4)	1/226 (0.4)
Creatinine	76/465 (16.3)	5/465 (1.1)	0/465	23/226 (10.2)	1/226 (0.4)	0/226
GGT	42/178 (23.6)	7/178 (3.9)	6/178 (3.4)	13/ 59 (22.0)	1/ 59 (1.7)	1/ 59 (1.7)
Glucose	246/461 (53.4)	90/461 (19.5)	38/461 (8.2)	117/227 (51.5)	35/227 (15.4)	18/227 (7.9)
Low	15/461 (3.3)	4/461 (0.9)	0/461	3/227 (1.3)	2/227 (0.9)	1/227 (0.4)
High	238/461 (51.6)	88/461 (19.1)	38/461 (8.2)	115/227 (50.7)	34/227 (15.0)	17/227 (7.5)
Magnesium	44/442 (10.0)	3/442 (0.7)	5/442 (1.1)	11/218 (5.0)	0/218	0/218
Low	30/442 (6.8)	0/442	2/442 (0.5)	9/218 (4.1)	0/218	0/218
High	15/442 (3.4)	3/442 (0.7)	3/442 (0.7)	2/218 (0.9)	0/218	0/218
Potassium	206/470 (43.8)	35/470 (7.4)	12/470 (2.6)	88/228 (38.6)	15/228 (6.6)	8/228 (3.5)
Low	65/470 (13.8)	7/470 (1.5)	7/470 (1.5)	24/228 (10.5)	4/228 (1.8)	4/228 (1.8)
High	150/470 (31.9)	28/470 (6.0)	5/470 (1.1)	65/228 (28.5)	11/228 (4.8)	4/228 (1.8)
Sodium	210/470 (44.7)	19/470 (4.0)	18/470 (3.8)	86/228 (37.7)	7/228 (3.1)	7/228 (3.1)
Low	157/470 (33.4)	17/470 (3.6)	17/470 (3.6)	68/228 (29.8)	7/228 (3.1)	7/228 (3.1)
High	56/470 (11.9)	2/470 (0.4)	1/470 (0.2)	19/228 (8.3)	0/228	0/228
Total Bilirubin	28/469 (6.0)	5/469 (1.1)	0/469	14/229 (6.1)	1/229 (0.4)	0/229

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.
ALT alanine aminotransferase; AST aspartate aminotransferase; CTCAE Common Terminology Criteria for Adverse Events (version 4); GGT gamma glutamyl transferase.
Source: Table 11.3.10.4.2

Liver parameters

Table 64: Liver function abnormalities on treatment (safety analysis set)

Parameter	Number (%) of patients Durvalumab (N=475)	 Placebo (N=234)
ALT		
≥3x - ≤5x ULN	17 (3.6)	3 (1.3)
>5x - ≤8x ULN	7 (1.5)	1 (0.4)
>8x - ≤10x ULN	0	0
>10x - ≤20x ULN	4 (0.8)	0
>20x ULN	0	0
AST		
≥3x - ≤5x ULN	5 (1.1)	4 (1.7)
>5x - ≤8x ULN	10 (2.1)	0
>8x - ≤10x ULN	2 (0.4)	1 (0.4)
>10x - ≤20x ULN	0	0
>20x ULN	1 (0.2)	0
Total bilirubin		
≥2x - ≤3x ULN	0	2 (0.9)
>3x - ≤5x ULN	0	0
>5x ULN	0	0
ALT or AST		
≥3x - ≤5x ULN	17 (3.6)	6 (2.6)
>5x - ≤8x ULN	10 (2.1)	0
>8x - ≤10x ULN	2 (0.4)	1 (0.4)
>10x - ≤20x ULN	3 (0.6)	0
>20x ULN	1 (0.2)	0
Potential Hy's law [a]		
(ALT or AST ≥3x ULN) and total bilirubin ≥2x ULN	0	0

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).
ALT alanine aminotransferase, AST aspartate aminotransferase, ULN upper limit of normal.
Source: Table 11.3.10.5.1

Kidney parameters

Table 65: Creatinine clearance, baseline versus minimum value on treatment (PACIFIC - Safety analysis set)

			Minimum value during treatment (%) [b]				
Group	Baseline assessment	Patient at baseline [a]	Normal	Mild Impairment	Moderate Impairment	Severe Impairment	Kidney Failure
MEDI4736 (N=475)	Normal	187	98 (21.3)	80 (17.4)	9 (2.0)	0	0
	Mild Impairment	217	5 (1.1)	153 (33.2)	59 (12.8)	0	0
	Moderate Impairment	57	0	4 (0.9)	50 (10.8)	3 (0.7)	0
	Severe Impairment	0	0	0	0	0	0
	Kidney Failure	0	0	0	0	0	0
	Total Evaluable	461	103 (22.3)	237 (51.4)	118 (25.6)	3 (0.7)	0
Placebo (N=234)	Normal	90	50 (22.5)	39 (17.6)	1 (0.5)	0	0
	Mild Impairment	98	3 (1.4)	72 (32.4)	23 (10.4)	0	0
	Moderate Impairment	34	0	4 (1.8)	30 (13.5)	0	0
	Severe Impairment	0	0	0	0	0	0
	Kidney Failure	0	0	0	0	0	0
	Total Evaluable	222	53 (23.9)	115 (51.8)	54 (24.3)	0	0

[a] Patients with a baseline value and at least one on-treatment value. Percentages have been calculated using the number of patients with a baseline value and a post baseline value.
[b] 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).
Baseline is defined as the last result obtained prior to the start of study treatment.
Creatinine clearance is derived according to the Cockroft-Gault formula.
Normal: Glomerular filtration rate (GFR)>= 90 mL/min; Mild Impairment: GFR >= 60 - < 90 mL/min; Moderate Impairment: GFR >= 30 - < 60 mL/min; Severe Impairment: GFR >= 15 - < 30 mL/min; Kidney Failure: GFR < 15 mL/min.

Severe renal impairment was observed in 3 patients treated with durvalumab vs no patients treated with placebo. All of these 3 patients entered the study with moderate renal impairment.

Table 66: Reversibility of creatinine clearance based on laboratory assessment date ≤90 days after last dose or <date of subsequent therapy, whichever occurred first – PACIFIC - Safety analysis set

	Durvalumab		**Placebo**	
	N	**n, %**	**N**	**n, %**
Patients shifting into a worse renal impairment category from baseline*	461	151 (32.8)	222	63 (28.4)
Patients whose shift from baseline was reversible and transient**	125	105 (84.0)	52	48 (92.3)

*Evaluable patients defined as patients with a baseline CrCl value and an on-treatment CrCl value.
** Evaluable patients defined as patients with a subsequent CrCl value after shifted to the worst on-treatment CrCl value. Reversible and transient is defined as a subsequent CrCl value that is higher than the worst CrCl value and in a better impairment category.
Data Source: 11.3.10.3.3.A, Appendix 1.

Thyroid parameters

Table 67: Abnormal on-treatment thyroid tests (safety analysis set)

	Number (%) of patients	
Thyroid function tests	**Durvalumab (N=475)**	**Placebo (N=234)**
Elevated TSH >ULN	134 (28.2)	36 (15.4)
Elevated TSH >ULN with TSH ≤ULN at baseline	111 (23.4)	24 (10.3)
Elevated TSH >3 x ULN	53 (11.2)	6 (2.6)
Elevated TSH >3 x ULN with TSH ≤ULN at baseline	42 (8.8)	2 (0.9)
Elevated TSH >10 x ULN	23 (4.8)	1 (0.4)
Elevated TSH >10 x ULN with TSH ≤ULN at baseline	18 (3.8)	0
Low TSH <LLN	160 (33.7)	37 (15.8)
Low TSH <LLN with TSH ≥LLN at baseline	117 (24.6)	29 (12.4)

Derived from laboratory assessments between the start of treatment and up to and including 30 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first).
LLN lower limit of normal TSH thyroid stimulating hormone, ULN upper limit of normal.

Immunogenicity

Of the 1570 patients who were treated with durvalumab 10 mg/kg every 2 weeks and evaluable for the presence of ADAs, 2.9% (45/1570) of patients tested positive for treatment-emergent ADAs. Neutralising antibodies (nAbs) against durvalumab were detected in 0.5% (8/1570) of patients.

Data from the PACIFIC trial are described below.

Table 68: Number (%) of patients who had at least 1 AE in any category by ADA category (ADA-evaluable)

AE Category [a]	Durvalumab 10 mg/kg Q2W N=401	Placebo N=200
Treatment-emergent ADA positive		
Number of patients in ADA category	7	5
Any AE	7 (100.0)	5 (100.0)
Any AE causally related to treatment [b]	6 (85.7)	4 (80.0)
Any AE of CTCAE Grade 3 or 4	2 (28.6)	1 (20.0)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	1 (14.3)	1 (20.0)
Any AE with outcome of death	0	1 (20.0)
Any SAE (including events with outcome of death)	3 (42.9)	1 (20.0)
Any AE leading to discontinuation of study treatment	3 (42.9)	1 (20.0)
Any AESI	6 (85.7)	4 (80.0)
ADA positive		
Number of patients in ADA category	18	10
Any AE	17 (94.4)	10 (100.0)
Any AE causally related to treatment [b]	13 (72.2)	6 (60.0)
Any AE of CTCAE Grade 3 or 4	4 (22.2)	2 (20.0)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	2 (11.1)	2 (20.0)
Any AE with outcome of death	0	1 (10.0)
Any SAE (including events with outcome of death)	4 (22.2)	1 (10.0)

Any AE leading to discontinuation of study treatment	3 (16.7)	1 (10.0)
Any AESI	13 (72.2)	5 (50.0)
ADA negative		
Number of patients in ADA category	383	190
Any AE	373 (97.4)	180 (94.7)
Any AE causally related to treatment [b]	262 (68.4)	104 (54.7)
Any AE of CTCAE Grade 3 or 4	115 (30.0)	49 (25.8)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	41 (10.7)	8 (4.2)
Any AE with outcome of death	11 (2.9)	8 (.2)
Any SAE (including events with outcome of death)	102 (26.6)	35 (18.4)
Any AE leading to discontinuation of study treatment	49 (12.8)	16 (8.4)
Any AESI	263 (68.7)	94 (49.5)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the Investigator. Missing responses are counted as related.
Number of patients in the ADA category are included in the denominator N calculation
ADA-evaluable population includes patients who have non-missing baseline ADA and at least 1 non-missing post-baseline ADA results.
Treatment-emergent (ADA incidence) is defined as the sum of both treatment-induced (post-baseline ADA-positive only) and treatment-boosted ADA.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).
ADA antidrug antibody; AE adverse event; AESI adverse event of special interest; CTCAE Common Terminology Criteria for Adverse Events; SAE serious adverse event; Q2W every 2 weeks.

No patients with positive ADA status experienced infusion-related reactions. Three patients treated with durvalumab were nAb-positive and did not report AEs suggestive of an infusion reaction or hypersensitivity type reaction. The types of AEs reported in ADA-positive patients were similar to those reported in patients who were ADA-negative (Data not shown).

Local tolerance

In the combined safety database with durvalumab monotherapy, infusion related reactions occurred in 35 (1.9%) patients, including Grade 3 in 5 (0.3%) patients.

Safety in special populations

- Safety in the different age groups

Table 69: Number of patients reporting at least one advserse event within the SOCs/SMQs of most relevance to elderly patients (safety analysis set) (Age <65)

	Number (%) of patients		
	Pacific		
	MEDI4736 (N=260)	Placebo (N=129)	Monotherapy Pool (N=1068)
Total AEs	251 (96.5)	120 (93.0)	1034 (96.8)
Serious AEs - Total	64 (24.6)	24 (18.6)	380 (35.6)
Fatal	4 (1.5)	5 (3.9)	50 (4.7)
Hospitalization/prolong existing hospitalization	58 (22.3)	21 (16.3)	357 (33.4)
Life-threatening	7 (2.7)	1 (0.8)	39 (3.7)
Persistent or Significant Disability/incapacity	0	0	4 (0.4)
Other (medically Serious Event)	12 (4.6)	5 (3.9)	33 (3.1)
Congenital Abnormality/Birth Defect	0	0	0
AE leading to drop-out	33 (12.7)	8 (6.2)	92 (8.6)
Psychiatric disorders	40 (15.4)	22 (17.1)	181 (16.9)
Nervous system disorders	100 (38.5)	33 (25.6)	356 (33.3)
Accidents and injuries	14 (5.4)	3 (2.3)	59 (5.5)
Cardiac disorders	18 (6.9)	13 (10.1)	88 (8.2)
Vascular disorders	35 (13.5)	9 (7.0)	135 (12.6)
Cerebrovascular disorders	1 (0.4)	0	9 (0.8)
Infections and infestations	142 (54.6)	56 (43.4)	448 (41.9)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	29 (11.2)	9 (7.0)	126 (11.8)

Table 70: Number of patients reporting at least one adverse event within the SOCs/SMQs of most relevance to elderly patients (safety analysis set) (Age 65-74)

	Number (%) of patients		
	Pacific		
	MEDI4736 (N=179)	Placebo (N=87)	Monotherapy Pool (N=633)
Total AEs	173 (96.6)	85 (97.7)	616 (97.3)
Serious AEs - Total	55 (30.7)	26 (29.9)	241 (38.1)
Fatal	15 (8.4)	9 (10.3)	41 (6.5)
Hospitalization/prolong existing hospitalization	49 (27.4)	23 (26.4)	217 (34.3)
Life-threatening	7 (3.9)	3 (3.4)	19 (3.0)
Persistent or Significant Disability/incapacity	0	0	6 (0.9)
Other (medically Serious Event)	11 (6.1)	3 (3.4)	35 (5.5)
Congenital Abnormality/Birth Defect	0	0	0
AE leading to drop-out	30 (16.8)	14 (16.1)	68 (10.7)
Psychiatric disorders	25 (14.0)	15 (17.2)	110 (17.4)
Nervous system disorders	55 (30.7)	32 (36.8)	199 (31.4)
Accidents and injuries	16 (8.9)	7 (8.0)	37 (5.8)
Cardiac disorders	23 (12.8)	9 (10.3)	68 (10.7)
Vascular disorders	31 (17.3)	13 (14.9)	86 (13.6)
Cerebrovascular disorders	3 (1.7)	0	9 (1.4)
Infections and infestations	107 (59.8)	44 (50.6)	293 (46.3)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	21 (11.7)	15 (17.2)	73 (11.5)

Table 71: Number of patients reporting at least one advserse event within the SOCs/SMQs of most relevance to elderly patients (safety analysis set) (Age 75-84)

	Number (%) of patients		
	Pacific		
	MEDI4736 (N=36)	Placebo (N=16)	Monotherapy Pool (N=181)
Total AEs	36 (100.0)	16 (100.0)	177 (97.8)
Serious AEs - Total	17 (47.2)	2 (12.5)	79 (43.6)
Fatal	2 (5.6)	0	10 (5.5)
Hospitalization/prolong existing hospitalization	16 (44.4)	2 (12.5)	76 (42.0)
Life-threatening	2 (5.6)	1 (6.3)	8 (4.4)
Persistent or Significant Disability/incapacity	0	0	0
Other (medically Serious Event)	1 (2.8)	0	5 (2.8)
Congenital Abnormality/Birth Defect	0	0	0
AE leading to drop-out	10 (27.8)	0	18 (9.9)
Psychiatric disorders	8 (22.2)	1 (6.3)	36 (19.9)
Nervous system disorders	11 (30.6)	7 (43.8)	52 (28.7)
Accidents and injuries	4 (11.1)	1 (6.3)	16 (8.8)
Cardiac disorders	10 (27.8)	2 (12.5)	30 (16.6)
Vascular disorders	8 (22.2)	0	30 (16.6)
Cerebrovascular disorders	0	1 (6.3)	2 (1.1)
Infections and infestations	17 (47.2)	9 (56.3)	61 (33.7)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	6 (16.7)	1 (6.3)	32 (17.7)

The number of patients > 85 years is very limited. Two patients in the PACIFIC trial (in the placebno arm) and 7 patients in the monotherapy pool safety dataset.

- Safety in subgroups by histology (squamous vs. others)

Table 72 Adverse events in any category by histology with adverse event start date ≤90 days after last dose or ≤date of subsequent therapy, whichever occurred first – Safety analysis set

	Number (%) of patients [a]			
	Durvalumab		Placebo	
Adverse event (AE) category	Squamous (N=221)	All other (N=254)	Squamous (N=102)	All other (N=132)
Any AE	211 (95.5)	249 (98.0)	96 (94.1)	126 (95.5)
Any AE causally related to treatment [b]	139 (62.9)	183 (72.0)	54 (52.9)	71 (53.8)
Any AE of CTCAE Grade 3 or 4	75 (33.9)	77 (30.3)	33 (32.4)	32 (24.2)
Any AE of CTCAE Grade 3 or 4, causally related to treatment [b]	27 (12.2)	30 (11.8)	7 (6.9)	4 (3.0)
Any AE with outcome = death	13 (5.9)	8 (3.1)	7 (6.9)	7 (5.3)
Any AE with outcome = death, causally related to treatment [b]	6 (2.7)	1 (0.4)	3 (2.9)	0
Any SAE (including events with outcome = death)	73 (33.0)	63 (24.8)	29 (28.4)	24 (18.2)
Any SAE (including events with outcome = death), causally related to treatment [b]	24 (10.9)	16 (6.3)	7 (6.9)	1 (0.8)
Any AE leading to discontinuation of study treatment	39 (17.6)	34 (13.4)	15 (14.7)	8 (6.1)
Any AE leading to discontinuation of study treatment, causally related to treatment [b]	24 (10.9)	23 (9.1)	7 (6.9)	1 (0.8)
Any AE leading to dose delay [c]	90 (40.7)	112 (44.1)	29 (28.4)	43 (32.6)

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 one category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] 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 pre-treatment 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).
Data source: Table 11.3.2.1.1.C, Appendix 1

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies on drug-drug interaction.

Discontinuation due to adverse events

Table 73: AE leading to discontinuation of study treatment by SOC and PT (safety analysis set)

System organ class/ Preferred term	Number (%) of patients [a]	
	Durvalumab (N=475)	Placebo (N=234)
Patients with an AE leading to discontinuation of study treatment [b]	**73 (15.4)**	**23 (9.8)**
Infections and infestations	**11 (2.3)**	**6 (2.6)**
Lung infection	1 (0.2)	1 (0.4)
Pneumocystis jirovecii pneumonia	1 (0.2)	0
Pneumonia	5 (1.1)	3 (1.3)
Pneumonia adenoviral	1 (0.2)	0
Pneumonia bacterial	1 (0.2)	0
Pneumonia necrotising	0	1 (0.4)
Sepsis	1 (0.2)	0
Tuberculosis	1 (0.2)	0
West Nile viral infection	0	1 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**1 (0.2)**	**1 (0.4)**
Papillary thyroid cancer	0	1 (0.4)
Prostate cancer	1 (0.2)	0
Metabolism and nutrition disorders	**1 (0.2)**	**1 (0.4)**
Hypokalaemia	0	1 (0.4)
Type 1 diabetes mellitus	1 (0.2)	0
Nervous system disorders	**3 (0.6)**	**0**
Cerebrovascular accident	1 (0.2)	0
Hypoaesthesia	1 (0.2)	0
Neuropathy peripheral	1 (0.2)	0
Cardiac disorders	**5 (1.1)**	**2 (0.9)**
Cardiac arrest	1 (0.2)	1 (0.4)
Cardiomyopathy	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0
Eosinophilic myocarditis	0	1 (0.4)
Myocardial infarction	1 (0.2)	0
Pericardial effusion	1 (0.2)	0
Respiratory, thoracic, and mediastinal disorders	**30 (6.3)**	**7 (3.0)**
Acute interstitial pneumonitis	1 (0.2)	0
Dyspnoea	3 (0.6)	0
Emphysema	1 (0.2)	0
Haemoptysis	1 (0.2)	0
Hypoxia	1 (0.2)	0
Interstitial lung disease	0	1 (0.4)
Pneumonitis	23 (4.8)	6 (2.6)
Gastrointestinal disorders	**3 (0.6)**	**1 (0.4)**
Diarrhoea	1 (0.2)	1 (0.4)
Enteritis	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Skin and subcutaneous tissue disorders	**2 (0.4)**	**0**
Erythema	1 (0.2)	0
Lichen planus	1 (0.2)	0

Musculoskeletal and connective tissue disorders	**5 (1.1)**	**1 (0.4)**
Arthralgia	1 (0.2)	0
Arthritis	1 (0.2)	0
Myopathy	1 (0.2)	0
Pain in extremity	0	1 (0.4)
Polymyalgia rheumatica	1 (0.2)	0
Scleroderma	1 (0.2)	0
Renal and urinary disorders	**2 (0.4)**	**0**
Glomerulonephritis membranous	1 (0.2)	0
Renal tubular acidosis	1 (0.2)	0
General disorders and administration site conditions	**2 (0.4)**	**1 (0.4)**
Asthenia	1 (0.2)	0
Death	1 (0.2)	1 (0.4)
Investigations	**2 (0.4)**	**0**
AST increased	1 (0.2)	0
Transaminases increased	1 (0.2)	0
Injury, poisoning, and procedural complications	**6 (1.3)**	**4 (1.7)**
Post procedural fistula	0	1 (0.4)
Radiation pneumonitis	6 (1.3)	3 (1.3)

a Number (%) of patients with an AE leading to discontinuation of study treatment, sorted by international order for SOC and alphabetically for PT.
b Action taken, study treatment permanently stopped.
Patients with multiple AEs leading to discontinuation are counted once for each SOC / PT.
Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).
MedDRA version 19.1.
AE, adverse events; AST aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; PT preferred term; SOC system organ class.
Source: Table 11.3.4.2.1

AEs leading to dose modification or interruption

Table 74: Most common AEs leading to dose delays (frequency >1%) (safety analysis set)

System organ class/ Preferred term	Number (%) of patients [a] Durvalumab (N=475)	Placebo (N=234)
Patients with any AE leading to dose delay [b]	**202 (42.5)**	**72 (30.8)**
Infections and infestations	**65 (13.7)**	**25 (10.7)**
Bronchitis	6 (1.3)	6 (2.6)
Herpes zoster	8 (1.7)	1 (0.4)
Lung infection	6 (1.3)	3 (1.3)
Pneumonia	31 (6.5)	7 (3.0)
Upper respiratory tract infection	5 (1.1)	6 (2.6)
Blood and lymphatic system disorders	**10 (2.1)**	**8 (3.4)**
Anaemia	8 (1.7)	4 (1.7)
Endocrine disorders	**15 (3.2)**	**0**
Hyperthyroidism	5 (1.1)	0
Hypothyroidism	8 (1.7)	0
Metabolism and nutrition disorders	**7 (1.5)**	**6 (2.6)**
Nervous system disorders	**6 (1.3)**	**3 (1.3)**
Cardiac disorders	**8 (1.7)**	**0**
Respiratory, thoracic, and mediastinal disorders	**54 (11.4)**	**15 (6.4)**
Chronic obstructive pulmonary disease	5 (1.1)	1 (0.4)
Cough	11 (2.3)	1 (0.4)
Dyspnoea	9 (1.9)	4 (1.7)
Pneumonitis	24 (5.1)	7 (3.0)
Pneumothorax	2 (0.4)	3 (1.3)
Gastrointestinal disorders	**14 (2.9)**	**5 (2.1)**
Diarrhoea	6 (1.3)	3 (1.3)
Skin and subcutaneous tissue disorders	**12 (2.5)**	**2 (0.9)**
Musculoskeletal and connective tissue disorders	**10 (2.1)**	**1 (0.4)**
General disorders and administration site conditions	**19 (4.0)**	**8 (3.4)**
Fatigue	3 (0.6)	3 (1.3)
Pyrexia	9 (1.9)	0
Investigations	**23 (4.8)**	**5 (2.1)**
ALT increased	5 (1.1)	2 (0.9)
Blood creatinine increased	5 (1.1)	0
Injury, poisoning, and procedural complications	**40 (8.4)**	**14 (6.0)**
Radiation pneumonitis	39 (8.2)	14 (6.0)

a Number (%) of patients with an AE leading to dose delay, sorted by international order for SOC and alphabetically for PT.

b Action taken for the AE recorded on the CRF was that the dose was interrupted. From referring to the dosing CRF page, an AE is the only reason causing this treatment delay. Patients with multiple AEs are counted once for each SOC / PT.

Patients may have had more than 1 AE leading to dose change or temporary discontinuation of study treatment.

Includes AEs with an onset date on or after the date of first dose or pre-treatment 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).

MedDRA version 19.1.

AE adverse event; ALT alanine aminotransferase; CRF clinical report form; MedDRA Medical Dictionary for Regulatory Activities; PT preferred term; SOC system organ class.

Source: Table 11.3.2.8

Comparison of adverse events between the durvalumab group in PACIFIC and the Monotherapy Pool

The patient population in PACIFIC differed from that in the Monotherapy Pool in that PACIFIC included patients who had undergone chemoradiation within 6 weeks of enrolling in the study and the pooled dataset included patients who had advanced late-stage disease and had received multiple prior lines of therapy. Aside from these (per-protocol) differences, the demographic and baseline characteristics of the durvalumab-treated patients were similar, although the Monotherapy Pool included fewer male patients, fewer patients located in Europe, and fewer current smokers.
The treatment duration for patients in the Monotherapy Pool was shorter (17.9 week) than for patients in the durvalumab group in PACIFIC (44.0 weeks), which is likely reflective of the patient population included in the pooled data.

With the exception of the events of pneumonitis/radiation pneumonitis and pulmonary infection events (which were higher in both treatment groups of PACIFIC than in the Monotherapy Pool), the type, incidence and severity of AEs reported in the Monotherapy Pool were generally similar to those reported in the durvalumab group of PACIFIC, with no new or unexpected safety findings identified within this larger pooled dataset.

There was a higher incidence in the Monotherapy Pool of Grade 3 or Grade 4 AEs (43.9% vs 32.0% in the durvalumab group of PACIFIC) and SAEs (37.2% vs 28.6% in the durvalumab group of PACIFIC), which may be accounted for by the differences in patient population in the 2 datasets. The exposure-adjusted rate for Grade 3 or Grade 4 events per 100 patient-years was 94.0 in the Monotherapy Pool and 47.5 in the PACIFIC durvalumab group.

The higher rate of discontinuation due to AEs in the durvalumab group of PACIFIC (15.4% vs 9.4% in the Monotherapy Pool) is largely due to the higher incidence of pneumonitis, which resulted in discontinuation of study treatment for 4.8% of patients in the durvalumab group of PACIFIC and 1.5% of patients in the Monotherapy Pool; the rate of discontinuation in the PACIFIC placebo group was 2.6%.

Excluding patients with infusion-related/hypersensitivity/anaphylactic reactions, AESIs were reported for 1048 patients (55.5%) in the Monotherapy Pool, which was lower than the 65.5% reported for the durvalumab group of PACIFIC. The corresponding exposure-adjusted rate was 98.2 AESIs per 100 patient-years for the durvalumab group, as compared to 82.1 per 100 patient-years for the placebo group.

Given that all except 1 of the patients with radiation pneumonitis were from PACIFIC, an additional analysis was conducted comparing the durvalumab group in PACIFIC and a pooled dataset that included only ATLANTIC and Study 1108. Within this smaller pool, the incidence of AESIs of pneumonitis was 2.3% and the incidence of imAEs of pneumonitis was 2.0%, which confirms that the incidence of this event is driven by its occurrence in PACIFIC, in patients with recent chemoradiation.

Among the other AESIs, the results from the Monotherapy Pool were largely consistent with those from the durvalumab group in PACIFIC. For example,

- Dermatitis/rash:

  AESIs, 25.8% Monotherapy Pool and 32.6% durvalumab in PACIFIC;

- Diarrhea/colitis:

  AESIs, 17.8% Monotherapy Pool and 18.9% durvalumab in PACIFIC;

- Hyperthyroidism:

AESI, 7.1% Monotherapy Pool and 10.1% durvalumab in PACIFIC;

Post marketing experience

The Applicant has provided the data of the 3rd quarterly Periodic Adverse Drug Experience Report (PADER) for Imfinzi (durvalumab), covering the reporting period from 01 November 2017 to 31 January 2018. The data are summarized below:

There were 297 reports that met the criteria for inclusion in this periodic report. Of the 297 reports (179 initial, 118 follow-up), 280 met criteria for expedited reporting and 17 were classified as non-expedited. Of the 280 expedited reports (regardless of the causality), there were 5 reports of drug-induced liver injury (DILI), 2 reports of encephalopathy, 1 report of autoimmune, encephalitis, and 1 report of encephalomyelitis. Determination of causality is difficult in these reports. The applicant did not identify any new risk that would change the benefit/risk profile of durvalumab. There were 52 reports with event(s) that had a fatal outcome : 7 indicated sudden death, 5 fatal outcome (diarrhea, hepatitis, pneumonitis/respiratory failure, hemorrhagic colitis, and pneumonitis/hepatitis), 9 were not causally related to durvalumab, 11 involved an infection, 3 had alternative causes, 3 had substantial confounding explanations/confounders, 6 had disease progression and/or underlying disease that contributed to the fatal outcomes, 2 reports of interstitial lung disease, 2 additional reports involving possible immune-mediated events and the remaining 4 reports contained limited information for causal assessment.

2.6.1. Discussion on clinical safety

The pivotal safety analysis set from the PACIFIC study included patients in the relevant treatment setting for the proposed indication, i.e. post-chemoradiation. Of 709 patients, 475 patients received durvalumab, and 234 patients received placebo. The median duration of therapy was 44 weeks in the durvalumab arm. The Applicant has provided updated safety data (from the 90-DSU), with approximately 5 months of additional follow-up (new data cut-off date: 31/07/2017) and an additional 3.5 patient years of exposure to durvalumab treatment. Nearly all patients had completed the 12 mths of tx at the 13 Feb DCO – a large portion of patients continue in the study for follow up for progression and survival. During these additional 5 months, 20 patients were re-treated (12 and 8 patients, respectively in the durvalumab and placebo groups, respectively). Almost all of them were ongoing retreatment at the DCO of the 90-DSU (one patient in the durvalumab group completed 12 months of re-treatment). The safety profile of durvalumab is clinically manageable with no major safety concerns. No new safety findings were observed during the additional follow-up.

Almost every patient in the pivotal study experienced at least one AE. Treatment-related AEs were reported more frequent in durvalumab-treated patients (67.8% vs. 53.4% for placebo, respectively). The proportion of placebo-treated patients with treatment-related AEs seems surprisingly high. It needs to be noted that patients were randomized into the PACIFIC study after 1 to 42 days (initially) or 14-42days (after study amendment#3) from the end of the previous therapy. The Applicant presented AEs data occurring in the following time points from the start of treatment: 0-3 months, 3-6 months and > 6 months (data not shown). Overall, no major concerns have been identified. The majority of events were reported within 3 months from the start of treatment. The main differences in frequency between both treatment groups can be mostly accounted for risks already described for durvalumab and other PD-L1 inhibitors (e.g., immune-mediated events, infections).

In the PACIFIC study, the most frequent adverse reactions were cough (40.2% vs 30.3% in placebo), upper respiratory tract infections (26.1% vs 11.5% in placebo) and rash (21.7% vs 12.0% in placebo). The most frequent Grade 3-4 adverse reaction was pneumonia (6.5% vs 5.6% in placebo). The overall incidence of Grade 3 or 4 adverse reactions was 12.8% in the durvalumab arm vs 9.8% in placebo.

Immune-mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab.

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the durvalumab-treated group and 58 (24.8%) in the placebo group, including Grade 3 (3.4% vs 3.0%) and Grade 5 (1.1% vs 1.7%).

Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging.

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab (see section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment with durvalumab, and as indicated based on clinical evaluation.

Immune-mediated colitis

Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab. Patients should be monitored for signs and symptoms of colitis or diarrhoea.

Immune-mediated endocrinopathies

Hypothyroidism and hyperthyroidism

Immune-mediated hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving durvalumab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation.

Adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency.

Type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus.

Hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab.

Immune-mediated rash

Immune-mediated rash or dermatitis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab. Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis.

Other immune-mediated adverse reactions

Given the mechanism of action of durvalumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions were reported in less than 1% of patients treated with durvalumab monotherapy in clinical trials (n = 1889): myocarditis, myositis, polymyositis. Patients should be monitored for signs and symptoms. Events of pancreatitis have been reported in patients in the clinical study programme. Patients should be monitored for signs and symptoms.

Infusion related reactions

Patients should be monitored for signs and symptoms of infusion related reactions. Severe infusion related reactions have been reported in patients receiving durvalumab (see sections 4.4 and 4.8 of the SmPC).

Overall, 15.4% vs 9.8% of the patients discontinued treatment due to AEs. The most common AEs leading to discontinuations were pneumonia, pneumonitis and radiation pneumonitis, which is considered expectable and acceptable in this setting. The rate drops, however, if only treatment-related events are included (9.9% vs 3.4%). Overall, 35 patients died due to any AE, but treatment-related deaths were rare and balanced between the treatment arms.

Some decreases in baseline creatinine clearance were observed in both treatment groups. The shifts in creatinine clearance from baseline to a worse renal impairment seemed reversible and transient in the majority of the patients in both groups (durvalumab and placebo).

Hypertension and hypotension were more common in the durvalumab arm. The data submitted on ECG abnormalities are currently of no concern (data not shown), and durvalumab is not at this point in time considered cardiotoxic.

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients. Data from NSCLC patients 75 years of age or older are limited.

Patients were enrolled in the pivotal study regardless of their PD-L1 expression. However, the type, incidence, and severity of AEs were comparable across PD-L1 status in both treatment arms. Overall, there

was no observable pattern that would suggest a different safety profile of durvalumab based on PD L1 status (approximately 39% had PD-L1 $\leq$25%, 24.2% had PD-L1 $\geq$ 25 and 36 % had an unknown status).

The Applicant presented data that show ADA prevalence of approximately 4.5-5% in both treatment arms. There seems to be no difference between ADA positive and negative patients in terms of safety, but data are too limited to draw any firm conclusions.

Regarding safety, although some AEs categories were numerically higher in the subset of patients with squamous histology (Any AEs related to treatment, Any SAEs) the same trend is observed in the placebo group.

Women of childbearing potential should use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab. There are no data on the use of durvalumab in pregnant women. Based on its mechanism of action and non-clinical data available, durvalumab has the potential to impact maintenance of pregnancy. Human IgG1 is known to cross the placental barrier and placental transfer of durvalumab was confirmed in animal studies. Durvalumab may cause foetal harm when administered to a pregnant woman and is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

It is unknown whether durvalumab is secreted in human breast milk. In humans, antibodies may be transferred to breast milk, but the potential for absorption and harm to the newborn is unknown. However, a potential risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue or abstain from durvalumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

There are no data on the potential effects of durvalumab on fertility in humans or animals (see section 4.6 of the SmPC).
At the time of this assessment, durvalumab has been on the market in the US for over 6 months. The Applicant has provided the data of the 3rd quarterly Periodic Adverse Drug Experience Report (PADER) for durvalumab, covering the reporting period from 01 November 2017 to 31 January 2018. The adverse events reported during this reporting period seem to be consistent with the safety profile of durvalumab assessed in this application. No new signals have been identified.

2.6.2. Conclusions on the clinical safety

The safety profile of durvalumab was as expected for PDL1-inhibitors. Cough, fatigue, dyspnea, pneumonitis, diarrhea and lung infections were observed. Most of the toxicity was clinically manageable and treatment-related deaths were rare. The discontinuation rate was 15.4% in the durvalumab arm, which is considered acceptable in this patient population.

Overall, the safety profile of durvalumab seems acceptable and in line with other PD-L1-inhibitors.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Immune-mediated pneumonitis Immune-mediated hepatitis Immune-mediated colitis or diarrhoea Immune-mediated hypothyroidism Immune-mediated hyperthyroidism Immune-mediated adrenal insufficiency Immune-mediated hypophysitis or hypopituitarism Immune-mediated T1DM Immune-mediated nephritis Immune-mediated rash or dermatitis Immune-mediated myocarditis Immune-mediated myositis/polymyositis Infusion-related reaction
Important potential risks	Immune-mediated pancreatitis Other rare potential immune-mediated adverse reaction (eg, myasthenia gravis and Guillain-Barré syndrome)
Missing information	Patients with moderate or severe hepatic impairment Patients with severe renal impairment Patients with prior Grade ≥3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment or any unresolved imAE >Grade 1 Patients with pre-existing autoimmune disease Patients with pre-existing active infection including tuberculosis, hepatitis B, hepatitis C, or HIV Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving Imfinzi Female patients who are pregnant or breastfeeding

Pharmacovigilance plan

There are no additional pharmacovigilance activities for this product. Routine pharmacovigilance activities are considered sufficient to address the safety concerns of Imfinzi.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Immune-mediated pneumonitis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated pneumonitis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated hepatitis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated hepatitis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated colitis or diarrhoea	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated colitis or diarrhoea • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated hypothyroidism	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated hypothyroidism • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated hyperthyroidism	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated hyperthyroidism • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated adrenal insufficiency	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated adrenal insufficiency • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated hypophysitis or hypopituitarism	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated hypophysitis or hypopituitarism • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated T1DM	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated T1DM • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated nephritis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated nephritis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated rash or dermatitis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated rash or dermatitis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated myocarditis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated myocarditis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction
Immune-mediated myositis/polymyositis	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage immune-mediated myositis/polymyositis • PL Section 2 where advice is given on how to detect early signs and symptoms • PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for adverse reaction

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion-related reaction	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice is given on how to identify and manage infusion-related reaction • PL Section 2 where advice is given on how to detect early signs and symptoms	Routine pharmacovigilance activities
Important potential risks		
Immune-mediated pancreatitis	Routine risk minimisation measures: • SmPC Section 4.4 for other immune-mediated adverse reactions • SmPC Sections 4.2 and 4.4 for monitoring and management of an imAE • PL Section 2 on how to detect early signs and symptoms	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow up form for adverse react
Other rare potential immune-mediated adverse reactions (eg, myasthenia gravis and Guillain-Barré syndrome)	Routine risk minimisation measures: • SmPC Section 4.4 for other immune-mediated adverse reactions • SmPC Sections 4.2 and 4.4 for monitoring and management of an imAE • PL Section 2 on how to detect early signs and symptoms	Routine pharmacovigilance activities
Missing information		
Patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • SmPC Sections 4.2 and 5.2 • PL Section 2	Routine pharmacovigilance activities
Patients with severe renal impairment	Routine risk minimisation measures: • SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with prior Grade ≥3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment or any unresolved imAE >Grade 1	Routine risk minimisation measures: • SmPC Section 5.1 • SmPC Sections 4.2 and 4.4 for monitoring and management of an imAE	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for imAR to include history of prior Grade ≥3 imAE while receiving immunotherapy/ history of pre-existing autoimmune disease
Patients with pre-existing autoimmune disease	Routine risk minimisation measures: • SmPC Section 5.1 • SmPC Sections 4.2 and 4.4 for monitoring and management of an imAE • PL Section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up form for imAR to include history of prior Grade ≥3 imAE while receiving immunotherapy/ history of pre-existing autoimmune disease
Patients with pre-existing active infection including tuberculosis, hepatitis B, hepatitis C, or HIV	Routine risk minimisation measures: • SmPC Section 5.1	Routine pharmacovigilance activities
Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving Imfinzi	Routine risk minimisation measures: • SmPC Section 5.1	Routine pharmacovigilance activities
Female patients who are pregnant or breastfeeding	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2	Routine pharmacovigilance activities

Routine risk minimisations measures are considered sufficient to minimise the safety concerns of Imfinzi.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 01 May 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that durvalumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers durvalumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imfinzi (durvalumab) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

3. Benefit-Risk Balance

3.1. Therapeutic Context

The following indication is applied for:

Durvalumab is indicated for the treatment of patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

3.1.1. Disease or condition

Locally advanced disease (Stage IIIA and IIIB) comprises approximately 30% of the NSCLC diagnoses. Approximately, one-third of the patients with Stage IIIA disease are considered operable. However, the majority of patients with Stage IIIA/B have inoperable (unresectable) disease, and are amenable to receiving curative intention chemoradiation treatment. The biological characteristics of locally advanced, Stage III disease are poorly defined; the clinical characteristics associated with prognosis are nodal station involvement, size of primary tumour, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status (PS).

3.1.2. Available therapies and unmet medical need

There are no established treatments for patients that have completed curative intent chemoradiotherapy. The majority of these patients will eventually relapse. It is seen that patients relapse relatively fast, and approximately 65% relapse within 12 months in the placebo arm. This is in line with the clinical reality (Goldstraw et al., 2016). Thus, there is an unmet medical need, which durvalumab attempts to fulfil.

3.1.3. Main clinical studies

The Applicant has provided one pivotal study (PACIFIC) to support the claimed indication. The PACIFIC study is a double-blind, randomised, place-controlled study. The study design is acceptable in this patient population. The inclusion criteria clearly define the patient population as unresectable stage III NSCLC, who have received at least 2 cycles of platinum-based chemotherapy concurrent with radiotherapy.

3.2. Favourable effects

The study met both of its pre-specified endpoints, PFS by BICR and OS. Median PFS was improved by 11.2 months in the durvalumab arm (16.8 vs 5.6 months in the durvalumab and placebo arm respectively). The HR is 0.52 (98.90%CI:0.39, 0.70) , p<0.0001). This difference is statistically highly significant. The Applicant presents OS interim data, which are 61% of the target number of final event. The results show an OS benefit in favour of durvalumab, the threshold for demonstrating superiority was crossed, and thus the Applicant considers the results as final. However, OS data are not fully mature yet, especially in the durvalumab arm.

The Applicant has also provided PFS2 data as requested. These results are in line the PFS and OS data, confirming the benefit of early treatment with durvalumab in the proposed patient population. Overall, the totality of evidence clearly shows that early treatment with durvalumab not only improves PFS, but also PFS2 and OS. The results are considered clinically relevant in a patient population with high risk of relapse and a dismal prognosis.

Secondary endpoints included to provide additional evidence of clinical benefit all showed consistency with the PFS results. An ORR 28.4% (95% CI 24.28, 32.89) vs 16% (95% CI 11.31, 21.59) was observed in durvalumab and placebo arms respectively (p<0.001). Median DoR was not reached in the durvalumab arm and it was 13.8 months in the placebo group.

A median TTDM time of 23.2 months (95%CI 23.2, NR) was observed for durvalumab vs. 14.6 months (95%CI 10.6, 18.6) (Δ 8.6 months). Updated results continue to favour durvalumab.

Time to first subsequent therapy, which indirectly could reflect the quality of life of patients, was longer in the durvalumab arm (19.1 months; 95%CI: 16.6, NR) than in placebo arm (11.3 months; 95%CI: 9.0, 15.8) (HR 0.62; 95% CI: 0.49, 0.78; p<0.0001).

3.3. Uncertainties and limitations about favourable effects

The study recruited all-comers, and the subgroup analyses showed efficacy in patients with PD-L1 expression >= 25%, PD-L1 expression < 25% and PD-L1 expression "unknown". However, as discussed above, it is not entirely clear how and why the cut-off is at 25%. The Applicant has been asked to provide subgroup analyses in patients with <1%, >= 1%, 5% and 50%, and compare and discuss these results with the results based the on the 25% cut-off. The Applicant provided a retrospective analysis of PFS by PD-L1 1% cut-off. This was done by BICR. In total, information on PD-L1 expression was available for 451 patients (63%). Of these, 148 patients had PD-L1 expression below 1%, and 303 patients had an expression over 1%. The results show that durvalumab is effective regardless of PD-L1 expression in terms of PFS, however, the size of the effect is considerably lower in the PD-L1 negative patients (10.7 vs 5.6 months).

Looking at the OS data (provided after the formal responses), there is an uncertainty about the benefit of durvalumab in patients with PD-L1 <1%. Many of the patients in the placebo arm received immunotherapy post progression, which could have influenced the outcome, the extent of which cannot be determined. Data indicate that patients with PD-L1 <1% could be better off by treatment with immunotherapy at progression compared to early use in the switch maintenance setting. The Applicant argued that there is in imbalance in squamous vs. non-squamous histology that could bias the results. However, retrospective multivariate analysis showed no statistically significant differences between the two histologies. Other imbalances are also mentioned, and there seems to inconsistencies between ORR, PFS and OS. The limitations in the interpretation of post hoc exploratory subgroup analysis are acknowledged, however the pattern of the curves of PFS and OS according to PD-L1 expression suggest a correlation between PD-L1 expression and benefit. The Applicant has not convincingly demonstrated that the use of durvalumab in patients with PD-L1 <1% is justified. The study is critically weakened by the fact that the applicant did not stratify per PD-L1 expression. This may seem illogical considering that an anti-PD-L1 was being investigated in the PACIFIC study. Moreover, durvalumab is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). It is therefore considered reasonable that PD-L1 expression could play an important role in the efficacy of this medicinal product, reinforcing the rationale for a benefit driven by PD-L1 ≥1% patients.

The lack of data beyond 12-months of treatment precludes from concluding about B/R with different treatment duration. Treatment duration should be limited to pivotal clinical trial conditions. The Applicant has revised section 4.2 accordingly.

The Applicant has provided a post-hoc analysis, which shows that there seems to be no difference between the treatment groups with regards to patients, who were treated through progression. This is now reflected in the SmPC.

3.4. Unfavourable effects

Almost all of the patients in both treatment groups experienced AEs (96.8% vs. 94.9%, for durvalumab and placebo, respectively). Treatment-related AEs were reported more frequent in durvalumab-treated patients (67.8% vs. 53.4% for placebo, respectively).

The most common AEs were: cough (35.4% and 25.2% for durvalumab and placebo, respectively), pyrexia (14.7% and 9.0%), pneumonia (13.1% and 7.7%), pruritus (12.2% and 4.7%), hypothyroidism (11.6% and 1.7%), and hyperthyroidism (7.4% and 1.7%).

Grade 3-4 events were 32.0% and 27.8%, for durvalumab and placebo respectively. The proportion of patients who experienced SAEs was 28.6% and 22.6%, for durvalumab and placebo, respectively. SAEs were more frequently reported in the respiratory, thoracic disorder SOC for both groups.

A total of 311 patients (65.5%) in the durvalumab group and 114 patients (48.7%) in the placebo group experienced an AESI during the study. The most frequently reported AESIs were the combined term of pneumonitis/radiation pneumonitis (33.9% in the durvalumab group and 24.8% in the placebo group), the combined term of dermatitis/rash (32.6% vs. 17.9%), the combined term of diarrhea/colitis (18.9% vs 19.7%), hypothyroidism (13.3% vs. 3.0%), and hyperthyroidism (10.1% vs. 3.0%).

A total of 15.4% of patients receiving durvalumab and 9.8% receiving placebo had AEs leading to discontinuation of study medication. The most frequent AE leading to treatment discontinuation were respiratory/thoracic disorders (6.3% and 3.0%, for durvalumab and placebo, respectively), followed by infection (2.3% and 2.6, for durvalumab and placebo, respectively).

Overall, the safety profile of durvalumab seems acceptable and in line with other PDL1-inhibitors.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of durvalumab seems acceptable and in line with other PDL1-inhibitors.

3.6. Effects Table

Table 75: Effects Table for durvalumab for the treatment of patients with locally advanced, unresectable, NSCLC whose disease has not progressed following platinum-based chemoradiation therapy (data cut-off: 13 February 2017 and 22 March 2018 for PFS and OS)

Effect	Short Description	Unit	Durvalumab	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by BICR	Progression free survival by blinded independent central review	Months	16.8	5.6	Median PFS in the placebo arm is considerable shorter than what is observed in the clinical setting.	
OS	Overall survival	months	NR	28.7		
PFS2	Time to second progression or death	Months	28.3	17.1		

Effect	Short Description	Unit	Durvalumab	Placebo	Uncertainties/ Strength of evidence	References
Unfavourable Effects (Grade 3 or 4)						
Pneumonia		%	4.4	4.3		
Anaemia		%	2.9	3.4		
Hypertension		%	2.1	0.9		
Pneumonitis		%	1.7	2.1		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

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. Outcomes from PACIFIC trial show statistically significant results in terms PFS supported by OS data.

The safety profile of durvalumab can be considered as expected with immune check-point inhibitors. Immune-related AEs occur more frequently in the durvalumab arm. Of most concern is pneumonitis. However, the majority of the AEs are clinically manageable.

All in all, treatment with durvalumab offers a valuable option for patients with unresectable locally advanced NSCLC, in delaying the progression disease and prolonging survival.

3.7.2. Balance of benefits and risks

The gain in PFS and OS is considered clinically meaningful. This represents a valuable option for patients in the locally advanced setting of NSCLC. However, due to the uncertainties identified in patients whose tumours express PD-L1 <1%, it is not possible to determine the benefit/risk balance in that patient population, which has therefore been excluded from the authorised indication. Such restriction is also supported by the mechanism of action of Imfinzi.

The safety profile seems manageable and acceptable, which is considered important in a population where there is not an actual treatment.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Imfinzi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imfinzi is favourable in the following indication:

"Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy (see section 5.1)"

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable.

Obligation to conduct post-authorisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that durvalumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.