15 December 2022
EMA/42901/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: durvalumab

Procedure No. EMEA/H/C/004771/II/0041

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALB	Serum albumin
ALK	Anaplastic lymphoma kinase
BICR	Blinded Independent Central Review
BLA	Biologics License Application
BOR	Best objective response
bTMB	Blood tumor mutational burden
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CR	Complete response
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ES-SCLC	Extensive-stage small cell lung cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MAA	Marketing Authorization Application
mAb	Monoclonal antibody
MTP	Multiple testing procedure
Mut/Mb	Mutations per megabase
nAb	Neutralizing antibody
NLR	Neutrophil-to-lymphocyte ratio
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
QxW	Every x week
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SoC	Standard-of-care
SOC	System organ class
sPD-L1	Soluble programmed cell death ligand-1
TC	Tumor cell
TMB	Tumor mutation burden
TTD	Time to deterioration
UC	Urothelial carcinoma
V_1	Central volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 13 December 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include first-line treatment, with Imfinzi in combination with tremelimumab and platinum-based chemotherapy, of adults with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations, based on final results from Study D419MC00004 (POSEIDON); This was a Phase III, randomised, multicentre, open-label, comparative global study to determine the efficacy and safety of tremelimumab and durvalumab or durvalumab in combination with platinum based chemotherapy for first-line treatment in patients with metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.2. Version 5.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0106/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0106/2021 was not yet completed as some measures were deferred.

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 MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date	13 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	21 March 2022
PRAC Rapporteur Assessment Report	24 March 2022
PRAC members comments	30 March 2022
CHMP Co-Rapporteur Critique	4 April 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	30 September 2022
PRAC Rapporteur Assessment Report	16 September 2022
PRAC members comments	21 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur Assessment Report	12 October 2022
Request for supplementary information (RSI)	13 October 2022
CHMP and PRAC Rapporteurs Joint AR (JAR)	02 December 2022
Comments from PRAC and CHMP	07 December 2022
Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Metastatic non-small cell lung cancer with no EGFR or ALK aberrations, regardless of tumoral PD-L1 expression.

State the claimed therapeutic indication

The initially claimed therapeutic indication in section 4.1 of the SmPC was:

IMJUDO in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations.

The indication was updated during the procedure to:

IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitizing EGFR mutations or ALK positive mutations.

Epidemiology

Lung cancer is the second most commonly diagnosed cancer and remains the leading cause of cancer death around the globe (Sung et al 2021; GLOBOCAN 2021). In Europe, an estimated 312,645 patients were foreseen to be diagnosed with lung cancer in 2021, accounting for approximately 25% of all cancer diagnoses, and an estimated 267,700 lung cancer associated deaths were foreseen to occur, accounting for approximately one in 5 cancer related mortalities (Lung Cancer Europe 2021). In the US, an estimated 235,760 new cases of lung cancer were foreseen to be diagnosed in 2021, accounting for about 25% of all cancer diagnoses, and an estimated 131,880 lung cancer associated deaths will occur, accounting for approximately 1 in 4 cancer related mortalities (American Cancer Society 2021).

Biologic features

Non-small cell lung cancer (NSCLC) comprises approximately 85% of all newly diagnosed lung cancer cases. It includes several histological subtypes of which non-squamous (e.g., adenocarcinoma, large cell carcinoma) and squamous cell carcinoma are the most common (Aisner and Marshall 2012).

Clinical presentation, diagnosis and stage/prognosis

Despite advances made in screening, early detection, and staging, the majority of lung cancer patients are diagnosed when the disease has advanced into the metastatic stage and is not amenable to surgical resection (Herbst et al 2018). Furthermore, a significant percentage of patients with early

stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their metastatic disease (Pisters and Le Chevalier 2005).

Management

The first line (1L) treatment of metastatic NSCLC has evolved from the empirical use of cytotoxic chemotherapies based on physician's preference to a hallmark of personalized medicine, with subsets of patients treated according to the genetic alterations of their tumour and the status of programmed cell death ligand 1 (PD-L1), which predict for benefit from targeted therapies or immune checkpoint inhibitors (ICIs), respectively (Herbst et al 2018; Peters et al 2019).

In the past 5 years, substantial progress has been made in the frontline treatment of metastatic NSCLC with immunotherapy-based regimens demonstrating improved outcomes in this patient population (NCCN Clinical Practice Guidelines in Oncology Version 1.2020; ESMO Guidelines Committee 2019). Treatment selection in clinical practice is usually based on PD-L1 expression or histology. For patients with high PD-L1 expression (i.e., PD-L1 expressed in ≥50% of tumour cells), monotherapy with either pembrolizumab or atezolizumab or cemiplimab are acceptable and EMA-approved choices. Conversely, regardless of PD-L1 expression, a series of combinations of immunotherapy with histology-selected platinum-based chemotherapy have also shown survival benefits, which granted them EMA-approval for marketing. In most of such indications, it is clarified that patients with oncogene-driven tumours (e.g. EGFR, ALK) are directly excluded from treatment or should have failed appropriate targeted therapies before consideration for the given regimens:

- Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel for squamous histology
- Pembrolizumab + carboplatin + pemetrexed for non-squamous histology
- Atezolizumab + bevacizumab + carboplatin + paclitaxel for non-squamous histology
- Atezolizumab + carboplatin + nab-paclitaxel for non-squamous histology
- Nivolumab + ipilimumab + 2 cycles of platinum-doublet, regardless of histology

Of note, nivolumab + ipilimumab, a combination of PD-1/CTLA-4 inhibitors, showed improved survival benefits and durable responses as 1L treatment in patients with advanced NSCLC and PD-L1 expression >1% (Hellman et al [CheckMate-227] 2019); nevertheless, this regimen is not EMA-approved. More recently, the addition of chemotherapy to the nivolumab + ipilimumab combination showed efficacy benefit over chemotherapy alone with early disease control at all PD L1 expression levels (Paz-Ares et al [Checkmate 9LA] 2021), receiving a positive opinion from the CHMP in September 2020.

Unmet medical need: Immunotherapy-based treatments are the 1L standard-of-care in patients with advanced metastatic NSCLC whose tumours do not harbour driver mutations (NCCN Clinical Practice Guidelines in Oncology Version 2.2021). Notwithstanding these developments and the treatment options, the available treatment strategies extend long-term survival in only a minority of patients (Peters et al 2019; Grant et al 2021). Overall, newer treatment options are therefore required that can explore the potential of immunotherapy strategies and benefit a broader patient population.

2.1.2. About the product

Durvalumab is a monoclonal antibody targeting the programmed cell death ligand 1 (PD-L1). It is approved for the treatment of locally advanced, unresectable, NSCLC in adult patients whose tumours express PD L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (EMEA/H/C/004771/0000). Durvalumab is also approved in combination with

standard-of-care platinum-based chemotherapy as 1L treatment of extensive stage small cell lung cancer (ES SCLC; EMEA/H/C/004771/II/0014/G).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The current type II variation for durvalumab in combination with tremelimumab and SoC chemotherapy for the proposed indication in metastatic NSCLC is based on efficacy data from a pivotal phase III, three-arm, randomised, multi-centre, open-label study in patients with metastatic NSCLC (POSEIDON). POSEIDON (D419MC00004) was designed to compare the efficacy and safety of durvalumab in combination with platinum-based chemotherapy with that of standard-of-care (SoC) chemotherapy alone for the first-line treatment in patients with metastatic NSCLC. Additionally, the study was also designed to compare the efficacy and safety of tremelimumab in combination with durvalumab and SoC chemotherapy with that of SoC in the same patient population. Additional supportive evidence of clinical efficacy is provided from the MYSTIC (D419AC00001) and NEPTUNE (D419AC00003) studies.

The clinical studies included in the type II variation for durvalumab are summarised in Table 1.

Table 1. Summary of clinical studies included in the application package

Study name Status[a] DCO	Phase Design	Patient population	Key outcome measures	No. of patients randomized
Pivotal Phase III study				
POSEIDON Complete 24 Jul 2019[b] 12 Mar 2021[c]	Phase III Randomized, open-label, comparative, multicenter	Patients with metastatic NSCLC who have not received prior 1L treatment, and who do not have *EGFR* or *ALK* target mutations	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, and vital signs	T + D + SoC: 338 D + SoC: 338 SoC: 337
Supportive Phase I-II studies				
Study 1108 Complete 16 Oct 2017	Phase I/IIb FTIH, open-label, dose-escalation, dose-expansion	Patients with advanced solid tumors, including NSCLC, that are refractory to standard therapy and for which no standard therapy exists	MTD or OBD Safety: AEs, laboratory evaluations, physical examinations, and vital signs	Escalation – D: 48 Expansion – D: 980
Japan 02 Complete 31 Mar 2018	Phase I Open-label, multicenter	Patients with advanced solid tumors, that are refractory to standard therapy and for which no standard therapy exists	MTD or OBD Safety: AEs, laboratory evaluations, physical examinations, vital signs	Escalation – D: 22 Expansion – D:116 Expansion – T + D: 124
Study 06 Complete 19 Nov 2019	Phase I open-label, dose-escalation, dose-expansion	Patients with advanced NSCLC	MTD, ORR (Dose expansion) Safety: AEs, laboratory evaluations, physical examinations, vital signs	Escalation – T + D: 102 Expansion – T + D: 355
Study 10 Complete 11 Apr 2018	Phase I open-label, multicenter	Patients with advanced solid tumors	ORR (PD-L1 negative UC) Safety: AEs, laboratory evaluations, physical examinations, vital signs	Exploration and Expansion – T + D: 379
ATLANTIC Complete 03 Jun 2016	Phase II Non-comparative, open-label, multicenter	Patients with locally advanced or metastatic NSCLC (Stage IIIB – IV) who have received at least 2 prior systemic treatment regimens	ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 444

Study name Status[a] DCO	Phase Design	Patient population	Key outcome measures	No. of patients randomized
CONDOR Complete 27 Aug 2018	Phase II Randomized, open-label, multicenter	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent	ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 67 T: 67 T + D: 133
DETERMINE Complete 24 Jan 2016	Phase IIb Randomized, double-blind	Patients with pleural or peritoneal malignant mesothelioma who had progressed following 1 or 2 prior treatments	OS Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	T: 382 Placebo: 189
D4884C00001 Complete 17 Feb 2018	Phase II Open-label, multicenter	Patients with advanced solid tumors	ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	T: 64
Study 22 Complete 06 Nov 2020	Phase I/II, randomized, open-label, multicenter, multipart	Patients with advanced hepatocellular carcinoma (HCC)	Primary: safety and tolerability	D: 107 T: 74 T + D: 205
Supportive Phase III studies				
ARCTIC Complete 09 Feb 2018	Phase III Randomized, open-label, multicenter	Patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who received at least 2 prior systemic treatments and do not have *EGFR* or *ALK* target mutations	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs	Sub-study A D: 62; SoC: 64 Sub-study B D: 117; T: 60 T + D: 174 SoC: 118
PACIFIC Complete 22 Mar 2018	Phase III Randomized, double-blind, placebo-controlled, multicenter	Patients with locally advanced, unresectable, Stage III NSCLC who have not progressed after definitive platinum-based concurrent chemoradiation	OS, PFS Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 476 Placebo: 237
MYSTIC Complete 01 Jun 2017 04 Oct 2018	Phase III Randomized, open-label, multicenter	Patients with Stage IV NSCLC who have not received prior chemotherapy or other systemic therapy and who do not have *EGFR* or *ALK* target mutations	OS and PFS in PD-L1 TC≥25% Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 374 T + D: 372 SoC: 372
CASPIAN Complete 11 Mar 2019 27 Jan 2020	Phase III Randomized, open-label, comparative, multicenter	Patients with ES-SCLC who have not received prior 1L treatment	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, and vital signs	T + D + EP: 268 D + EP: 268 EP: 269
NEPTUNE Complete 24 Jun 2019	Phase III Randomized, open-label, multicenter	Patients with Stage IV NSCLC who have not received prior chemotherapy or other systemic therapy and who do not have *EGFR* or *ALK* target mutations	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, and vital signs	T + D: 410 SoC: 413
EAGLE Complete 10 Sep 2018	Phase III Randomized, open-label, multicenter	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 240 T + D: 247 SoC: 249

T tremelimumab; D durvalumab; SoC standard-of-care chemotherapy.
Source: Clinical overview, p. 24/82

Scientific advice: The marketing authorisation holder (MAH) for durvalumab held several regulatory interactions with the US FDA during its development for metastatic NSCLC, but scientific advice concerning this application has not been sought from the CHMP. A presubmission meeting with the rapporteurs was held on 03 September 2021, mostly to agree on the contents of the application package.

Paediatric requirements: On 17 March 2021, a modification of an agreed paediatric investigation plan for durvalumab (EMEA-002028-PIP01-16-M02) was accepted by the EMA, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

2.1.4. General comments on compliance with GCP

GCP

A routine GCP inspection of study D419MC00004 (POSEIDON) was adopted at the CHMP meeting held in January 2022. No specific concerns were known to have been identified by the assessment at the time of adoption of the inspection request; general triggers were used in the choice of this dossier and the sites involved in line with the guideline "*Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections*". The purpose of the inspection was to verify efficacy and safety data reported in the Marketing Authorisation Application (MAA) for a sample of patients to be determined by the inspectors. Moreover, the compliance with GCP and applicable regulations was to be verified, in particular where it had an impact on the validity of the data or the ethical conduct of the study.

This routine GCP inspection was conducted at one investigational site in Germany (21-25 February 2022), the main CRO in the USA (11-17 March 2022), and the sponsor in Canada (21-25 March 2022). One critical finding was reported during the CRO inspection; major and minor findings were observed at all sites.

Although departures from GCP compliance were identified as there were one critical and several major findings observed during the inspections at all sites, the study was considered by the inspection team to have been conducted ethically and in compliance with GCP. The findings were deemed unlikely to impact the overall quality of the data. The inspection team concluded that the overall quality of the trial with the reported data had not been negatively affected, and that the data documented and reported in the Clinical Study Report (CSR) submitted in support of the MAA for Imfinzi could be used as basis for the assessment. The sponsor was however requested for a CSR addendum including a complete list of mis-stratified subjects to report overall survival in long-term follow up as part of the corrective action proposed for one of the major findings at the sponsor site.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Durvalumab is an IgG1 monoclonal antibody, a protein being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion. Durvalumab is expected to biodegrade in the environment and does not pose 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 corr2), durvalumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Durvalumab is human monoclonal antibody of the IgG1 kappa subclass. Antibodies are considered naturally occurring proteins, which are not expected to remain either stable or biologically active in the environment for any significant period. The justification for not performing any ERA studies is accepted.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

- **Tabular overview of clinical studies**

Table 2. Clinical pharmacology studies of durvalumab/tremelimumab

Study **Primary objectives** **Design**	**Phase**	**Patient type** **N (M/F)** **Age (median [range])**	**Dosing regimen**
D419MC00004 (POSEIDON) Efficacy versus SoC Open-label, randomized	III	Patients with metastatic NSCLC with tumors lacking activating EGFR mutations and ALK fusions 1013 (770/243) 64.0 y (27-87 y)	T + D + SoC: Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until PD AND Tremelimumab IV 75 mg Q3W for 4 doses and 1 additional dose at Week 16 AND SoC
D4190C00006 (Study 06) Safety, tolerability, and efficacy Open-label	I/Ib	Advanced NSCLC Dose-escalation: 18 (9/9) 66 y (49-78 y) Dose-expansion: 277 (164/113) 63 y (35-87 y)	Durvalumab IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4190C00002 (Japan Study 02) Safety and tolerability. Open-label, non-randomized	I/Ib	Biliary tract carcinoma 65 (43/22); 62 y (28-78 y) Esophageal carcinoma 59 (56/3); 62 y (42-77 y)	Dose-expansion phase: Durvalumab IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4190C00010 (Study 10) Safety, tolerability, and efficacy Open-label	I/Ib	Advanced solid tumors 327 (168/159) 62 y (25-85 y)	Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4190C00022 (Study 22) Safety and tolerability Open-label, randomized	I/II	Advanced HCC <u>Part 1</u>: 40 (30/10) 60.5 (47-87 y) <u>Parts 2 and 3</u>: 332 (284/48) 64.0 (26-89 y)	Parts 2 and 3: T: Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses IV followed by Q12W IV T75 + D: Tremelimumab 75 mg (1 mg/kg) × 4 doses

		China Cohort: 14 (13/1) 49.5 (26-66 y) Part 4: 47 (41/6) 64.0 (37-84 y)	IV + durvalumab 1500 mg (20 mg/kg) Q4W IV T300 + D: Tremelimumab 300 mg (4 mg/kg) × 1 dose IV + durvalumab 1500 mg (20 mg/kg) Q4W IV
D419AC00001 (MYSTIC) Efficacy versus SoC Open-label, randomized	III	Advanced or metastatic NSCLC 372 (266/106) 66 y (28-87 y)	Durvalumab IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D419AC00003 (NEPTUNE) Efficacy Open-label, randomized	III	Patients with EGFR and ALK wild-type advanced or metastatic NSCLC 410 (297/113) 63 y (27-83 y)	Durvalumab IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4191C00004 (ARCTIC) Efficacy versus SoC Open-label, randomized	III	Locally advanced or metastatic NSCLC Sub-study B: 60 (39/21) 63.5 y (45-81 y)	Tremelimumab IV 10 mg/kg Q4W for 24 weeks followed by 10 mg/kg Q12W for 24 weeks
		Locally advanced or metastatic NSCLC Sub-study B: 174 (115/59) 62.5 y (26-81 y)	Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W for 18 doses AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D419QC00001 (CASPIAN) Safety and efficacy Open-label, randomized	III	Patients with ES-SCLC in combination with EP 268 (202/66) 63 y (36-88 y)	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until PD AND tremelimumab IV 75 mg Q3W for 4 doses AND EP for 4 cycles
D4193C00003 (CONDOR) Efficacy Open-label, randomized	II/IIb	Recurrent or metastatic HNSCC expressing low/no PD-L1 67 (53/14) 61 y (42-77 y)	Tremelimumab IV 10 mg/kg Q4W for 7 doses then Q12W for 2 doses
		Recurrent or metastatic HNSCC expressing low/no PD-L1 133 (113/20) 62 y (26-81 y)	Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W to complete 12 months of treatment AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4193C00002 (EAGLE) Efficacy versus SoC Open-label, randomized	III	Recurrent or metastatic HNSCC 247 (209/38) 61 y (23-81 y)	Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W for 12 months or until PD AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4884C00001 Efficacy and safety. Open-label	II/IIb	Urothelial cancer: 32 (26/6); 66.5 y (44-81 y) TNBC: 12 (0/12); 58.5 y (42-85 y) Pancreatic ductal adenocarcinoma 20 (11/9); 60 y (41-72 y)	Tremelimumab IV 750 mg Q4W for 7 doses, then Q12W for 2 doses
			Durvalumab IV 1500 mg Q4W for 4 doses AND Tremelimumab IV 75 mg/kg Q4W for 4 doses, then Durvalumab IV 1500 mg Q4W for up to 8 months
D4880C00003 (DETERMINE) Efficacy and safety. Double-blind, randomized, placebocontrolled	II/IIb	Unresectable pleural or peritoneal mesothelioma 382 (283/99) 66 y (28-87 y)	Tremelimumab IV 10 mg/kg Q4W for 7 doses (6 months), then Q12W

ALK, anaplastic lymphoma kinase; D, durvalumab; DCO, data cutoff; EGFR, epidermal growth factor receptor; EP, etoposide and carboplatin or cisplatin; ES-SCLC, extensive-stage small cell lung cancer; F, female; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; M, male; N, total number of patients; NCA, non-compartmental analysis; NSCLC, non-small cell lung cancer; PD, progression of

disease; PD-L1, programmed death ligand-1; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; SoC, standard of care chemotherapy; T, tremelimumab; TNBC, triple-negative breast cancer.

2.3.2. Pharmacokinetics

Durvalumab population PK analysis

The primary objectives of the durvalumab population PK analysis were to:

- characterize the pharmacokinetics of durvalumab using combined data from D419MC00004, CD-ON-MEDI4736-1108, D4191C00003, D4191C00001 and D419QC00001(referred to as POSEIDON, Study 1108, ATLANTIC, PACIFIC and CASPIAN, respectively).
- assess the correlation between predefined categorical and continuous covariates and individual Empirical Bayes Estimates (EBEs).
- derive individual predicted exposure metrics of durvalumab for patients participating in the POSEIDON study based on individual EBEs from the population PK models.

Durvalumab population PK dataset

The PopPK of durvalumab has been characterized based on data from Studies 1108, ATLANTIC, and PACIFIC following monotherapy of durvalumab. To evaluate whether the PK data of durvalumab in combination with SoC from POSEIDON are consistent with those in previous monotherapy studies, the existing durvalumab PopPK model was updated by combining durvalumab PK data from previous monotherapy studies (Study 1108, ATLANTIC, and PACIFIC), from combination with chemotherapy study (CASPIAN), and from POSEIDON when administered in combination with tremelimumab and chemotherapy.

The population PK analysis was carried out using PK samples of durvalumab from Study 1108, POSEIDON, ATLANTIC, PACIFIC and CASPIAN, which included 11683 serum concentration samples from a total of 2827 patients. No patients were excluded during model development. 21 samples (0.2%) were excluded from the analysis due to non-BLQ pre-dose samples or physiologically impossible ALB, CrCL or sPD-L1 values and another 133 samples (1.1%) with durvalumab serum concentrations below the lower limit of quantification (LLOQ) were also excluded from this analysis.

Based on the extended database, the PK of durvalumab was well described using a 2-compartment model with time-dependent CL. IIV was characterized on CL, V1, and Tmax, being 28%, 24%, and 25%, respectively. PK parameter estimates of the final durvalumab model along with percent relative standard error (%RSE), results of non-parametric bootstrap analysis and shrinkage can be seen in Table 3.

The relationships between the covariates and the model parameters are described in the following equations:

$$CL_{cat.cov} = 1_{comb=0} \cdot (1 - 0.166_{comb=1}) \cdot (1 - 0.0958_{comb=2}) \cdot 1_{ECOGbin=0} \cdot (1 - 0.505_{ECOGbin=1}) \cdot 1_{male} \cdot (1 - 0.168_{female})$$

$$CL_{cont.cov} = \left(\frac{alb_i}{39}\right)^{-0.605} \cdot \left(\frac{CrCL_i}{85.66}\right)^{0.112} \cdot \left(\frac{LDH_i}{247}\right)^{0.0492} \cdot \left(\frac{WT_i}{69.4}\right)^{0.337}$$

$$CL_{T,i} = 0.297 \cdot CL_{cat.cov}.CL_{cont.cov} \cdot exp\left(\frac{T_{max} \cdot t}{TC_{50} + t}\right) \cdot \exp(\eta_i)$$

where $CL_{cat.cov}$, $CL_{cont.cov}$ and $CL_{T,i}$ represent the impact of categorical and continuous covariates and the individual total CL including the time-dependent decrease of CL respectively.

$$V_{c,i} = 3.40 \cdot \left(\frac{WT_i}{69.4}\right)^{0.494} \cdot 1_{male} \cdot (1 - 0.141_{female})$$

Note: alb_i = albumin concentration at baseline, $CrCL_i$ = creatinine clearance at baseline, LDH_i = lactate dehydrogenase at baseline, WT_i = body weight at baseline.

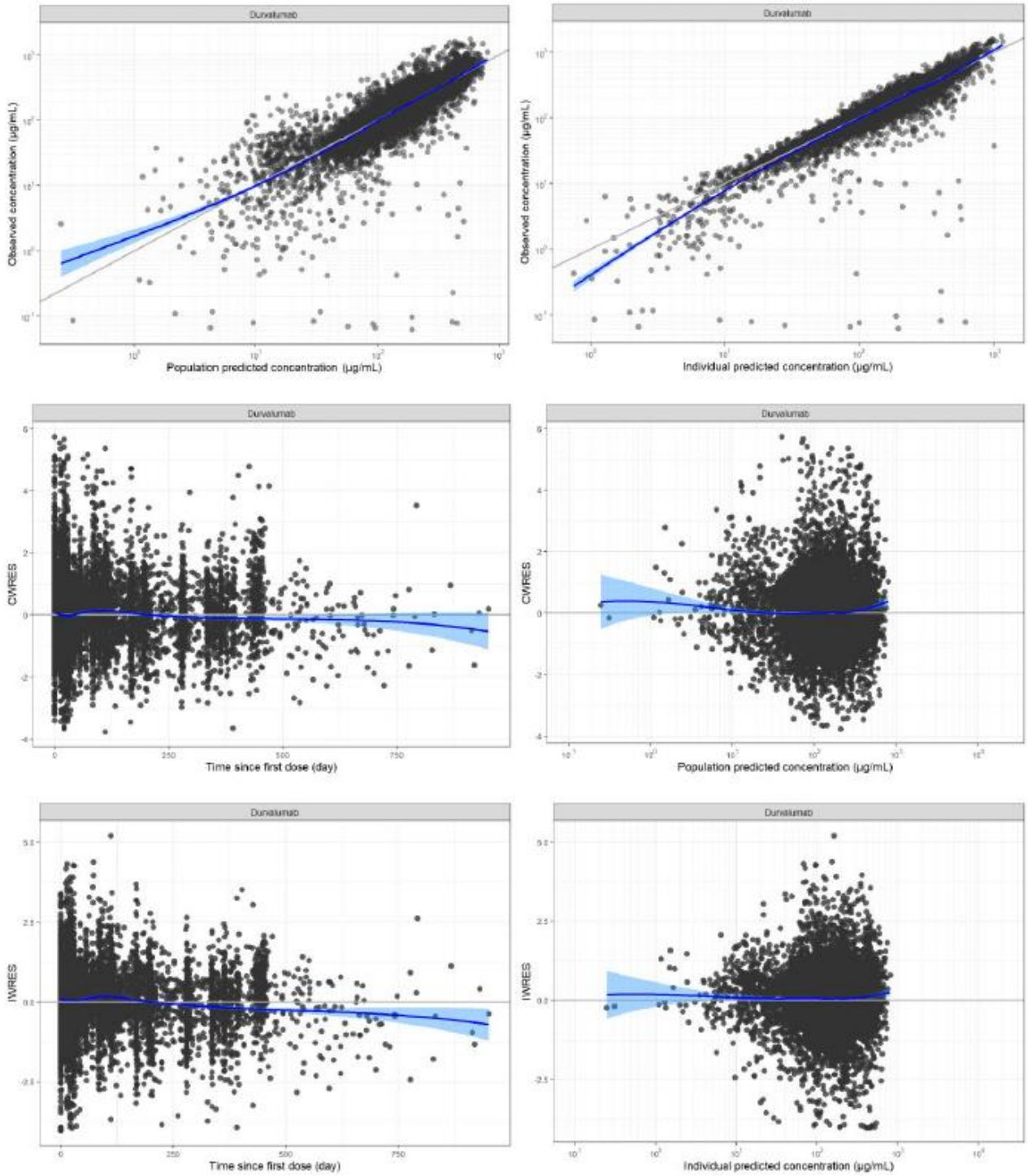
GOF-plots of DV vs. PRED/IPRED, CWRES vs. time since first dose, CWRES vs. PRED, WRES vs. time since first dose and WRES vs. PRED can be seen in Figure 1. A pcVPC of the final durvalumab model for POSEIDON is shown in Figure 2.

Table 3. Population PK Model Parameter Estimates (Final Model)

Parameter	Estimate	RSE (%)	Bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.297	1.57	[0.281 ; 0.313]	--	L/day
V1	3.40	0.737	[3.35 ; 3.45]	--	L
V2	2.07	3.04	[1.92 ; 2.22]	--	L
Q	0.451	4.98	[0.376 ; 0.543]	--	L/day
Tmax	-0.487	5.01	[-0.542 ; -0.423]	--	--
TC_{50}	68.9	7.32	[47.8 ; 100]	--	day
LAM	1.00	--	--	--	--
Covariates					
Albumin on CL	-0.605	15.5	[-0.824 ; -0.449]	--	--
Creatinine clearance on CL	0.112	19.5	[0.0626 ; 0.151]	--	--
ECOG status on CL	-0.0505	27.3	[-0.0770 ; -0.0221]	--	--
LDH on CL	0.0492	25.1	[0.0246 ; 0.0730]	--	--
Sex on CL	-0.168	7.83	[-0.195 ; -0.140]	--	--
COMB1 on CL	-0.166	9.87	[-0.202 ; -0.133]	--	--
COMB 2 on CL	-0.0958	25.4	[-0.141 ; -0.0505]	--	--
Bodyweight on CL	0.337	10.5	[0.268 ; 0.420]	--	--
Sex on V1	-0.141	8.76	[-0.163 ; -0.119]	--	--
Bodyweight on V1	0.494	6.07	[0.438 ; 0.554]	--	--
Interindividual Variability					
ETA CL	0.0801	6.18	[0.0694 ; 0.0898]	19.2	--
Cov CL-V1	0.0358	7.72	[0.0303 ; 0.0415]	--	--
ETA V1	0.0565	8.35	[0.0480 ; 0.0647]	26.0	--
ETA Tmax	0.0644	17.1	[0.0419 ; 0.0933]	56.3	--
Residual Variability					
Proportional component	0.248	1.85	[0.239 ; 0.256]	13.6	--
Additive component	5.12	12.6	[3.86 ; 6.38]	13.6	µg/mL

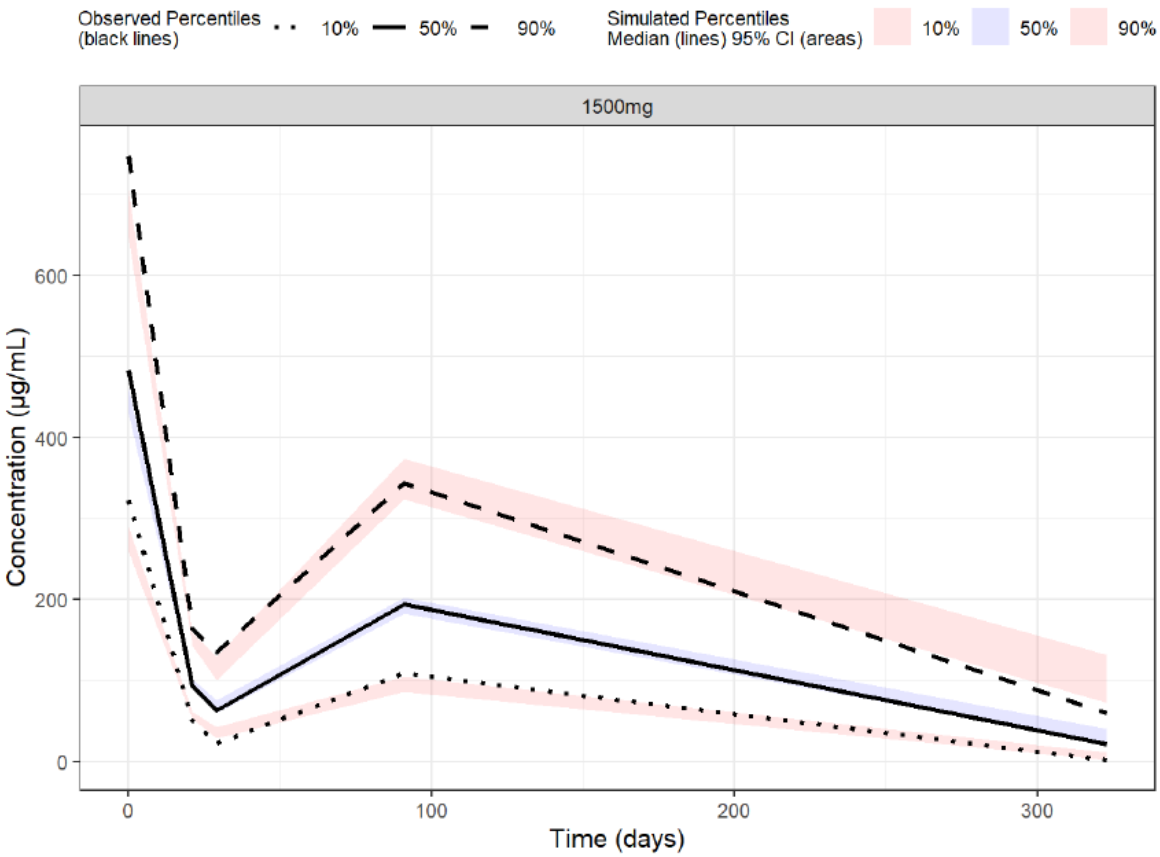
Source: az-durvalumab-pk-model-poseidon-v3.Rmd, Reference: 3781a5:7d4acc
Abbreviations: CI=confidence interval, COMB1=durvalumab+SOC, COMB2=durvalumab+tremelimumab+SOC, Cov=Covariance, ECOG=Eastern Cooperative Oncology Group, ETA=random effect, LAM=Hill factor, LDH=lactate dehydrogenase, RSE=relative standard error, CL=clearance, V1=central volume of distribution, Q=inter-compartmental clearance, PK=pharmacokinetics, SOC=standard of care, V2=peripheral volume of distribution, Tmax=maximum change of CL over time, TC50: time to 50% change of CL over time.
Note: 38 runs with minimization terminated were skipped when calculating the bootstrap results.

Figure 1: **Final Model – Basic Goodness of Fit Plots**



Source: az-durvalumab-pk-final-model-poseidon-v4.Rmd (references: Source: az-durvalumab-pk-model-poseidon-v3.Rmd, Reference: d4d6c7:18aff6, 9a3886:78e195, 38da4d:5276c2, 2209f2:ad2e4b, 57538e:60fc4c, f94879:df7ae9)
Note: the blue line is a trend line through the data points, the blue area is the 95% confidence interval around it.
Abbreviations: CWRES=conditional weighted residuals, IWRES=individual weighted residuals.

Figure 2: **PcVPC of the Final Model vs Time per Dose – POSEIDON Study (Linear scale)**



Source: az-durva-pk-model-evaluation-final-v3.docx, Reference: 3a16fe:60f8ee
Note: The solid and dashed lines represent the median, 10th, and 90th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.
Abbreviations: CI=confidence interval, pcVPC=prediction-corrected visual predictive check

The final model of durvalumab PK was a 2-compartment model with time-dependent CL. Residuals were described by a combined additive and proportional error model. IIV was included on CL, V1 and Tmax and %CV was moderate (28%, 24%, and 25%, respectively). Structural model parameters were estimated with good precision (RSE<10%) and covariate parameters were estimated with adequate precision (RSE<25%). Shrinkage was low/moderate in IIV terms on CL and V1, whereas shrinkage was high on Tmax (56.3%), hence the information for this effect is limited. After the SCM procedure, the final model included the following statistically significant covariate effects on CL: WT, ALB, combination therapy, sex, CrCL, LDH, and ECOG; and on V1: WT and sex. Of all covariates, only ALB had an impact greater than 20% at the 5th percentile on CL and only WT had a greater impact than 20% at the 95th percentile on V1. The effect of body weight was allometrically scaled with estimated exponents of 0.337 and 0.494 for CL and V1, respectively, indicating that the effect of body weight was less than proportional, which is generally common for mAbs.

The final model was evaluated by means of non-parametric bootstrap analysis (n=500), RSEs, GOF-plots and VPCs. The number of replicates in the bootstrap analysis was initially planned to be 1000 but was reduced to 500 due to extensive run times. No major model misspecifications were indicated by GOF-plots. The bootstrap 2.5 and 97.5 percentiles did not contain the null. 38 bootstrap runs were not minimizing, which yields a bootstrap convergence rate of 92.4% (462/500). Bootstrap 95% CIs of Tmax are notably wide.

The pcVPC of durvalumab concentration vs. time indicated that the predicted data was consistent with the observed percentiles in POSEIDON. In the first 20 days, slight model under-predictions in the 10th and 90th percentiles were noted in POSEIDON. Overall, the pcVPCs also showed good agreement between the model prediction and the observed durvalumab serum concentrations for each dose and each study. However, simulated percentile CI bands are overlapping heavily in 3 mg/kg, 15 mg/kg and 20 mg/kg dosing regimens and CI bands are also overlapping in the pcVPC of the CASPIAN study.

The model evaluation based on the GOF shows adequate performance in the vast majority of the observations with a slight individual misspecification at the lower range of observations, possibly due to the lack of inclusion BLQ methods (M1 method), which can slightly underpredict the elimination process. However, this issue is considered of minor relevance.

The clinical relevance study suggested a roughtly clinical relevant changes of AUCss due to sex (20.1%), durva+chemo (19.7%) and low ALB (-17.2%) and on Cmax due to low body weight (17.9%) and sex (18.6%) which are very close to the clinical relevance of 20%.

No information was provided regarding observed AUCss, Cminss and Cmaxss in the study population. (Sparse PK data in POSEIDON study). The exposure comparison across the different dose regimens proposed suggested minor impact in terms of AUC.

QTcF modelling analysis

Linear mixed-effects exposure-response modelling with an intercept was conducted to characterize the relationship of change from baseline of QTcF (ΔQTcF) with durvalumab or tremelimumab serum concentrations. The concentration-ΔQTcF analysis population consisted of 293 observations from 67 patients administered durvalumab and 254 observations from 66 patients administered tremelimumab from Study 06. Unscheduled concentration-QTcF observations and non-central ECG records were excluded from the analysis.

For durvalumab, the slope for the relationship of ΔQTcF to durvalumab concentration was 0.0048 ms per µg/mL (p = 0.112), with a mean intercept of 0.082 ms (p = 0.950; 90% CI: -2.24, 2.24 ms; Table 4).

The slope or the intercept for tremelimumab and durvalumab were significantly different from 0. The slope for the relationship of ΔQTcF to tremelimumab concentration was -0.012 ms per µg/mL (p = 0.531), and the mean intercept was 0.581 ms (p = 0.629; 90% CI: 1.41, 2.57 ms; Table 5).

Table 4: **Parameter estimates of durvalumab PK- ΔQTcF relationship**

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.08205	1.2916	0.9495	-2.0726	2.2367	0.000012
Slope (ms/µg/mL)	0.004841	0.003007	0.1123	-0.00018	0.009858	0.003814
Inter individual variability on intercept	7.8721	0.8472	<.0001	6.4588	9.2855	0.000021
Model error	9.4501	0.4275	<.0001	8.7369	10.1633	-8.91E-6

PK pharmacokinetic

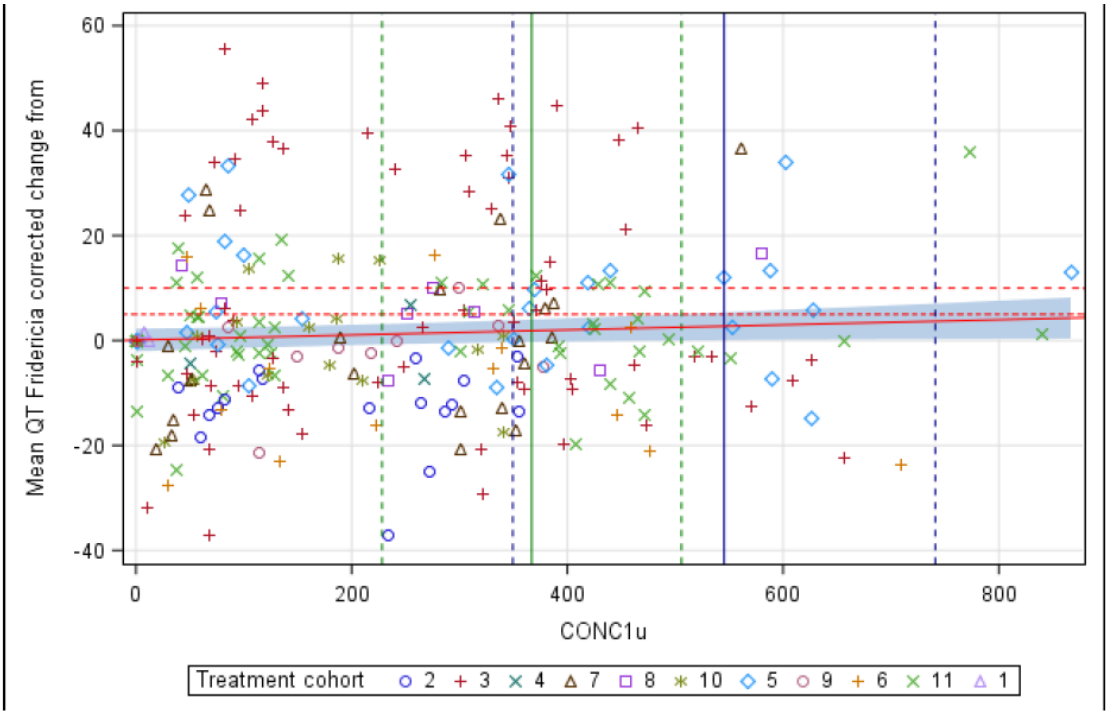
Table 5: **Parameter estimates of tremelimumab PK- ΔQTcF relationship**

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.5806	1.1952	0.6288	-1.4137	2.5749	-1.01E-6
Slope (ms/ µg/mL)	-0.01225	0.01945	0.5312	-0.04470	0.02021	-0.00007
Inter individual variability on intercept	7.5385	0.8414	<.0001	6.1345	8.9425	-2.99E-6
Model error	9.2338	0.4544	<.0001	8.4755	9.9921	4.764E-6

PK pharmacokinetic

The upper bound of the 90% 2-sided CI for ΔQTcF was less than 10 ms, and the highest observed concentration of durvalumab and tremelimumab had a predicted mean ΔQTcF of less than 5 ms (Figure 3 Figure 4 and Table 6).

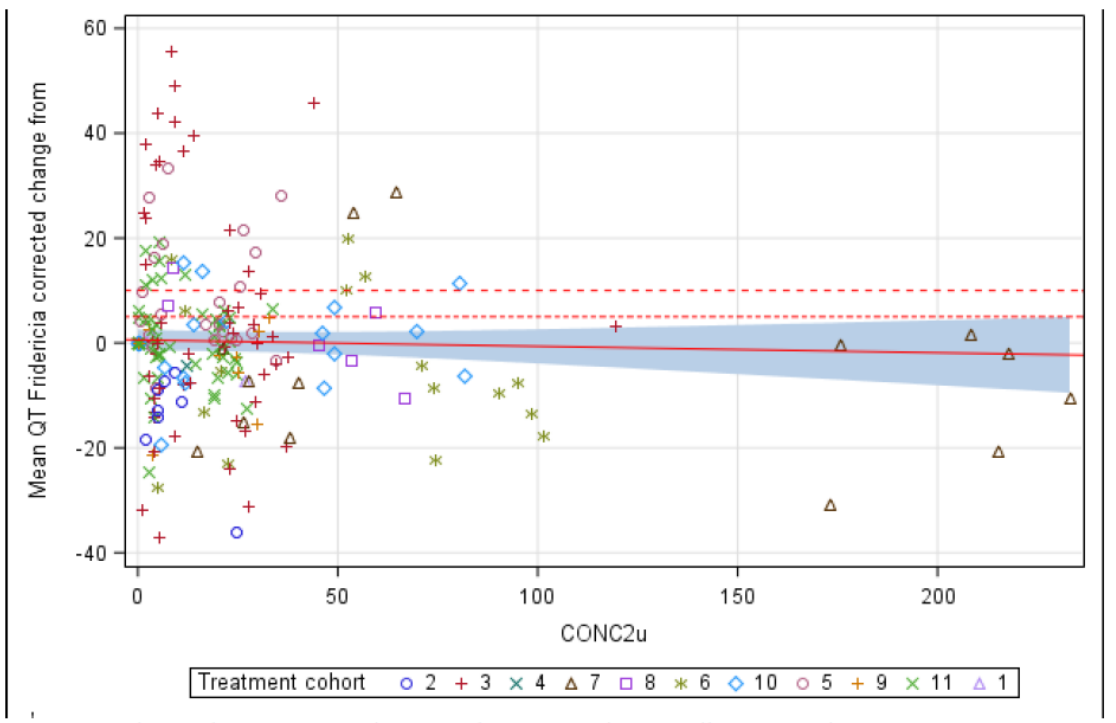
Figure 3: **QTcF (change from baseline) versus concentration of durvalumab on intercept full data**



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Green dashed vertical lines are observed median +/- IQR predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Green solid line is median predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Blue dashed vertical lines are observed median +/- IQR(interquartile range) predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Blue solid line is median predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg

Figure 4: **QTcF (change from baseline) versus concentration of tremelimumab on intercept full data**



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg Tremelimumab; 8: 20 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 9: 10 mg/kg durvalumab (Q2W) + 1 mg/kg Tremelimumab; 10: 10 mg/kg durvalumab (Q2W) + 3 mg/kg Tremelimumab; 11: 20 mg/kg durvalumab (Q4W) + 1 mg/kg tremelimumab (Q4W)/ 20 mg/kg durvalumab (Q4W)

Table 6: **Summary of maximum observed durvalumab or tremelimumab serum concentration and predicted mean and CI of ΔQTcF**

	Observed Cmax (µg/mL)	Cohort	Dosing regimen	Predicted mean ΔQTcF (ms)	90% CI of predicted mean ΔQTcF (ms)
Durvalumab	866.6	10	20mg/kg durvalumab, 1mg/kg tremelimumab	4.28	(0.36, 8.20)
Tremelimumab	233	4	10mg/kg durvalumab, 15mg/kg tremelimumab	-2.27	(-9.49, 4.96)

ΔQTcF change from baseline of QTcF; CI confidence interval; Cmax maximum plasma concentration; QTcF Fridericia's heart rate corrected QT interval.

Absorption

Durvalumab is administered intravenously and the bioavailability is 100%.

Distribution

Distribution studies have not been conducted for durvalumab with this application.

Elimination

No new studies regarding the metabolism of durvalumab metabolism have been conducted.

No new data has been provided from POSEIDON on elimination.

Dose proportionality and time dependencies

In Study D4190C00006 (Study 06), an approximately dose-proportional increase in PK exposure (Cmax and AUC0-28) of tremelimumab was observed over the dose range of 1 to 10 mg/kg tremelimumab Q4W when administered in combination with durvalumab (Table 7). Exposure following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. The PK profile for tremelimumab is shown in Figure 5.

Based on the final Population PK model using POSEIDON data, time-dependent CL was identified for tremelimumab in combination with durvalumab, but not with tremelimumab monotherapy.

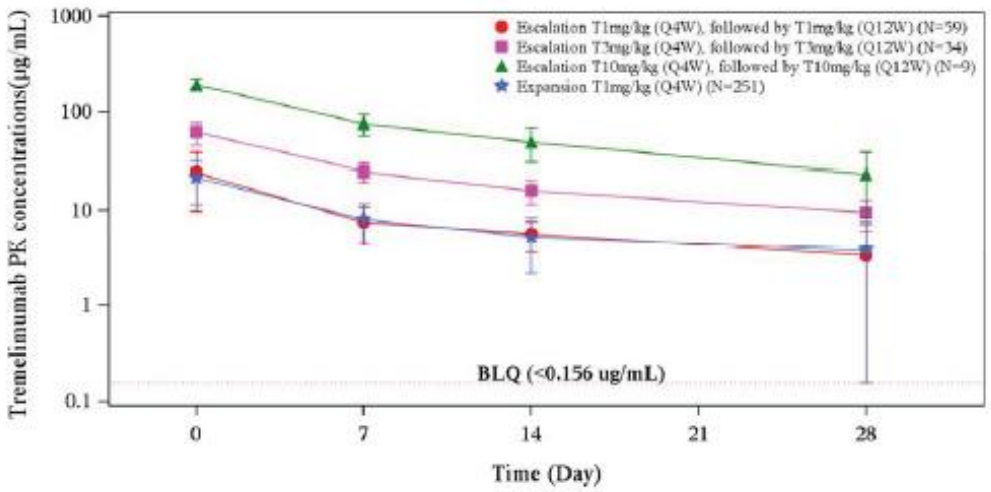
Table 7. Dose-normalized tremelimumab PK parameters following administration of tremelimumab and durvalumab combination (Study 06)

Dose level	Tremelimumab geometric mean (n, geometric %CV)	
	Cmax_D (µg/mL/mg)	**AUC0-28_D (µg·day/mL/mg)**
T1 Q4W Escalation (N = 59)	0.319 (55, 37.8)	2.82 (36, 39.3)
T3 Q4W Escalation (N = 34)	0.258 (32, 60.7)	2.83 (17, 21.1)
T10 Q4W Escalation (N = 9)	0.261 (9, 26.1)	2.45 (9, 32.2)
T1 Q4W Expansion (N = 251)	0.288 (200, 41.3)	3.41 (14, 45.9)

Note: All data are depicted as geometric mean (n, geometric %CV), and rounded to 3 significant digits.
AUC0-28_D, dose-normalized area under the serum concentration-time curve from Day 1 to Day 29;
Cmax_D, dose-normalized maximum serum concentration after the first dose; CV, coefficient of variation;
PK, pharmacokinetic; Q4W, every 4 weeks; T1, tremelimumab 1 mg/kg; T3, tremelimumab 3 mg/kg;
T10, tremelimumab 10 mg/kg.

The PK profile for tremelimumab is shown in Figure 5.

Figure 5: **Mean (SD) Tremelimumab PK Concentration-time Profiles After the First Dose by Tremelimumab Dose Following IV Administration of the Combination of Durvalumab and Tremelimumab (Study 06)**



BLQ, below the limit of quantification; IV, intravenous; PK, pharmacokinetic; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation.

An approximately dose-proportional increase in PK exposure (C_{max} and AUC_{0-28}) of durvalumab was observed over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W when administered in combination with tremelimumab Q4W (Table 8).

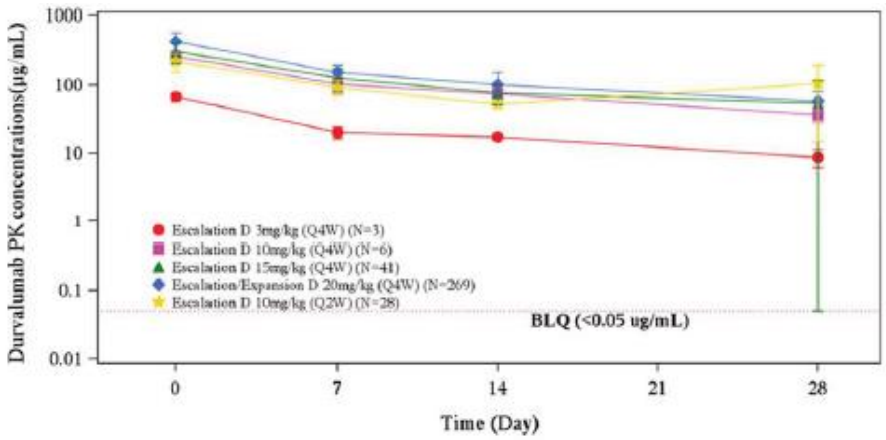
Table 8: **Dose-normalized Durvalumab PK Parameters Following Administration of Durvalumab and Tremelimumab Combination (Study 06)**

Dose level	Durvalumab geometric mean (n, geometric %CV)	
	Cmax_D (μg/mL/mg)	AUC_{0-28}_D (μg·day/mL/mg)
D3 Q4W Escalation (N = 3)	0.277 (2, 14.8)	2.64 (2, 7.0)
D10 Q4W Escalation (N = 6)	0.330 (3, 40.1)	3.47 (3, 39.6)
D15 Q4W Escalation (N = 41)	0.268 (35, 33.7)	2.75 (28, 26.4)
D20 Q4W Escalation and Expansion (N = 269)	0.292 (231, 51.8)	2.89 (24, 31.2)
D10 Q2W Escalation (N = 28)	0.319 (27, 24.7)	NC

Note: All data are depicted as geometric mean (n, geometric %CV), and rounded to 3 significant digits.
AUC_{0-28}_D, dose-normalized area under the serum concentration-time curve from Day 1 to Day 29;
C_{max}_D, dose-normalized maximum serum concentration after the first dose; CV, coefficient of variation;
D3, durvalumab 3 mg/kg; D10, durvalumab 10 mg/kg; D15, durvalumab 15 mg/kg; D20, durvalumab 20 mg/kg;
NC, not calculated; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Table 52, Study 06 CSR, Module 5.3.5.2.

The PK profile for durvalumab is shown in Figure 6.

Figure 6: **Mean (SD) PK Concentration-time Profiles After the First Dose by Durvalumab Dose Following IV Administration of the Combination of Durvalumab and Tremelimumab (Study 06)**



BLQ, below the limit of quantification; IV, intravenous; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

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 original 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 (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$).

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with tremelimumab or durvalumab.

In POSEIDON, no clinically meaningful PK drug-drug interactions between tremelimumab or durvalumab and SoC were identified. In addition, PK of abraxane and gemcitabine were similar between SoC only, durvalumab + SoC, and durvalumab + tremelimumab + SoC groups, suggesting that combination with durvalumab and tremelimumab does not have an impact on the PK of abraxane and gemcitabine.

Additionally, based on population PK analysis, concomitant durvalumab and platinum-based chemotherapy treatment did not seem to impact the PK of tremelimumab in terms of Cmax, CL or AUC.

Pharmacokinetics using human biomaterials

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

Immunogenicity

In the D + SoC arm of POSEIDON, 6.7% (19 of 285) of evaluable patients developed treatment-emergent ADA against durvalumab and the nAb prevalence was 1.1% (3 of 285 evaluable patients). In the T + D + SoC arm of the POSEIDON study, 10.1% (29 of 286) of evaluable patients developed treatment-emergent ADA against durvalumab and the nAb prevalence was 1.0% (3 of 286 evaluable patients).

In the POSEIDON and CASPIAN T + D + SoC pool, 6.1% (29 of 477) of evaluable patients developed treatment-emergent ADA against durvalumab and the nAb prevalence was 0.8% (4 of 477 evaluable patients). In the D + T pan-tumor pool, a durvalumab ADA incidence of 2.5% (35 of 1379 patients; ADA-evaluable population) was observed. The prevalence of durvalumab ADA was 6.2% (86 of 1379 patients). Durvalumab nAb were detected in 0.7% of patients (9 of 1379 patients).

The median of maximum durvalumab ADA titer of patients with treatment-emergent ADA was low at 4 times the minimum-required dilution across all treatment regimens and pools (with the exception of the durvalumab 1500 mg Q3W and tremelimumab 75 mg Q3W pan-tumor pool, with a median maximum titer of 8 [n = 1]).

The prevalence and incidence of durvalumab ADA were numerically higher in patients receiving treatment with T + D + SoC in POSEIDON (14.7% and 10.1%, respectively) when compared with the D + SoC group in POSEIDON (11.6% and 6.7%, respectively) and with the POSEIDON and CASPIAN T + D + SoC pool (10.1% and 6.1%, respectively).

Levels of nAb remained low across all treatments (1.1% of patients receiving D + SoC in POSEIDON, 1.0% patients receiving T + D + SoC in POSEIDON, and 0.8% of patients in the POSEIDON and CASPIAN T + D + SoC pool).

2.3.3. Pharmacodynamics

Mechanism of action

Durvalumab is a human IgG1k mAb that binds to programmed cell death ligand-1 (PD-L1) and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Expression of PD-L1 can be induced by inflammatory signals and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interactions with PD-1 and CD80 (B7.1). By binding to its receptors PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody-dependent cell-mediated cytotoxicity (ADCC).

Tremelimumab is a human IgG2 mAb directed against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to CD80 and CD86 ligands on antigen-presenting cells, sending an inhibitory signal and preventing CD28-mediated T-cell co-stimulation, thus limiting T-cell activation. Tremelimumab blocks these events, leading to prolongation and enhancement of T-cell activation and expansion.

Durvalumab and tremelimumab are checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response triggered by chemotherapy. Tremelimumab mediated blockade of CTLA-4 functions early in the immune response, lowering the threshold for T cell activation, allowing more T cells to be activated and increasing the diversity of the T cell population. This increases the probability that a T cell recognizing a tumor neoantigen can become activated. Durvalumab blockade of PD-L1 is expected to function mainly during the effector phase of T cell function, once T cells enter the tumor, where it acts to block local suppression of T-cell function by PD-L1, enhancing the ability of activated anti-tumor T cells to target and kill tumor cells.

Primary pharmacology

In Study 06, Study 10 and Study 22, circulating lymphocytes (T, B, and NK cells) and proliferating (Ki67+) T cell subsets were quantified using validated flow cytometry-based assays.

The data for Study 06 and Study 10 demonstrated that 15 or 20 mg/kg Q4W durvalumab (combined with doses as low as 1 mg/kg Q4W of tremelimumab) result in significant elevations in proliferating CD4+ and CD8+ T cell quantities, demonstrating a pharmacodynamic effect consistent with the proposed mechanisms of action of both therapeutic agents. The elevations in proliferating T cell quantities were dose proportional to tremelimumab.

In Study 22, significant and consistent increases in CD4+Ki67+ T cells were observed in the T300 + D, T, and T75 + D treatment arms and increases in CD8+Ki67+ T cells were observed in all treatment arms. The increases peaked on Day 15. Findings indicated a potential saturable pharmacodynamic effect on this lymphocyte population. Among all monitored lymphocyte populations, median CD8+Ki67+ T cell counts from patients with CR/PR were elevated at the highest levels above those of stable disease and PD patients. Pairwise analysis using the Wilcoxon method revealed significant differences between median CD8+Ki67+ T cell counts in CR/PR patients vs stable disease or PD patients ($p < 0.01$).

Secondary pharmacology

Overall, concentration-QTc-analysis did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF. The predicted mean ΔQTcF and upper 90% CI at the maximum observed concentration for tremelimumab or durvalumab in the dataset were below the threshold of clinical concern. See section QTcF modelling analysis under section 2.3.2 Pharmacokinetics.

Exposure-response relationships

The final PopPK models of tremelimumab and durvalumab were used to derive individual predicted exposure metrics for the E-R analyses.

The E-R analysis was based on patients from POSEIDON, for whom the different exposure metrics could be calculated (n = 322 for durvalumab + standard of care (SOC) arm and n = 326 for durvalumab + tremelimumab + SOC arm). Both overall survival (OS) and progression-free survival (PFS) were explored by Kaplan-Meier (KM) estimates and analysed by Cox proportional hazard (CPH) models based on data from patients receiving the durvalumab + tremelimumab + SOC. Demographic characteristics, baseline covariates and exposure metrics were tested using a forward-addition and backward-elimination method and with significant levels of $p<0.01$ and $p<0.001$, respectively.

The parameter estimates from the final OS CPH model are presented in Table 9. The result suggested that having non-squamous tumours and a high $C_{min,Dose\ 5\ Treme}$ was significantly associated with longer OS.

The exposure-efficacy on OS did not identify any significant exposure-efficacy relationship, although a trend of longer OS was observed in patients with higher durvalumab exposure.

Table 9: **Final CPH Model for OS**

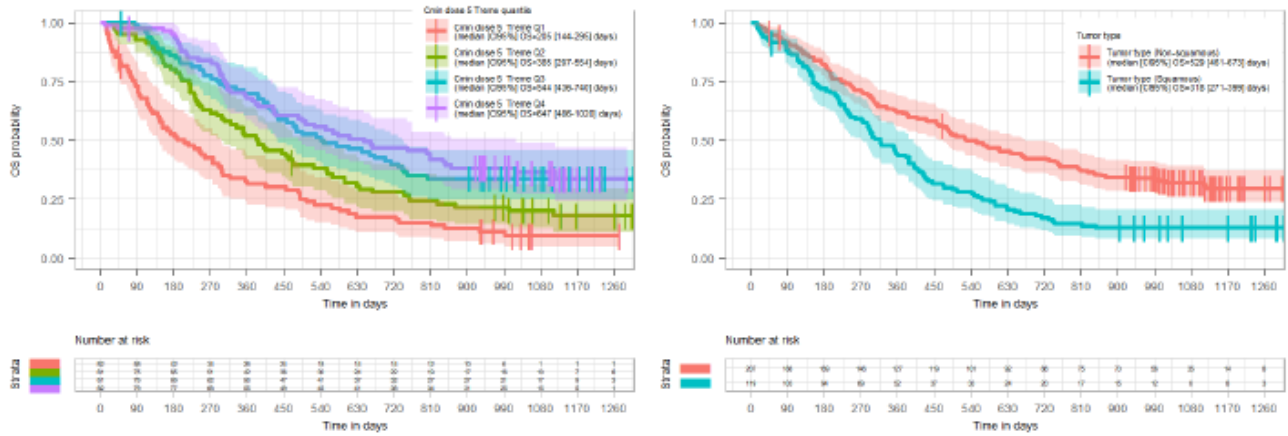
Predictor	β	exp(β)	95% CI β	p-value	AIC
PCMINSST	-0.1929841	0.8244951	[-0.272; -0.114]	< 0.001	2490.77
TUMTYP22	0.5396068	1.7153323	[0.280; 0.799]	< 0.001	

Note: p-value from Wald test.

β, coefficient of the final CPH model, AIC, Akaike information criterion; CI, confidence interval; $C_{min,\ Dose\ 5\ Treme}$, minimum serum concentration for tremelimumab following the 5th dosing cycle; CPH, Cox proportional-hazards; exp(β), hazard ratio; OS, overall survival; PCMINSST, predicted $C_{min,\ Dose\ 5\ Treme}$; PK, pharmacokinetic(s); TUMTYP22, tumor type (squamous cells).

Source: Table 28, Population PK and Exposure-Response Report, Module 5.3.3.5.

Figure 7: **OS Kaplan Meier Plots Stratified by Significant Covariates**



Source: az-durvalumab-os-post-process-poseidon-v12.Rmd, Reference: 6bdfcf:4accf1
Abbreviation: OS=overall survival, Cmin=minimum serum concentration

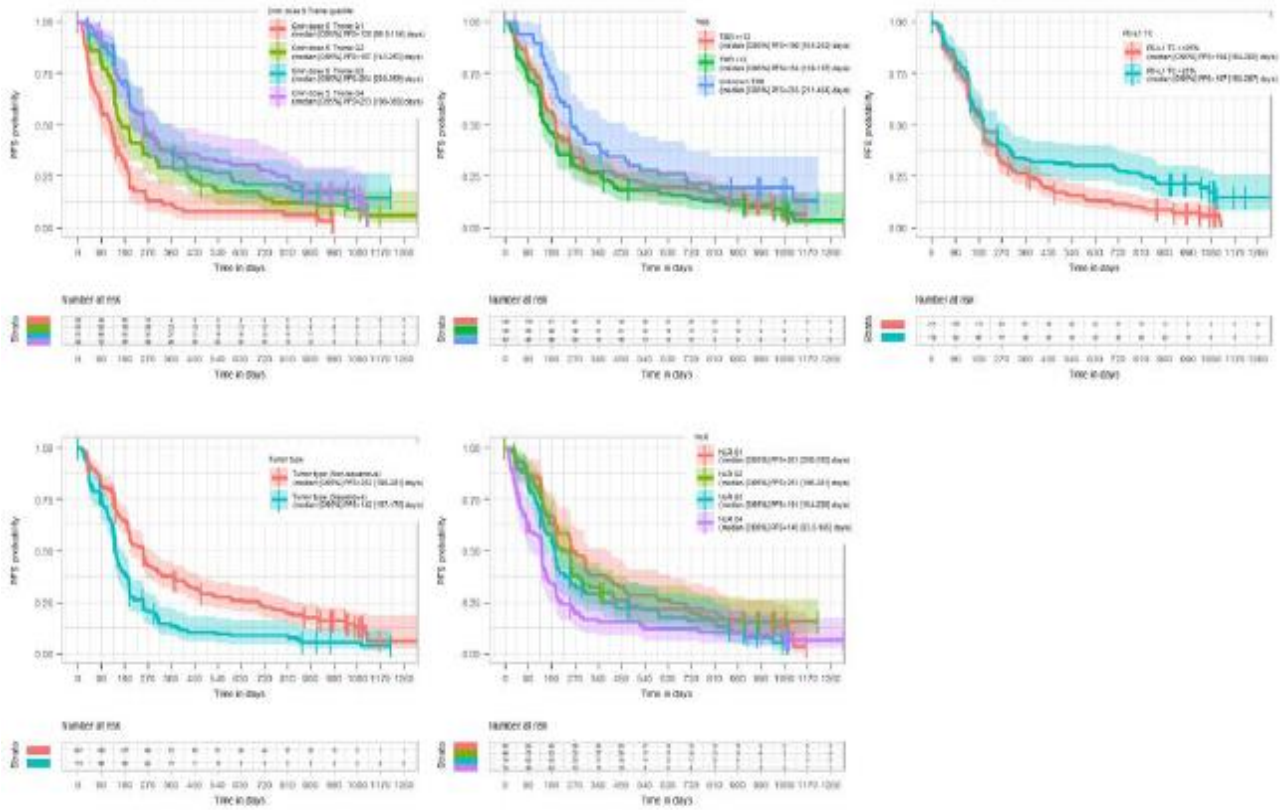
The following covariates for PFS were statistically significant: patients having high tumour mutational burden (>12 mutations per megabase), high percentage of PD-L1 T cells (<25%), non-squamous tumour lesions and low NLR (Q1). The parameter estimates from the final PFS CPH model are presented in Table 10. The results suggested that having non-squamous tumours, a high $C_{min,Dose\ 5\ Treme}$, a low NLR, less than 25% of PD-L1 TC or less than 12 mutations per megabase was significantly associated with longer PFS (Figure 8). The proportional hazard assumption was supported by a non-significant relationship between residuals and time except for the covariate logNLR. No exposure-PFS relationship was established after durvalumab administration, although the same trend as in OS was observed. The exposure-PFS analysis after tremelimumab administration allowed to include the predicted Cmin at dose 5 in the cox regression analysis with additional covariates. The result suggests that higher Cmin levels after 5 doses of tremelimumab are associated with higher PFS.

Table 10: **Final CPH Model for Progression-Free Survival**

Predictor	β	exp(β)	95% CI β	*P* value	AIC
PCMINSST	-0.1184131	0.8883290	[-0.190 ; -0.0472]	0.00113	2696.95
TUMTYP22	0.7480232	2.1128192	[0.489 ; 1.01]	< 0.001	
logNLR	0.4365548	1.5473671	[0.209 ; 0.664]	< 0.001	
PDTC251	-0.5192562	0.5949629	[-0.781 ; -0.257]	< 0.001	
TMB1221	0.2904671	1.3370519	[0.0281 ; 0.553]	0.0300	
TMB1222	-0.3820577	0.6824557	[-0.741 ; -0.0233]	0.0369	

Source: az-durvalumab-pfs-triplet-v25.Rmd, Reference: 1956bf:aa8a26
Abbreviation: AIC=Akaike's information criteria, TMB=tumor mutational burden

Figure 8: **PFS Kaplan Meier Plots Stratified by Significant Covariates**



Abbreviation: PFS= progression free survival, Cmin= minimum serum concentration, TMB= tumour mutational burden, NLR=neutrophil to lymphocyte ratio

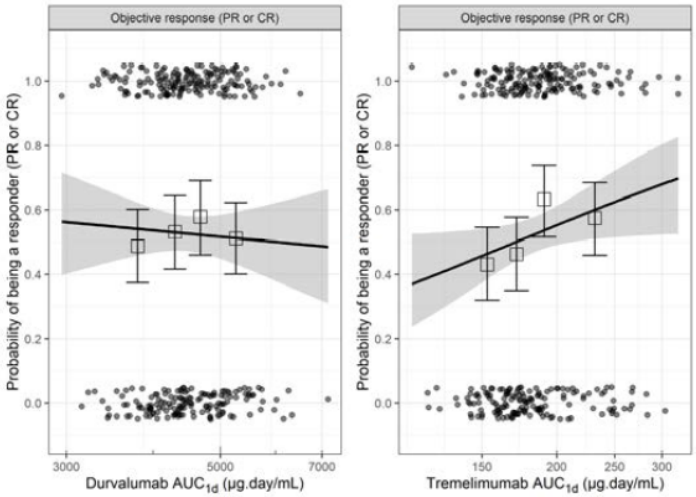
In addition to OS and PFS, the impact of durvalumab and tremelimumab on the ORR was investigated using a logistic regression approach. For this analysis, ORR was dichotomized such that PR and above was given a value of 1 (responder), and SD or worse was given a value of 0 (non-responder). Logistic regression models for assessing effect of durvalumab and tremelimumab were based on 319 and 318 patients, respectively. None of the exposure metrics for either drug was found to be significant. The relatively large p-values (Table 11) show that none of the exposure metrics has a statistically significant impact (at the prespecified significance level of $\alpha = 0.001$) on the probability of being a responder.

Table 11: Summary of the Effect of Different Exposures Metrics on the Probability of Being a Responder (PR or CR)

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P-value (based on LRT)	Loglikelihood	AIC	Number of patients
Durvalumab Cmax after first dose	-0.00149 (62.8)	(-0.00335, 0.000325)	0.108	-219.4	442.7	319
Durvalumab Cmin after first dose	0.00236 (196)	(-0.00673, 0.0115)	0.61	-220.5	445.1	319
Durvalumab AUC after first dose	-8.68e-05 (195)	(-0.000421, 0.000246)	0.609	-220.5	445.1	319
Durvalumab Cmax steady-state	-0.000464 (146)	(-0.0018, 0.00086)	0.492	-220.4	444.8	319
Durvalumab Cmin steady-state	0.00106 (112)	(-0.00127, 0.00342)	0.372	-220.3	444.5	319
Durvalumab AUC steady-state	2.32e-05 (165)	(-5.19e-05, 9.91e-05)	0.545	-220.5	445	319
Tremelimumab Cmax after first dose	0.0287 (59.2)	(-0.00382, 0.0632)	0.084	-218.5	441.1	318
Tremelimumab Cmin after first dose	0.19 (64.5)	(-0.0475, 0.436)	0.117	-218.8	441.6	318
Tremelimumab AUC after first dose	0.0061 (53.4)	(-2e-04, 0.0126)	0.058	-218.2	440.4	318
Tremelimumab Cmax,Dose 5	0.0349 (52.3)	(-7.03e-05, 0.0719)	0.05	-218.1	440.2	318
Tremelimumab Cmin,Dose 5	0.0523 (106)	(-0.0504, 0.17)	0.326	-219.5	443.1	318
Tremelimumab AUC,Dose 5	0.00434 (59.5)	(-0.00042, 0.00968)	0.075	-218.4	440.9	318

Source: az-durvalumab-orr-poseidon-v5.Rmd, Reference: 06b67a:e2bec8
Abbreviations: AIC=Akaike's information criteria, AUC=area under the serum concentration-time curve, Cmax=maximum serum concentration, Cmin=minimum serum concentration, CR=complete response, LRT=likelihood ratio test, PR=partial response, SOC=standard of care

Figure 9: **Relationship between the probability of being a responder (PR or CR) and AUC after first dose of durvalumab and tremelimumab**



Note: The black solid circles are the observed probability of Response and the error bars are the standard errors for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The black lines the logistic regression between 2 variables and the gray area represents the associated CI.

AUC, area under the serum concentration-time curve; CI, confidence interval; CR, complete response; PK, pharmacokinetic(s); PR, partial response.

ORR was analysed with linear logistic regression models. None of the effects of exposure metrics on the probability of being a responder were statistically significant based on the likelihood-ratio-test.

Exposure-safety relationship

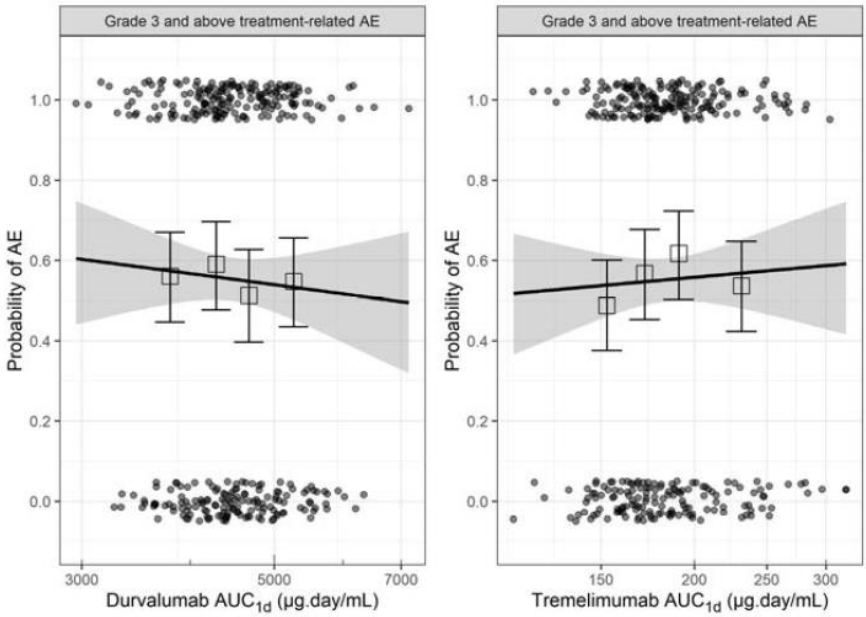
For variables used in the safety analysis (Grade 3+ AE, Grade 3+ AESI, AE leading to treatment discontinuation), exposure boxplots were stratified by response values, and the probability of response was plotted vs exposure, after binning patients according to exposure quartiles. All categorical variables were converted to binary responses and analysed with linear logistic regression models. The predicted logistic regression curve and the observed adverse event rate in relevant bins of the observed data were plotted for all exposure-safety analyses. Safety endpoints were graphically evaluated and results were confirmed by logistic regression models that did not identify any significant impact of tremelimumab/durvalumab exposure on the incidence of the investigated AEs.

Of the 330 patients in the T+D+SoC arm, 3 did not have durvalumab exposure metrics while 4 did not have tremelimumab exposure metrics hence 327 and 326 patients were analyzed in the logistic regression models for durvalumab and tremelimumab respectively.

The relationship between the probability of having Grade 3 and above treatment-related AEs and AUC after the first dose of durvalumab and tremelimumab is shown in Figure 10Figure 10. The relationship between the probability of having Grade 3 and above treatment-related AESIs and AUC after the first dose of durvalumab and tremelimumab is shown in Figure 11.

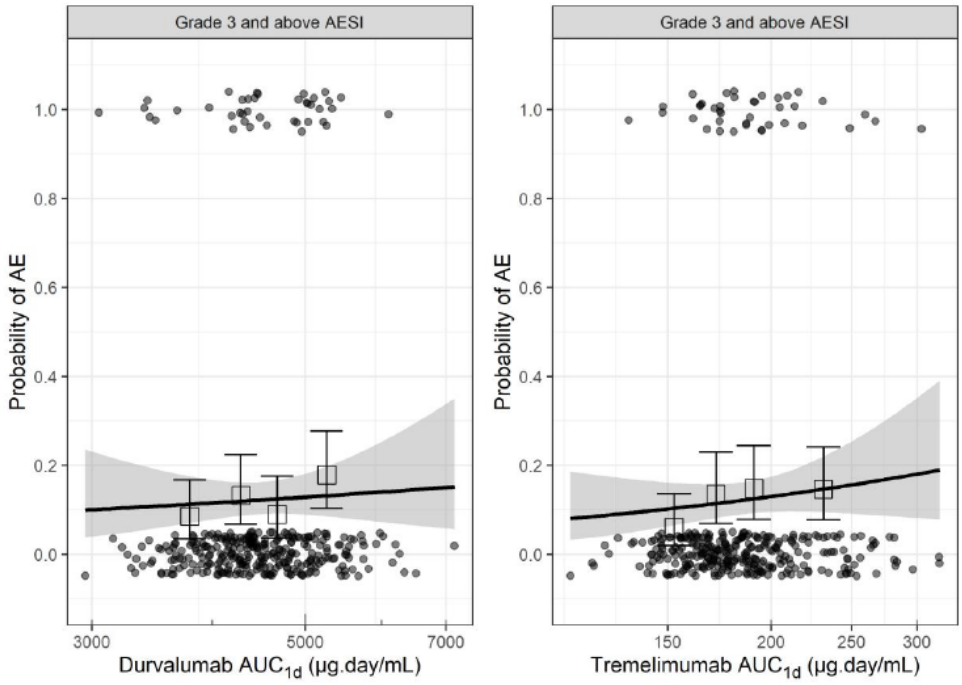
Although not statistically significant, it was notable that the coefficients for the effect of durvalumab on probability of Grade 3 and above treatment-related AEs were negative, suggesting a counterintuitive decrease in the probability of AEs with increasing exposure. However, these effects were small and not statistically significant. In general, the apparent overlap in the distribution of exposure between the patients that had and those that did not have AEs suggested no clear relationship between exposure and the probability of having AEs.

Figure 10: **Relationship between the probability of having Grade 3 and above treatment-related AEs and AUC after the first dose of durvalumab and tremelimumab**



Note: The black solid circles are the observed probability of Response and the error bars are the standard errors for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The black lines the logistic regression between 2 variables and the gray area represents the associated CI.
AE, adverse event; AUC, area under the serum concentration-time curve; CI, confidence interval; PK, pharmacokinetic(s).

Figure 11: **Relationship between the probability of having grade 3 and above AESI and AUC after first dose for durvalumab and tremelimumab**



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 400028:5b2d38
Abbreviations: AE=adverse event, AESI=adverse event of special interest, AUC=area under the serum concentration-time curve
Note: the black solid circles are the observed probability of Response and the error bars are the standard errors for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The black lines the logistic regression between two variables and the gray area represents the associated confidence interval.

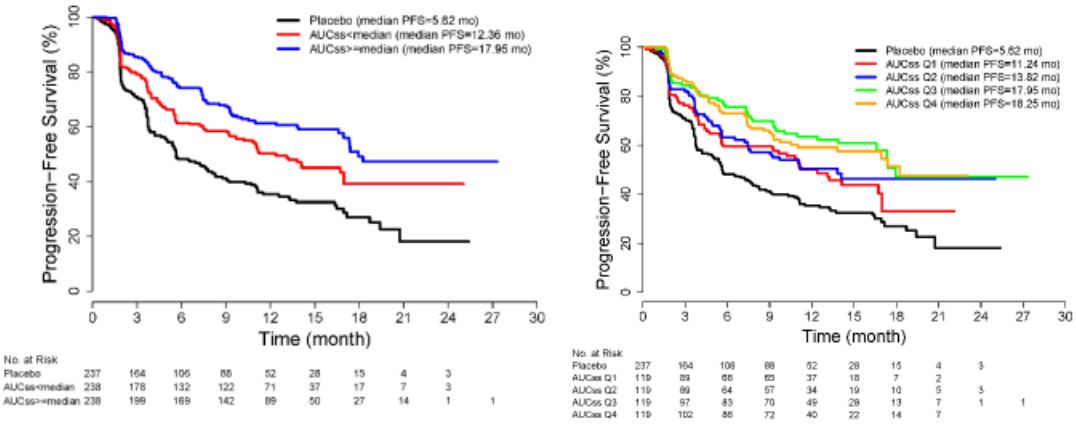
2.3.4. Dose response studies

Exposure-efficacy relationship

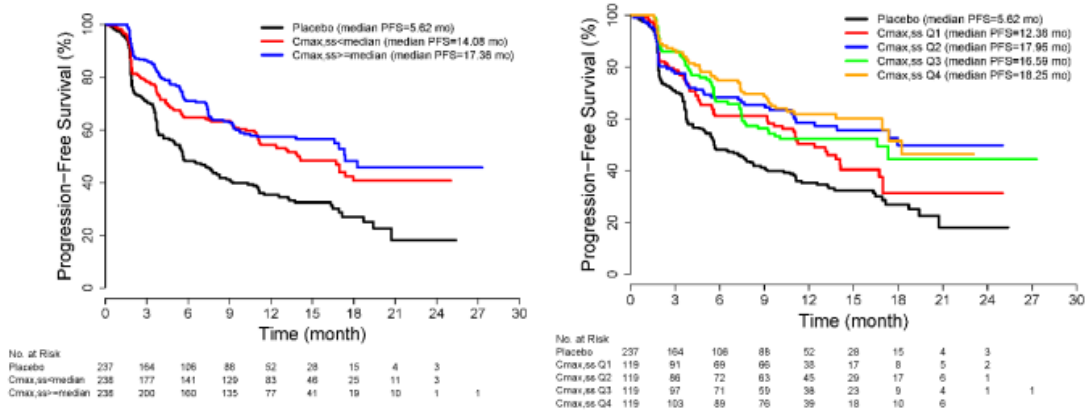
The Progression-free survival (PFS) Kaplan-Meier curves in the durvalumab-treated patients stratified by model predicted exposures at steady state and overlaid with patients in the placebo group are presented in Figure 12. Durvalumab treatment led to longer PFS compared to placebo. Patients with AUCss and Cmin,ss exposure above the median had slightly longer PFS compared to those with exposure below the median.

Figure 12. Progression-free survival profiles stratified by durvalumab exposure categories

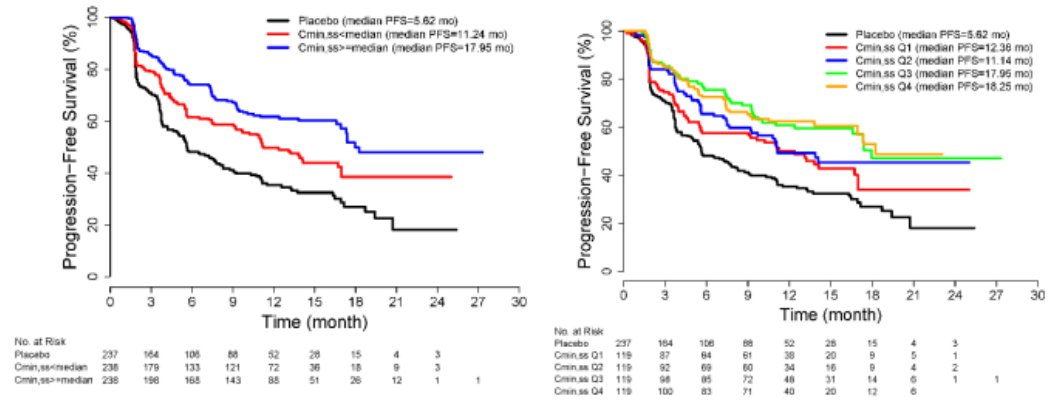
AUCss



Cmax



Cmin



In order to assess whether the time-varying CL is a confounding factor on the exposure response relationship, the relationship between PFS and AUCss 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 AUCss. Therefore, the trend of longer PFS with higher AUCss 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.

2.3.5. Discussion on clinical pharmacology

Durvalumab and tremelimumab are checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response triggered by chemotherapy. Tremelimumab mediated blockade of CTLA-4 functions early in the immune response, lowering the threshold for T cell activation, allowing more T cells to be activated and increasing the diversity of the T cell population. This increases the probability that a T cell recognizing a tumor neoantigen can become activated. Durvalumab blockade of PD-L1 is expected to function mainly during the effector phase of T cell function, once T cells enter the tumor, where it acts to block local suppression of T-cell function by PD-L1, enhancing the ability of activated anti-tumor T cells to target and kill tumor cells.

Durvalumab (Imfinzi) was approved in 2018 in the EU for treatment of adults with locally advanced, unresectable non-small cell lung cancer (NSCLC), whose tumors express PD-L1 on ≥ 1% of TCs and whose disease has not progressed following platinum-based chemoradiation therapy.

The clinical pharmacology of durvalumab as monotherapy has previously been described adequately.

The MAH is currently seeking marketing approval for the use of durvalumab in combination with tremelimumab and platinum-based chemotherapy for the first-line treatment of patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations.

The purpose of the present application is to update the product information for durvalumab when given in combination with tremelimumab.

The Phase III study POSEIDON is the pivotal study for this application, which provided limited new PK/PD data.

The durvalumab PopPK model was updated by including 11683 serum PK samples from 2827 patients. The model was based on a pooled dataset from 5 Studies: Study 1108, POSEIDON, ATLANTIC, PACIFIC and CASPIAN. A total of 154 samples (1.3%) were excluded from the analysis and the M1-method for handling outlier/BLQ-data is considered acceptable. Parameter estimates did not significantly change after reintroduction of excluded data. The final model of durvalumab PK was a 2-compartment model with time-dependent CL. Residuals were described by a combined additive and proportional error model. The final durvalumab PopPK model included the following statistically significant covariate effects on CL: body weight, albumin, combination therapy, sex, creatinine clearance, lactate dehydrogenase, and eastern cooperative oncology group; and on V1: body weight and sex. The final model was evaluated by means of non-parametric bootstrap analysis (n=500), RSEs, GOF-plots and pcVPCs. The covariate analysis allowed to partially explain the relevance of the covariate effects identified. Overall, the final parameter estimates, parameter precision (RSE) and 95% confidence intervals from the bootstrap analysis demonstrate the statistical and adequacy of the final population model developed. The overall evaluation of the final population PK through the pcVPC suggests the adequacy of the current structure over the POSEIDON study.

Changes on AUCss due to sex, durva+chemo and low ALB and on Cmax due to low body weight and sex are very close to the clinical relevance of 20%. Prediction-corrected VPCs stratified by clinical treatment, body weight, sex and albumin suggested that the durvalumab PopPK model adequately captures different subgroups of populations and no dose adjustments may be needed based on the clinical relevance analysis.

Linear mixed-effects exposure-response modelling with an intercept was conducted to characterize the relationship of change from baseline of QTcF (ΔQTcF) with durvalumab or tremelimumab serum concentrations. The slope or the intercept for tremelimumab and durvalumab were significantly different from 0. However, for both tremelimumab and durvalumab, the upper bound of the 90% CI for ΔQTcF was less than 10 ms, and the highest observed concentration had a predicted mean ΔQTcF of less than 5 ms. These values were lower than the prolongation levels of concern as established in the ICH E14 industry guidance for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. The normality assumption was largely met and no hysteresis was apparent in the ΔQTcF vs. tremelimumab concentration plots.

Both overall survival (OS) and progression-free survival (PFS) were explored by Kaplan-Meier (KM) estimates and analysed by Cox proportional hazard (CPH) models based on data from patients receiving the durvalumab + tremelimumab + SOC. Models were evaluated by graphically superimposing model-predictions over the observed data. The proportional hazard assumption was supported by a non-significant relationship between residuals and time except for the covariate logNLR.

In POSEIDON, no clinically meaningful PK drug-drug interactions between tremelimumab or durvalumab and SoC were identified. In addition, PK of abraxane and gemcitabine were similar between SoC only, durvalumab + SoC, and durvalumab + tremelimumab + SoC groups, suggesting that combination with durvalumab and tremelimumab does not have an impact on the PK of abraxane and gemcitabine.

Additionally, based on population PK analysis, concomitant durvalumab and platinum-based chemotherapy treatment did not seem to impact the PK of tremelimumab in terms of C_{max}, CL or AUC.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of durvalumab in combination with tremelimumab has overall been adequately described.

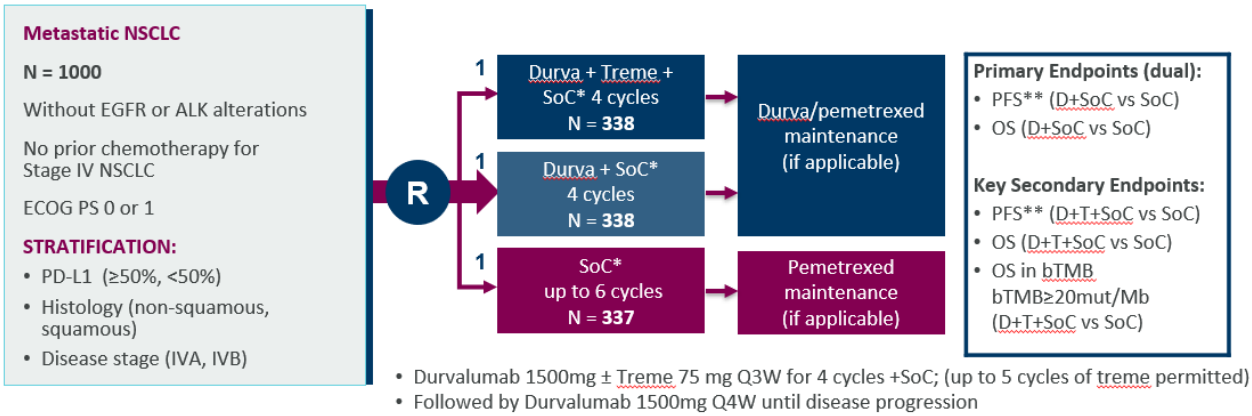
2.4. Clinical efficacy

2.4.1. Main study(ies)

POSEIDON: A phase III, randomised, multicentre, open-label, comparative global study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with

platinum-based chemotherapy for first-line treatment in patients with metastatic non-small-cell lung cancer

Figure 13. Study design - POSEIDON



*Investigator choice of chemotherapy, Standard of Care (SoC): NSQ (Pemetrexed+Platinum or Abraxane+Carbo); SQ (Gemcitabine+Platinum or Abraxane+Carbo)
**By BICR

Dual primary endpoints were BICR-assessed PFS according to RECIST 1.1 and OS compared between arms 2 and 3 (D+SoC vs. SoC) from the ITT population. As key secondary endpoints, BICR-assessed PFS and OS comparisons were done between arms 1 and 3 (T+D+SoC vs. SoC), also in the ITT.

Tumour scans and response assessments according to RECIST 1.1 were performed at screening (as baseline) with follow-ups at week 6 ±1 week from the date of randomization, at week 12 ±1 week from the date of randomization, and then every 8 weeks ±1 week until radiological disease progression.

The applicant states that even if the study was open-label, the study team were blinded to aggregate treatment information, and during the programming and preparation of statistical outputs, data were dummy blinded prior to database lock and study unblinding.

Crossover was not permitted as part of the study.

Methods

Study participants

POSEIDON was conducted at study centres in North and Latin America, Europe, Asia Pacific and Africa. Patients were recruited from 142 centres across Brazil (13 centres), Bulgaria (6 centres), Germany (10 centres), Hong Kong (1 centre), Hungary (5 centres), Japan (18 centres), South Korea (9 centres), Mexico (9 centres), Peru (5 centres), Poland (4 centres), Russia (9 centres), South Africa (7 centres), Taiwan (10 centres), Thailand (6 centres), Ukraine (10 centres), United Kingdom (5 centres), United States (12 centres) and Vietnam (3 centres).

Key inclusion criteria:

- Histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology; IASLC Staging Manual in Thoracic Oncology).
- Patients must have tumours that lack activating EGFR mutations (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and ALK fusions. If a patient

has squamous histology or is known to have a tumour with a KRAS mutation, then EGFR and ALK testing is not required.

- No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >12 months from end of last therapy.
- Tumour PD-L1 status, confirmed by a reference laboratory using the Ventana SP263 PD-L1 immunohistochemistry (IHC) assay, must be known prior to randomization. As such, all patients must be able to undergo a fresh tumour biopsy during screening or to provide an available tumour sample taken <3 months prior to enrollment.
- ECOG performance status of 0 or 1 at enrollment and randomization.
- At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
- No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.
- Adequate hepatic, renal and bone-marrow function.

Key exclusion criteria:

- Mixed small-cell lung cancer and NSCLC histology or sarcomatoid variant.
- Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- No radiation therapy is allowed, unless it is 1) definitive radiation that had been administered at least 12 months prior, 2) palliative radiation to brain, with associated criteria for stability or lack of symptoms, or 3) palliative radiation to painful bony lesions
- Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of the IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
- History of allogenic organ transplantation.
- Uncontrolled intercurrent illness
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). Exceptions: vitiligo, alopecia, hypothyroidism, chronic skin conditions that do not require systemic therapy, celiac disease controlled by diet alone.
- History of leptomeningeal carcinomatosis.
- Brain metastases or spinal cord compression unless the patient's condition is stable (asymptomatic; no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to the start of the IP.
- History of active primary immunodeficiency.

- Active infection including tuberculosis, HBV, HCV and HIV 1/2.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab, except physiological dose of systemic corticosteroids (< 10 mg/day prednisone or equivalent).
- Receiving live attenuated vaccine within 30 days before or after the start of tremelimumab or durvalumab.
- Pregnant or breastfeeding women.

Treatments

The full dosing scheme of POSEIDON is presented in Table 12.

Table 12. Dosing scheme - POSEIDON

Treatment arms	During chemotherapy (combination) stage 1 cycle=3 weeks (21 days)				Post-chemotherapy (maintenance) stage 1 cycle=4 weeks (28 days)		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
T + D + SoC chemotherapy (Treatment Arm 1)	T + D + SoC	T + D + SoC	T + D + SoC	T + D + SoC	D + pemetrexed[a]	T + D[b] + pemetrexed[a]	D + pemetrexed[a]
D + SoC chemotherapy (Treatment Arm 2)	D + SoC	D + SoC	D + SoC	D + SoC	D + pemetrexed[a]	D + pemetrexed[a]	D + pemetrexed[a]
SoC chemotherapy alone (Treatment Arm 3)	SoC	SoC	SoC	SoC[c]	pemetrexed[a]	pemetrexed[a]	pemetrexed[a]

T=tremelimumab; D=durvalumab; SoC=standard of care chemotherapy; PD=progressive disease.

The chosen platinum doublet was prespecified at randomisation before first study treatment and subsequent changes of regimen were not allowed, although switch between cisplatin and carboplatin were permitted. The following histology-based chemotherapy regimens were applicable to all 3 treatment arms:

- Nab-paclitaxel + carboplatin (squamous and non-squamous histologies): Nab-paclitaxel 100 mg/m2 on Days 1, 8, and 15 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (i.e., 4 cycles for the T + D + SoC chemotherapy and D + SoC chemotherapy arms and 4 to 6 cycles for the SoC chemotherapy arm).
- Gemcitabine + cisplatin (squamous histology only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 mg/m2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (i.e., 4 cycles for the T + D + SoC chemotherapy and D + SoC chemotherapy arms and 4 to 6 cycles for the SoC chemotherapy arm).
- Gemcitabine + carboplatin (squamous histology only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (i.e., 4 cycles for the T + D + SoC chemotherapy and D + SoC chemotherapy arms and 4 to 6 cycles for the SoC chemotherapy arm).
- Pemetrexed + carboplatin (non-squamous histology only): Pemetrexed 500 mg/m2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (i.e., 4 cycles for the T + D + SoC chemotherapy and D + SoC chemotherapy arms and 4 to 6 cycles for the SoC chemotherapy arm); then continued pemetrexed 500 mg/m2 maintenance (i.e., Q4W for the T + D + SoC chemotherapy and D + SoC chemotherapy arms.
- Pemetrexed + cisplatin (non-squamous histology only): Pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (i.e., 4 cycles for the T + D

+ SoC chemotherapy and D + SoC chemotherapy arms and 4 to 6 cycles for the SoC chemotherapy arm); then continued pemetrexed 500 mg/m2 maintenance (i.e., Q4W for the T + D + SoC chemotherapy and D + SoC chemotherapy arms.

*Note: For patients with non-squamous histology who received pemetrexed during induction, pemetrexed maintenance therapy could have been given either Q3W or Q4W dependent on investigator decision and local standards.

Arm 1: During chemotherapy, tremelimumab 75 mg IV Q3W + durvalumab 1500 mg IV Q3W + chemotherapy Q3W for 4 cycles. A fifth dose of tremelimumab 75 mg was to be given at Week 16 alongside durvalumab Dose 6. Post chemotherapy, durvalumab 1500 mg IV Q4W.

Arm 2: During chemotherapy, durvalumab 1500 mg IV Q3W and chemotherapy Q3W for 4 cycles. Post chemotherapy, durvalumab 1500 mg IV Q4W.

Arm 3: Chemotherapy Q3W alone for 4 cycles (any of the abovementioned 5 regimens). Patients could receive additional 2 cycles (a total of 6 cycles post-randomization), as clinically indicated, at Investigator's discretion.

The study design did not allow cross over among treatment arms.

Duration of treatment: Patients were treated until clinical progression or radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reductions and delays: Dose reductions of durvalumab and tremelimumab were not permitted. SoC-related toxicity management and dose adjustment, including dose reductions and delays, should be performed as indicated in the local prescribing information for the relevant agent. In the event that an AE could reasonably be attributed to SoC, dose adjustment of SoC was attempted before modifying the administration of durvalumab ± tremelimumab. In the event that SoC was delayed, durvalumab ± tremelimumab was also delayed.

Switch of platinum agent: In the event of unfavourable tolerability, patients could switch between cisplatin and carboplatin therapy at any point on study (assuming eligibility for the switched therapy is met).

Treatment beyond progression: Patients in arms 1 and 2 with objective radiological progression who, in the investigator's opinion, continued to receive benefit from their assigned treatment and who met the criteria for treatment in the setting of (PD) could continue to receive durvalumab monotherapy for as long as they were gaining clinical benefit.

Retreatment: Patients in Treatment Arm 1 (T + D + SoC chemotherapy) with radiological progression who, in the investigator's opinion, continued to receive benefit from their assigned treatment and who met the criteria for retreatment in the setting of PD, could have retreatment with durvalumab + tremelimumab combination therapy (only once).

*Note: For patients randomized to Treatment Arm 3, treatment beyond progression and retreatment was not permitted.

Objectives

The study objectives and criteria for evaluation of study POSEIDON are presented in Table 13.

Table 13. Objectives and endpoints - POSEIDON

Objective	Endpoints/variables
Primary	
• To assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients	• PFS in all patients using BICR assessments according to RECIST 1.1 • OS in all patients
Secondary	
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS	• PFS in all patients using BICR assessments according to RECIST 1.1 (key secondary objective) • OS in all patients (key secondary objective)
• To further assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BOR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To further assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, DoR, BOR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BOR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS and ORR	• PFS and ORR in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high

Objective	Endpoints/variables
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the PK of durvalumab + tremelimumab combination therapy and durvalumab monotherapy	• Concentrations of durvalumab and tremelimumab
• To investigate the immunogenicity of durvalumab and tremelimumab	• Presence of ADAs for durvalumab and tremelimumab
• To assess disease-related symptoms and HRQoL in patients treated with durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone using the EORTC QLQ-C30 v3, the QLQ-LC13 module, and WHO/ECOG performance status assessments	• EORTC QLQ-C30 • EORTC QLQ-LC13 • Changes in WHO/ECOG performance status
Safety	
• To assess the safety and tolerability profile of durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone	• AEs, physical examinations, laboratory findings, and vital signs

Outcomes/endpoints

Efficacy endpoints in POSEIDON were defined as presented in Table 14.

Table 14. Definitions of efficacy endpoints in POSEIDON

Endpoint	Definition
OS	Time from the date of randomization until death due to any cause.
PFS [a]	Time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression.
ORR [a]	The percentage of patients with at least 1 visit response of complete response (CR) or partial response (PR).
DoR [a]	The time from the date of first documented response until the first date of documented progression or death in the absence of disease progression.
BOR [a]	The best response a patient has had following randomization, but prior to starting any subsequent cancer therapy and up to and including RECIST 1.1 progression or the last evaluable assessment in the absence of RECIST 1.1 progression, as determined by BICR.

Endpoint	Definition
AFP12 [a]	The Kaplan-Meier estimate of PFS at 12 months.
PFS2 [b]	The time from the date of randomization to the earliest of the progression event subsequent to that used for the endpoint PFS or death.
PROs (EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, PRO-CTCAE)	EORTC QLQ-C30 and EORTC QLQ-LC13: time to deterioration, symptom improvement rate, HRQoL/function improvement rate. EQ-5D-5L: weighted health state index. PRO-CTCAE: AEs of specific CTCAE symptoms.

[a] According to RECIST 1.1 as assessed using BICR assessments.
[b] Defined by local clinical practice.

Sample size

The study will enrol approximately 2000 patients to randomize approximately 1000 patients in a 1:1:1 ratio to durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone (approximately 333 patients in each treatment arm), including at least 250 patients in each treatment arm with PD-L1 TC <50%.

The study is sized for dual primary endpoints to characterize the PFS and OS benefits of durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone in the intent-to- treat (ITT) population.

Dual Primary Endpoints:

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone (PFS in ITT population): Assuming the true PFS HR is 0.67 and the median PFS in SoC chemotherapy alone arm is 6 months, 497 PFS events from the global cohort (75% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of 0.9% (with overall alpha for PFS 1%), allowing for 1 interim analysis conducted at approximately 80% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.79. Assuming a recruitment period of 16 months, this analysis is anticipated to be 25 months from FPI.

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone (OS in ITT population): Assuming the true OS HR is 0.7 and the median OS in SoC arm is 12.9 months, 532 OS events (80% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of a 3.3% (with overall alpha for OS 4%), allowing for 3 interim analyses conducted at approximately 45%, 61% and 84% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.83. Assuming a recruitment period of 16 months, this analysis is anticipated to be 46 months from FPI.

Key secondary Endpoints:

Durvalumab + tremelimumab combination therapy + SoC chemotherapy versus SoC chemotherapy alone (PFS in ITT population): Assuming the true PFS HR is 0.51 and the median PFS in SoC chemotherapy alone arm is 6 months, 465 PFS events from the global cohort (70% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of 0.9% (with overall alpha for PFS 1%), allowing for 1 interim analysis conducted at approximately 80% of the target events (information fraction). The smallest treatment difference that is statistically significant will be an HR of 0.78. Assuming a recruitment period of 16 months, this analysis is anticipated to be 25 months from FPI.

Durvalumab + tremelimumab combination therapy + SoC chemotherapy versus SoC chemotherapy alone (OS in ITT population): Assuming the true OS HR is 0.7 and the median OS in SoC arm is 12.9 months, 532 OS events (80% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of a 3.3% (with overall alpha for OS 4%), allowing for 3 interim analyses conducted at approximately 45%, 61% and 84% of the target events (information fraction). The smallest treatment difference that is statistically significant will be an HR of 0.83. Assuming a recruitment period of 16 months, this analysis is anticipated to be 46 months from FPI.

Randomisation

The randomization scheme was produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list was produced for each of the randomization stratum. A blocked randomization was generated, and all centers used the same list to minimize any imbalance in the number of patients assigned to each treatment arm. Patients were identified to the IVRS/IWRS per country regulations. Randomization codes were assigned strictly sequentially, within each stratum, as patients become eligible for randomization. Patients who fulfill all of the inclusion criteria and none of the exclusion criteria were randomized in a 1:1:1 ratio according to the following stratification scheme:

- PD-L1 tumour expression status (PD-L1 expression on at least 50% of tumour cells [PD-L1 TC ≥50%] versus PD-L1 TC <50%)
- Disease stage (Stage IVA versus Stage IVB)
- Histology (non-squamous versus squamous)

Blinding (masking)

The study is open label. A BICR of images will be performed. Results of these independent reviews will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator. The BICR of all radiological scans will be performed to derive the ORR, PFS, DoR, BoR, and APF12 endpoints according to RECIST 1.1. The BICR will include assessment by RECIST 1.1. The imaging scans will be reviewed by 2 independent radiologists and will be adjudicated, if required, by a third independent radiologist who will choose the assessments of 1 of the 2 primary reviewers.

This study will use an external Independent Data Monitoring Committee (IDMC) to assess ongoing safety analyses as well as the interim efficacy analysis.

Statistical methods

Full analysis set

The full analysis set (FAS) will include all randomized patients. Treatment arms were to be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment were included in the analysis in the treatment arm to which they were randomized.

Analysis of primary and secondary endpoints

Progression-free survival

The dual primary PFS analysis was to be based on the BICR tumour assessments according to RECIST 1.1. The full analysis set will be used. The analysis used a stratified log-rank test adjusting for PD-L1 tumour expression (PD-L1 ≥50% versus PD-L1 <50%), histology (squamous versus non-squamous), and disease stage (Stage IVA and Stage IVB) for generation of the p-value. The covariates in the statistical modelling were to be based on the values entered into interactive voice response system (IVRS) at randomization, even if it is subsequently discovered that these values were incorrect.

The hazard ratio (HR) and its CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron and PD-L1 tumour expression (PD-L1≥ 50% versus PD-L1 <50%), histology (squamous versus non-squamous), and disease stage (Stage IVA and Stage IVB) included in the STRATA statement) and the CI calculated using a profile likelihood approach.

Key secondary PFS analysis was to be performed using the same methodology as for the dual primary PFS analysis described above.

Kaplan-Meier plots of PFS were to be presented by treatment arm and PD-L1 tumour status and TMB subgroup, where appropriate. Summaries of the number and percentage of subjects experiencing a PFS event and the type of event (RECIST 1.1 or death) were to be provided along with median PFS for each treatment. The assumption of proportionality was to be assessed.

Censoring rules for PFS: Subjects who have not progressed or died at the time of analysis were to be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit). If the subject has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within two visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window), in which case the date of death is used when deriving PFS.

Sensitivity analyses: The following sensitivity analyses will be performed for the treatment comparisons of the dual primary and key secondary endpoints based on the FAS:

- A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analysed using a stratified log-rank test.
- Attrition bias will be assessed by repeating the dual primary/key secondary PFS analysis except that the actual PFS event times, rather than the censored times, of subjects who progressed or died in the absence of progression immediately following two or more non-evaluable tumour assessments will be included. In addition, and within the same sensitivity analysis, subjects who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.
- Ascertainment bias will be assessed by analysing the site investigator data. The stratified log-rank test will be repeated on the programmatically derived PFS using the site investigator data.
- An additional sensitivity analysis will be performed with the covariates used in the statistical model derived from eCRF data rather than using the values from IVRS.

Consistency of treatment effect between subgroups: Interactions between treatment and stratification factors will be tested to rule out any qualitative interaction using the approach of Gail and

Simon (Gail and Simon 1985). This test will be performed separately for the treatment comparisons of the dual primary and key secondary endpoints based on the FAS.

Overall survival

OS will be analysed using stratified log-rank tests, using the same methodology as described for the PFS endpoints.

The assumption of proportionality will be assessed in the same way as for PFS.

Censoring rules for OS: Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Sensitivity analysis and additional supportive summaries: A three-component stratified max-combo test will be used as a sensitivity analysis with the same stratification factors as the primary analysis.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias with regards to the treatment comparisons of the dual primary and key secondary endpoints, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

A sensitivity analysis may be conducted to assess for the potential impact of COVID-19 deaths on OS.

Exploratory analyses of OS adjusting for the impact of subsequent immunotherapy or other investigational treatment may be performed if a sufficient proportion of subjects switch.

Objective response rate

The ORR will be compared using logistic regression models adjusting for the same factors as the PFS endpoints. The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favor the experimental arms) together with its associated profile likelihood 95% CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

If there are not enough responses for a meaningful analysis using logistic regression then a Fisher's exact test using mid p-values will be presented.

Interim analysis

Interim analyses for efficacy will be performed by IDMC as described below: One interim analysis of PFS will be performed when approximately 80% of the target PFS events have occurred across Arms 2 and 3. Three interim analyses of OS will be performed; the first at the time of the interim PFS analysis (approximately 45% of the target OS events in Arms 2 and 3), the second at the time of the primary PFS analysis (approximately 61% of the target OS events in Arms 2 and 3) and the third when approximately 84% of the target OS events have occurred in Arms 2 and 3. The interim analyses will be performed for the analyses specified in MTP. It is expected that global recruitment will have completed prior to the results of the interim analyses being available.

The Lan DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including the one interim analysis for superiority. The boundaries for the treatment comparison will be derived based upon the exact number of events at the time of analyses.

Multiple testing procedures for controlling the type 1 error rate

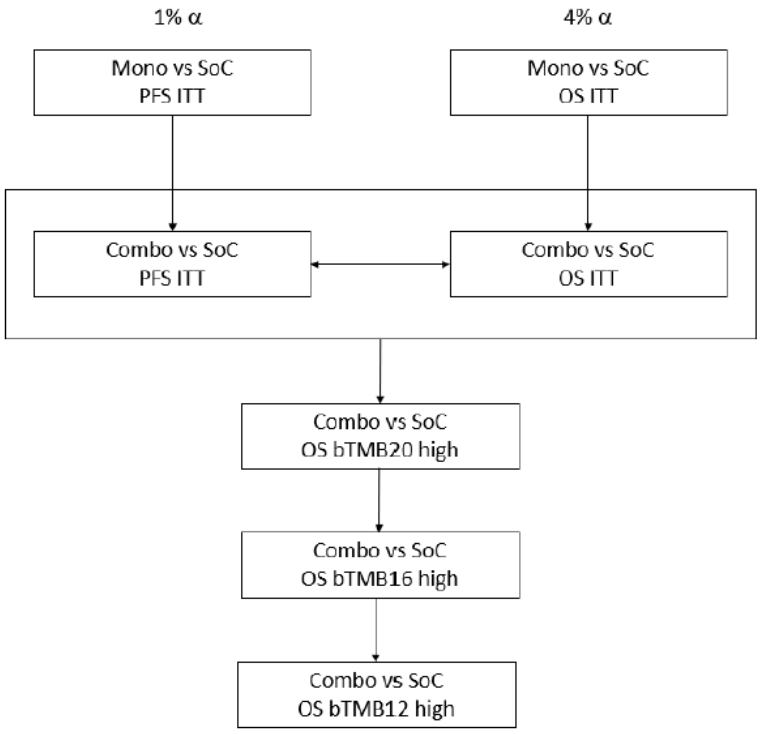
In order to strongly control the type I error at 5% (2-sided), a multiple testing procedure (MTP) with gatekeeping strategy will be used across the dual primary endpoints and the secondary endpoints included in MTP.

The dual primary endpoints: PFS and OS (durvalumab monotherapy +SoC chemotherapy versus SoC chemotherapy alone) in the ITT population (with PFS using BICR assessments per RECIST 1.1).

The key secondary endpoints: PFS and OS (durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone) in the ITT population (with PFS using BICR assessments per RECIST 1.1).

Hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order as outlined in Figure 6. According to alpha (test mass) splitting and alpha recycling, if the higher level hypothesis in the MTP is rejected for superiority, the next lower level hypothesis will then be tested. The test mass that becomes available after each rejected hypothesis is recycled to lower level hypotheses not yet rejected. This testing procedure stops when the entire test mass is allocated to non- rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all the dual primary endpoints and the secondary endpoints included in MTP.

Figure 14. Multiple testing procedures for controlling the type 1 error rate



Combo durvalumab + tremelimumab combination therapy + SoC chemotherapy; ITT Intent-to-treat; Mono durvalumab monotherapy + SoC chemotherapy; OS Overall survival; PFS Progression-free survival; SoC Standard of care; vs versus; bTMB20 high blood tumor mutational burden>=20 mut/Mb; bTMB16 high blood tumor mutational burden >=16 mut/Mb; bTMB12 high blood tumor mutational burden >=12 mut/Mb.

Amendment history

The following changes of analysis from protocol are based on CSP v4.0, dated 25-SEP-2018:

The SAP has been formulated to indicate that the following exploratory objective may not be produced, for the reason that the AZ imaging expert confirmed that AZ does not currently have the capacity of obtaining the data using irRECIST:

To explore irRECIST as an assessment methodology for clinical benefit of durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone with assessment by BICR has been changed to a potential.

The analysis of expected duration of response (EDoR) was not a required analysis, so not included for DoR endpoints in the SAP. This is consistent with other durvalumab studies.

The analysis of comparison of APF12 between treatment arms is removed to be consistent with other durvalumab studies.

Additional changes not included in SAP version 5.0

A post-hoc sensitivity analysis of ORR was added requiring confirmation of response no sooner than 4 weeks after the initial CR/PR was conducted.

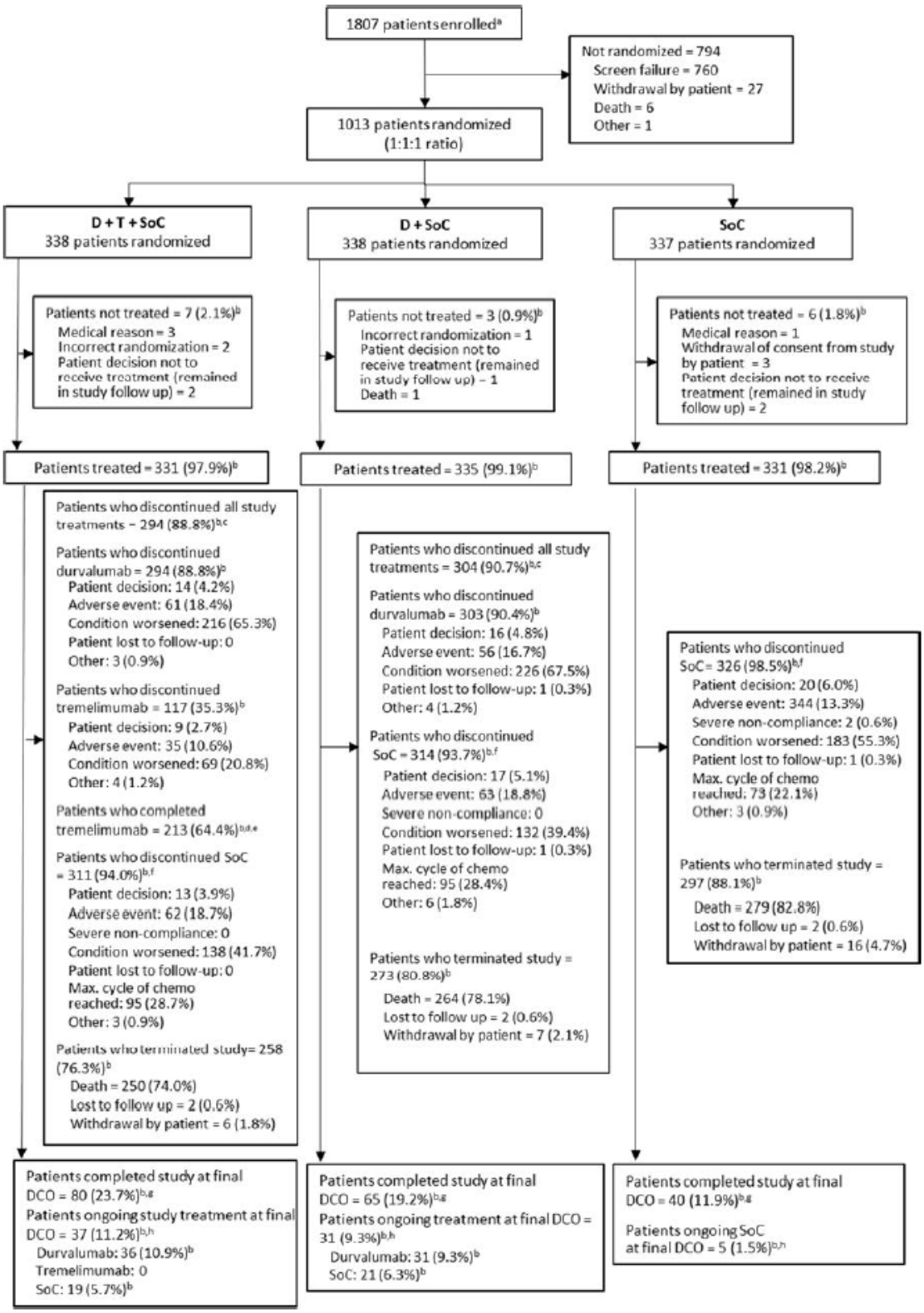
Symptom improvement rate was analysed using logistic regression, using Proc Logistic instead of Proc Genmod.

Results

Participant flow

A total of 1807 patients were screened into the POSEIDON study: of these, 1013 patients were randomized in a 1:1:1 ratio into one of the study arms (T + D + SoC, D + SoC or SoC alone arms) at 142 study centres across 18 countries in North and Latin America, Europe, Asia Pacific, and Africa. Patient disposition is summarised in the following figure.

Figure 15. Patient disposition - POSEIDON



Note: The category "condition worsened" corresponds to "disease progression".

A total of 760 patients failed screening. The majority of them did so because of eligibility criteria, particularly concerning EGFR/ALK status (36% of all screen failures), missing PD-L1 status (19%), or investigator judgement (8%).

The proportions of patients who discontinued any study treatment on account of adverse events are nearly identical in the experimental T+D+SoC and D+SoC arms (23% in each) and nearly double the proportion of discontinuations from the control SoC arm (13%).

Protocol deviations:

Table 15. Important protocol deviations - POSEIDON

Important protocol deviations[a]	Number (%) of patients			
	T+D+SoC (N=338)	D+SoC (N=338)	SoC (N=337)	Total (N=1013)
Number of patients with at least 1 important deviation	10 (3.0)	6 (1.8)	11 (3.3)	27 (2.7)
Baseline RECIST 1.1 scan >42 days before randomization	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
No baseline RECIST 1.1 assessment on or before date of randomization	0	0	1 (0.3)	1 (0.1)
Received prohibited concomitant systemic anti-cancer medications (including other anti-cancer agents)	0	0	1 (0.3)	1 (0.1)
Patient deviates from inclusion criteria 3, 4 or 5, or from exclusion criteria 5 as per the CSP	2 (0.6)	1 (0.3)	3 (0.9)	6 (0.6)
Patient randomized but who did not receive study treatment	7 (2.1)	3 (0.9)	6 (1.8)	16 (1.6)
Patient randomized who received treatment other than that to which they were randomized to	1 (0.3)	1 (0.3)	0	2 (0.2)
Number of patients with at least 1 COVID-19 related important protocol deviation	0	0	0	0

Important deviations are before the start of treatment and during treatment.

Note that the same patient may have had more than 1 important protocol deviation.

One patient was randomized to the T + D + SoC treatment arm and received SoC but no durvalumab and tremelimumab, and 1 patient was randomized to the D + SoC treatment arm and received SoC chemotherapy but no durvalumab.

One patient was randomized to the T + D + SoC treatment arm but did not receive SoC. This was not considered a protocol deviation (the patient was included in the T + D + SoC treatment arm).

Percentages are calculated from number of patients in the full analysis set in that treatment group.

CSP=clinical study protocol; D=durvalumab; N=number of patients in treatment arm; SoC=standard of care chemotherapy; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; T=tremelimumab.

Data cut-off date: 12MAR2021.

Recruitment

The first patient was screened on 01-JUN- 2017, and the first patient was randomized on 27-JUN-2017.

The last patient was randomised on 19-SEP-2018.

The median duration of survival follow-up (DCO 12-MAR-2021) in all patients across the 3 treatment arms was 12.52 months (range: 0.0 to 44.5). The median duration of follow up in all patients in the T + D + SoC arm was 13.63 months (range: 0.3 to 43.9), D + SoC was 12.73 months (range 0.0 to 44.5), and in the SoC alone arm was 11.17 months (range: 0.0 to 43.9).

Conduct of the study

Table 16. Protocol versions with dates

Global Document Name	Version No	Version Date
D419MC00004 Clinical Study Protocol	V1.0	10 Mar 2017
D419MC00004 Clinical Study Protocol	V2.0	12 Dec 2017
D419MC00004 Clinical Study Protocol	V3	16 Mar 2018
D419MC00004 Clinical Study Protocol	V4	25 Sep 2018
D419MC00004 Clinical Study Protocol	V5	20 Apr 2020

Table 17. Protocol amendments and other changes along study conduct - POSEIDON

Amendment number/ date	Key details of amendment	Main reason(s) for amendment
Original CSP (10 March 2017)		
Amendments 1 to 3 (after first patient randomized on 27 June 2017)		
Amendment 1 Protocol version 2.0 12 December 2017	A new inclusion criterion (8) regarding patient life expectancy was introduced.	To align with other clinical studies in lung cancer
	Modifications to inclusion criteria 2 regarding informed consent) and 11 (now 12) regarding laboratory values	Clarification
	Exclusion criterion 15 was divided into 2 criteria for spinal cord compression (now 15) and brain metastases (now 16) and further modifications added.	Clarification
	The maintenance schedule for pemetrexed was changed to Q3W or Q4W for Treatment Arm 3 (SoC), dependent on investigator decision and local standards.	To account for regional differences.
	Schedule of assessments for the treatment and retreatment periods was updated.	Clarification and to align with other changes to the CSP
	New text added to describe treatment after the final data cut-off	Clarification
	Modifications to text regarding which assessments should be done during retreatment.	Clarification
	It was clarified that one of the eligibility criteria for retreatment was having completed 5 dosing cycles comprising the combination of durvalumab and tremelimumab portion of the regimen.	To align to the treatment schedule.
	It was also clarified that a patient whose weight fell to 30 kg or below would receive weight-based dosing.	To be consistent with the rest of the treatment regimens in the protocol.
	PD-L1 TC<25% analysis set was removed from the objectives and relevant sections of the CSP.	It was initially included for potential analysis; however, no planned analysis was of interest at the time.
Amendment 2 Protocol version 3.0 16 March 2018	Sample size was increased from 801 to 1000 and OS final analysis maturity increased from 75% to 80%.	To adequately power OS of PD-L1<50% population.
	A new sub-section (Section 1.3.2.4: Standard of Care) was added to Section 1.3.2: Overall risks.	To address MHRA recommendation to include warnings of ototoxicity and nephrotoxicity for chemotherapy regimens as per the SmPCs.
	Section 3.8 (Restrictions) was updated as follows: • An additional note was added to instruct investigators to advise Male patients to consider cryoconservation of sperm prior to treatment because of the possibility of infertility due to gemcitabine therapy. • Contraception duration for SoC regimens was clarified.	MHRA recommendation
	A requirement of 20 unstained sections was added to Section 5.5.1 (Collection of patient samples for stratification by PD-L1)	In case a tissue block was not submitted for PD-L1 analysis.

Amendment number/ date	Key details of amendment	Main reason(s) for amendment
Amendment 3 Protocol version 4.0 25 September 2018	Primary and key secondary objectives and endpoints were updated as follows: • OS (D + SoC vs SoC) in the ITT population moved from secondary to dual primary objective. • PFS (T + D + SoC vs SoC) in the ITT population moved from dual primary to key secondary objective • OS (T + D + SoC vs SoC) in the ITT population added as key secondary objective. • OS and PFS in patients with PD-L1 TC <50% moved from key secondary to secondary endpoints The protocol was updated accordingly including power, critical values of HRs for PFS and OS analyses, projected number and percentage of PFS and OS events at interim/final analyses, projected alpha allocation at interim/final analyses and projected study duration.	• OS remains the 'gold standard' endpoint for immunotherapies; emerging data in immuno-oncology suggest that the treatment benefit of immunotherapies can more strongly manifest in OS compared to PFS (Borghaei et al 2015, Brahmer et al 2015, Fehrenbacher et al 2016). Furthermore, emerging data (KEYNOTE-189, KEYNOTE 407) indicated the importance of OS data of PD-1/PD-L1 in combination with chemotherapy (Gandhi et al [KEYNOTE-189] 2018;Paz-Ares et al 2018). • It became evident during the course of the study that PD-L1 expression alone did not appear to fully explain the OS benefit seen in patients treated with immunotherapies (Carbone et al 2017, Hui et al 2017).
	PD-L1 TC<25% analysis set (removed in Amendment 1, Protocol version 2.0) now reinstated for efficacy secondary endpoints.	To bring in line with PD-L1 TC<50% and TC<1%.
	Secondary objectives added to assess the association of TMB with the efficacy of D + SoC chemotherapy compared with SoC chemotherapy alone, T + D + SoC chemotherapy compared with SoC chemotherapy alone, and D + SoC chemotherapy compared with T + D + SoC chemotherapy.	Secondary endpoints added for TMB high patients in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2 for each treatment comparison. Data from multiple recent studies suggested that TMB may play an important role as a biomarker for patient selection.
	MTP was updated. One additional OS interim analysis was added at the timepoint of PFS interim analysis.	To reflect the updated primary/secondary endpoints.
Amendment 4 (after data cut-off for final analysis of PFS and RECIST-based endpoints [24 July 2019]) and prior to data cut-off for final analysis of OS and all other data [12 March 2021])		
Amendment 4 Protocol version 5.0 20 April 2020	Updated overall risks for durvalumab and tremelimumab therapy.	To align with latest durvalumab and tremelimumab IBs.
	Updated language based on the revised CSP template Appendix Hy's Law v3 to clarify how to identify and report case of potential Hy's law and Hy's Law cases.	To align with the latest version of how to identify and report cases of potential Hy's law per SOP.

A routine GCP inspection of study D419MC00004 (POSEIDON) was conducted at one investigational site in Germany (21-25 February 2022), the main CRO in the USA (11-17 March 2022), and the sponsor in Canada (21-25 March 2022). One critical finding was reported during the CRO inspection; major and minor findings were observed at all sites (see section 2.1.4).

Baseline data

Table 18. Baseline and patient characteristics, ITT - POSEIDON

	Number (%) of patients			
	T+D+SoC (N=338)	D+SoC (N=338)	SoC (N=337)	Total (N=1013)
Age (years)[a]				
n	338	338	337	1013
Mean (SD)	62.6 (9.43)	63.5 (9.10)	63.1 (9.87)	63.1 (9.47)
Median (range)	63.0 (27-87)	64.5 (32-87)	64.0 (32-84)	64.0 (27-87)
Age group (years) n (%)[a]				
≥18 - <50	29 (8.6)	27 (8.0)	30 (8.9)	86 (8.5)
≥50 - <65	162 (47.9)	142 (42.0)	146 (43.3)	450 (44.4)
≥65 - <75	112 (33.1)	130 (38.5)	121 (35.9)	363 (35.8)
≥75	35 (10.4)	39 (11.5)	40 (11.9)	114 (11.3)
Sex n (%)				
Male	269 (79.6)	253 (74.9)	248 (73.6)	770 (76.0)
Female	69 (20.4)	85 (25.1)	89 (26.4)	243 (24.0)
Race n (%)				
White	205 (60.7)	182 (53.8)	179 (53.1)	566 (55.9)
Black or African American	8 (2.4)	4 (1.2)	8 (2.4)	20 (2.0)
Asian	99 (29.3)	123 (36.4)	128 (38.0)	350 (34.6)
Native Hawaiian or other Pacific Islander	2 (0.6)	0	0	2 (0.2)
American Indian or Alaska Native	12 (3.6)	17 (5.0)	9 (2.7)	38 (3.8)
Other	12 (3.6)	12 (3.6)	13 (3.9)	37 (3.7)
Ethnic group n (%)				
Hispanic or Latino	51 (15.1)	54 (16.0)	55 (16.3)	160 (15.8)
Not Hispanic or Latino	287 (84.9)	284 (84.0)	282 (83.7)	853 (84.2)
Body Mass Index group (kg/m^2) n (%)				
n	335	338	335	1008
Underweight (<18.5)	21 (6.3)	23 (6.8)	29 (8.7)	73 (7.2)
Normal (18.5-25)	184 (54.9)	187 (55.3)	181 (54.0)	552 (54.8)
Overweight (25-30)	93 (27.8)	96 (28.4)	91 (27.2)	280 (27.8)
Obese (>30)	37 (11.0)	32 (9.5)	34 (10.1)	103 (10.2)
Missing	3	0	2	5
Smoking status n (%)				
Never	59 (17.5)	84 (24.9)	79 (23.4)	222 (21.9)
Current	84 (24.9)	64 (18.9)	66 (19.6)	214 (21.1)
Former	195 (57.7)	190 (56.2)	191 (56.7)	576 (56.9)
Missing	0	0	1 (0.3)	1 (0.1)

[a] Age at randomization.

Percentages are calculated from number of patients in the full analysis set in that treatment group.

Table 19. Patient Recruitment by Region (Full Analysis Set)

	Number (%) of patients			
Region	T + D + SoC (N = 338)	D + SoC (N = 338)	SoC (N = 337)	Total (N = 1013)
Europe	151 (44.7)	129 (38.2)	123 (36.5)	403 (39.8)
Asia	96 (28.4)	120 (35.5)	124 (36.8)	340 (33.6)
North America	44 (13.0)	46 (13.6)	40 (11.9)	130 (12.8)
South America	34 (10.1)	32 (9.5)	41 (12.2)	107 (10.6)
Africa	13 (3.8)	11 (3.3)	9 (2.7)	33 (3.3)

Table 20. Disease characteristics at screening, ITT - POSEIDON

	Number (%) of patients			
	T+D+SoC (N=338)	D+SoC (N=338)	SoC (N=337)	Total (N=1013)
ECOG performance status[a]				
Normal activity (0)	110 (32.5)	109 (32.2)	119 (35.3)	338 (33.4)
Restricted activity (1)	228 (67.5)	229 (67.8)	217 (64.4)	674 (66.5)
Missing	0	0	1 (0.3)	1 (0.1)
AJCC Staging				
IIIA	1 (0.3)	0	0	1 (0.1)
IIIB	1 (0.3)	1 (0.3)	0	2 (0.2)
IVA	171 (50.6)	170 (50.3)	166 (49.3)	507 (50.0)
IVB	165 (48.8)	167 (49.4)	170 (50.4)	502 (49.6)
Missing	0	0	1 (0.3)	1 (0.1)
Histology type				
Squamous	124 (36.7)	128 (37.9)	122 (36.2)	374 (36.9)
Squamous cell carcinoma	124 (36.7)	127 (37.6)	122 (36.2)	373 (36.8)
Other	0	1 (0.3)	0	1 (0.1)
Non-Squamous	214 (63.3)	209 (61.8)	214 (63.5)	637 (62.9)
Adenocarcinoma	208 (61.5)	203 (60.1)	211 (62.6)	622 (61.4)
Large cell carcinoma	2 (0.6)	5 (1.5)	3 (0.9)	10 (1.0)
Other	4 (1.2)	1 (0.3)	0	5 (0.5)
Other	0	1 (0.3)	0	1 (0.1)
Missing	0	0	1 (0.3)	1 (0.1)
Overall disease classification				
Metastatic[b]	337 (99.7)	336 (99.4)	336 (99.7)	1009 (99.6)
Locally advanced[c]	0	2 (0.6)	0	2 (0.2)
Missing	1 (0.3)	0	1 (0.3)	2 (0.2)
PD-L1 status[d]				

TC <50%	237 (70.1)	243 (71.9)	240 (71.2)	720 (71.1)
TC ≥50%	101 (29.9)	94 (27.8)	97 (28.8)	292 (28.8)
Missing	0	1 (0.3)	0	1 (0.1)

[a] ECOG performance status at baseline, where baseline is defined as the last evaluable assessment prior to randomization.

[b] Metastatic disease – patient has any metastatic site of disease.

[c] Locally advanced – patient has only locally advanced sites of disease.

[d] Stratification factor recorded on eCRF. PD-L1 tumor expression status is summarized based on laboratory data outside of the eCRF.

Table 21. Distribution of patients according to PD-L1 status by SP263 assay

	Number of patients			
	Durva + Treme + SoC	Durva + SoC	SoC	Total
Patients randomized	338	338	337	1013
Patients included in full analysis set [a]	338	338	337	1013
Patients included in PD-L1 TC<50% analysis set [b]	237	243	240	720
Patients excluded from PD-L1 TC<50% analysis set	101	95	97	293
PD-L1 status PD-L1 TC >=50%	101	94	97	292
No PD-L1 status	0	1	0	1
Patients included in PD-L1 TC<25% analysis set [c]	220	221	220	661
Patients excluded from PD-L1 TC<25% analysis set	118	117	117	352
PD-L1 status PD-L1 TC >=25%	118	116	117	351
No PD-L1 status	0	1	0	1
Patients included in PD-L1 TC<1% analysis set [d]	125	119	130	368
Patients excluded from PD-L1 TC<1% analysis set	213	225	207	645
PD-L1 status PD-L1 TC >=1%	213	224	207	644
No PD-L1 status	0	1	0	1

Table 22. Prior anticancer therapy, ITT - POSEIDON

	Number (%) of patients			
Previous treatment modalities	**T+D+SoC (N=338)**	**D+SoC (N=338)**	**SoC (N=337)**	**Total (N=1013)**
Cytotoxic chemotherapy	13 (3.8)	11 (3.3)	14 (4.2)	38 (3.8)
Adjuvant	10 (3.0)	7 (2.1)	8 (2.4)	25 (2.5)
Neo-adjuvant	2 (0.6)	1 (0.3)	0	3 (0.3)
Definitive	1 (0.3)	2 (0.6)	7 (2.1)	10 (1.0)
Missing	1 (0.3)	1 (0.3)	0	2 (0.2)
Radiotherapy	50 (14.8)	43 (12.7)	52 (15.4)	145 (14.3)
Adjuvant	8 (2.4)	6 (1.8)	2 (0.6)	16 (1.6)
Neo-adjuvant	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)
Palliative	34 (10.1)	32 (9.5)	42 (12.5)	108 (10.7)
Definitive	9 (2.7)	2 (0.6)	7 (2.1)	18 (1.8)
Not applicable	0	1 (0.3)	0	1 (0.1)

Numbers analysed

Table 23. Analysis sets - POSEIDON

	Number of patients			
	T+D+SoC	D+SoC	SoC	Total
Patients randomized	338	338	337	1013
Patients included in the full analysis set	338	338	337	1013
Patients included in the PD-L1 TC<50% analysis set	237	243	240	720
Patients included in the PD-L1 TC<25% analysis set	220	221	220	661
Patients included in the PD-L1 TC<1% analysis set	125	113	130	368
Patients with no PD-L1 status	0	1	0	1
Patients included in the bTMB20 high analysis set	75	77	75	227
Patients included in the bTMB16 high analysis set	108	94	102	304
Patients included in the bTMB12 high analysis set	152	137	140	429
Patients with no bTMB status	61	72	96	229
Patients included in the safety analysis set	330	334	333	997
Patients excluded from the safety analysis set (did not receive study treatment)	7	3	6	16
Patients included in the PK analysis set[a]	327	330	9	666
Patients excluded from the PK analysis set[b]	11	8	328	347
No post-dose data available	4	5	322	331

[a] Nine patients in the SoC alone arm were included in the PK analysis set due to PK samples taken in error, however, these patients were not included in the PK analyses.

[b] Patients could have been excluded for more than 1 reason.

Table 24. Analysis Sets (Full Analysis Set)

	Number (%) of Patients			
	T + D + SoC (N = 338)	D + SoC (N = 338)	SoC (N = 337)	Total (N = 1013)
Patients with measurable disease at baseline per BICR	335 (99.1)	330 (97.6)	332 (98.5)	997 (98.4)
Patients without measurable disease at baseline per BICR	3 (0.9)	8 (2.4)	5 (1.5)	16 (1.6)

Outcomes and estimation

The CSR reported the final analysis for the study, based on the DCO dates of 24-JUL-2019 (RECIST-related endpoints) and 12-MAR-2021 (all other data).

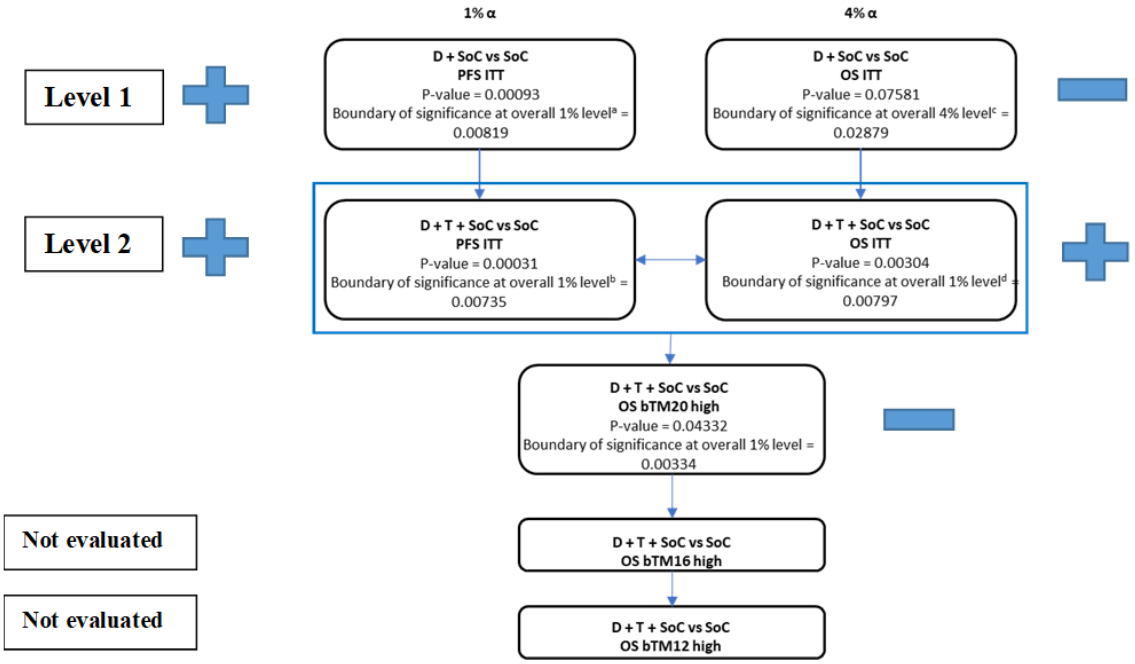
At the time of the PFS analysis DCO date (24-JUL-2019), the PFS data had reached 75.7% maturity (511 PFS events from 675 patients in the D + SoC and SoC alone arms).

At the time of the OS analysis DCO (12-MAR-2021), the OS data had reached 81.3% maturity (549 OS events from 675 patients in the D + SoC and SoC alone arms).

Outcomes of the multiple testing procedure (MTP) - POSEIDON:

The primary OS endpoint (D+SoC vs SoC) in study POSEIDON did not meet statistical significance. However, the other primary PFS endpoint that compared the same arms showed statistical superiority and thus alpha was propagated to the next testing level, in which OS and PFS were evaluated as key secondary endpoints in the T+D+SoC vs. SoC arms.

Table 25. Outcomes of the multiple testing procedure (MTP) – POSEIDON



Based on a Lan and DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.

Key secondary endpoint: Overall survival

Table 26. Overall survival in the ITT, DCO 12-MAR-2021

	Number (%) of patients		
	T + D + SoC (N = 338)	**D + SoC (N=338)**	**SoC (N = 337)**
HR [a,b], T+D+SoC vs SoC	0.77	0.86	
95% CI for HR	0.650, 0.916	0.724, 1.016	
2-sided p-value [c]	0.00304	0.07581	
Death, n (%)	251 (74.3)	264 (78.1)	285 (84.6)
Censored patients, n (%)	87 (25.7)	74 (21.9)	52 (15.4)
Still in survival follow-up [d]	80 (23.7)	65 (19.2)	40 (11.9)
Terminated prior to death [e]	7 (2.1)	9 (2.7)	12 (3.6)
Lost to follow-up	2 (0.6)	2 (0.6)	2 (0.6)
Withdrawn consent	5 (1.5)	6 (1.8)	10 (3.0)
Other	0	1 (0.3)	0
Median OS (months) [f] (95% CI) [h]	14.0 (11.7, 16.1)	13.1 (11.4, 14.7)	11.7 (10.5, 13.1)
OS rate at 12 months (%) [f] (95% CI) [h]	54.8 (49.3, 60.0)	53.2 (47.7, 58.4)	49.1 (43.6, 54.4)
OS rate at 18 months (%) [f] (95% CI) [h]	41.3 (36.0, 46.5)	38.1 (32.9, 49.3)	34.1 (29.0, 39.2)
OS rate at 24 months (%) [f] (95% CI) [h]	32.9 (27.9, 37.9)	29.6 (24.8, 34.6)	22.1 (17.8, 26.8)
OS rate at 36 months (%) [f] (95% CI) [h]	25.3 (20.8, 30.2)	20.3 (16.1, 25.0)	13.3 (9.8, 17.4)

[a] The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.

[b] A HR <1 favors T + D + SoC chemotherapy to be associated with a longer OS than SoC chemotherapy alone.

[c] P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.

[d] Includes patients known to be alive at data cutoff.

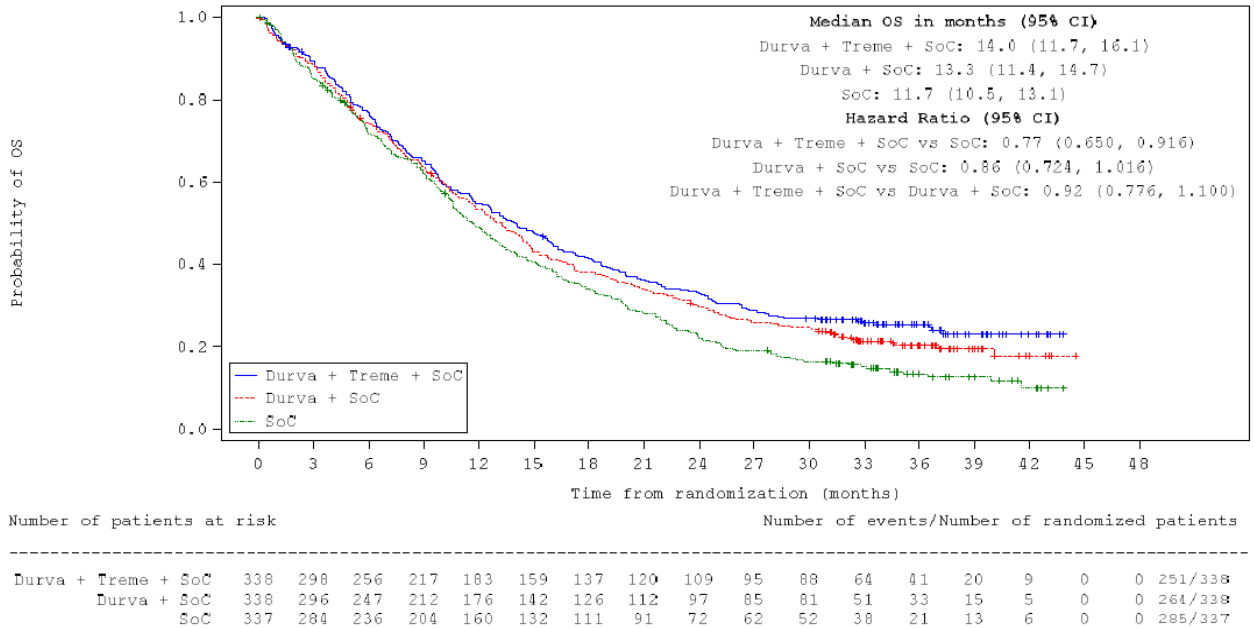
[e] Includes patients with unknown survival status or patients who were lost to follow-up.

[f] Calculated using Kaplan-Meier technique.

Patients not known to have died at the time of analysis were censored based on the last recorded date on which the patient was known to be alive.

There was 1 patient who died 1 day prior to randomization and was censored at Day 1.

Figure 16. Overall survival in the ITT, Kaplan-Meier curve, DCO 12-MAR-2021



Key secondary endpoint: Progression-free survival by BICR

Table 27. PFS by BICR in the ITT, DCO 24-JUL-2019

	Number (%) of patients		
	T + D + SoC (N = 338)	**D + SoC (N = 338)**	**SoC (N = 337)**
HR [a,b] vs T+D+SoC vs SoC	0.72	0.74	
95% CI [a]	0.600, 0.860	0.620, 0.885	
2-sided p-value [c]	0.00031	0.00093	
Total number of events, n (%) [d]	238 (70.4)	253 (74.9)	258 (76.6)
RECIST 1.1 progression	174 (51.5)	193 (57.1)	202 (59.9)
Death in the absence of progression	64 (18.9)	60 (17.8)	56 (16.6)
Censored patients, n (%)	100 (29.6)	85 (25.1)	79 (23.4)
Censored RECIST progression [e]	0	0	2 (0.6)
Censored death [f]	11 (3.3)	8 (2.4)	24 (7.1)
Progression-free at time of analysis	83 (24.6)	72 (21.3)	43 (12.8)
Lost to follow-up	0	0	0
Withdrawn consent	4 (1.2)	3 (0.9)	9 (2.7)
Discontinued study	2 (0.6)	2 (0.6)	1 (0.3)
Median progression-free survival (months) [g] (95% CI) [g]	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 5.8)
Progression-free survival rate at 12 months (%) [g] (95% CI) [g]	26.6 (21.7, 31.7)	24.4 (19.7, 29.5)	13.1 (9.3, 17.6)

[g] The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.

[h] A HR <1 favors T + D + SoC chemotherapy to be associated with a longer PFS than SoC chemotherapy alone.

[i] P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.

[j] Patients who had not progressed or died, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment or at Day 1 if there were no evaluable visits or no baseline data and patient did not die within 2 visits of baseline.

[k] RECIST progression event occurred after 2 or more missed visits or within 2 visits of baseline without any evaluable visits or baseline data.

[l] Death occurred after 2 or more missed visits in the absence of progression.

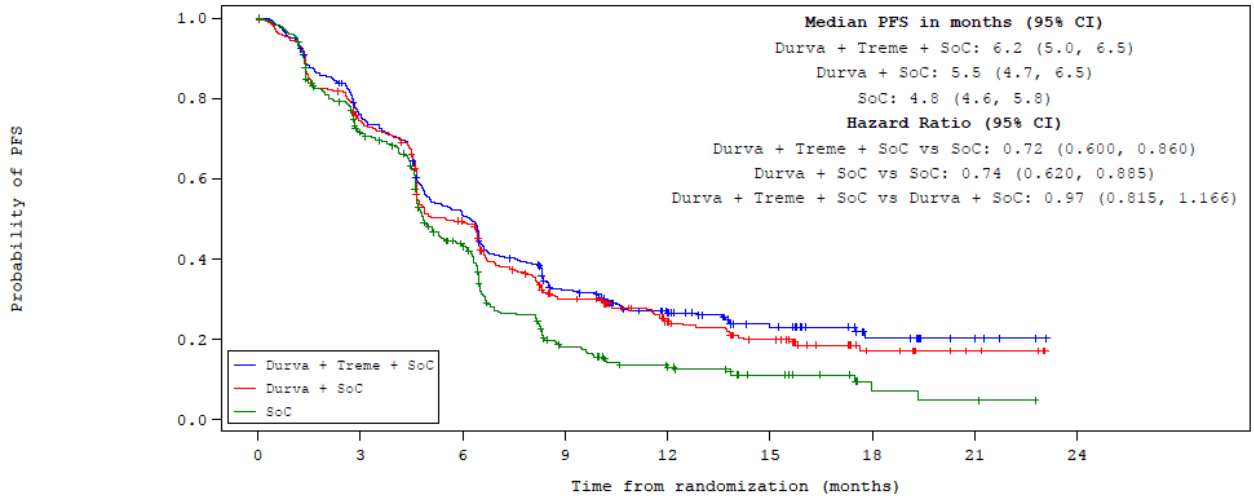
[m] Calculated using the Kaplan-Meier technique.

RECIST version 1.1 based on BICR assessment.

There was 1 patient who died 1 day prior to randomization and was censored at Day 1.

Median duration of PFS follow-up in all patients was 5.39 months in the T+D+SoC arm, 4.86 months in the D+ SoC arm and 4.63 months in the SoC arm.

Figure 17. PFS by BICR in the ITT, Kaplan-Meier curve, DCO 24-JUL-2019



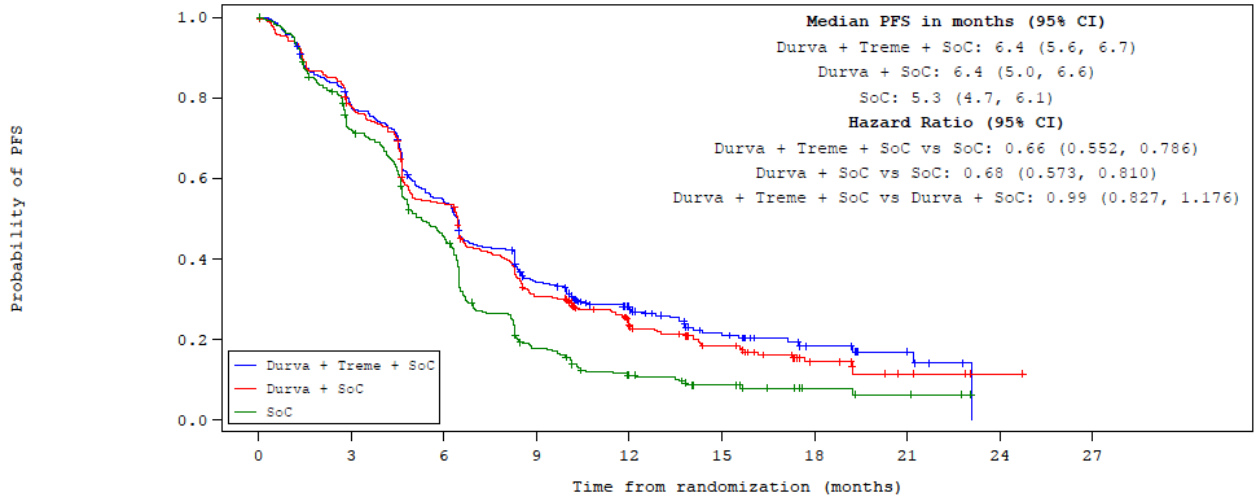
Number of patients at risk										Number of events/Number of randomized patients
Durva + Treme + SoC	338	243	161	94	56	32	13	5	0	238/338
Durva + SoC	338	246	158	88	53	35	11	4	0	253/338
SoC	337	219	121	43	23	12	3	2	0	258/337

Secondary endpoint: Progression free survival by investigator

Table 28. PFS by investigator in the ITT, DCO 24-JUL-2019

	Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)
Total events [a], n (%)	247 (73.1)	265 (78.4)	284 (84.3)
RECIST progression	190 (56.2)	200 (59.2)	221 (65.6)
Target Lesions [b]	98 (29.0)	101 (29.9)	117 (34.7)
Non Target Lesions [b]	67 (19.8)	53 (15.7)	78 (23.1)
New Lesions [b]	114 (33.7)	109 (32.2)	118 (35.0)
Death in the absence of progression	57 (16.9)	65 (19.2)	63 (18.7)
Censored patients, n (%)	91 (26.9)	73 (21.6)	53 (15.7)
Censored RECIST progression [c]	1 (0.3)	0	2 (0.6)
Censored death [d]	8 (2.4)	4 (1.2)	10 (3.0)
Progression-free at time of analysis	76 (22.5)	65 (19.2)	32 (9.5)
Lost to follow-up	0	0	0
Withdrawn consent	4 (1.2)	2 (0.6)	8 (2.4)
Discontinued study	2 (0.6)	2 (0.6)	1 (0.3)
Median progression-free survival (months) [e]	6.4	6.4	5.3
95% CI for median progression-free survival [e]	5.6, 6.7	5.0, 6.6	4.7, 6.1
Progression-free survival rate at 12 months (%) [e]	28.2	23.5	11.2
95% CI for progression-free survival rate at 12 months [e]	23.3, 33.3	18.9, 28.4	7.9, 15.1
Hazard ratio, Durva + Treme + SoC vs SoC [f]	0.66		
95% CI for hazard ratio	0.552, 0.786		
2-sided p-value [g]	<0.001		
Hazard ratio, Durva + SoC vs SoC [f]		0.68	
95% CI for hazard ratio		0.573, 0.810	
2-sided p-value [g]		<0.001	
Hazard ratio, Durva + Treme + SoC vs Durva + SoC [f]	0.99		
95% CI for hazard ratio	0.827, 1.176		
2-sided p-value [g]	0.885		

Figure 18. PFS by investigator in the ITT, Kaplan-Meier curve, DCO 24-JUL-2019



Number of patients at risk — Number of events/Number of randomized patients

Durva + Treme + SoC	338	251	172	104	64	33	14	6	0	0	247/338
Durva + SoC	338	258	174	97	57	36	14	5	1	0	265/338
SoC	337	229	141	53	24	14	5	3	0	0	284/337

Table 29. Disagreements between investigator and BIRC in the ITT, DCO 24-JUL-2019

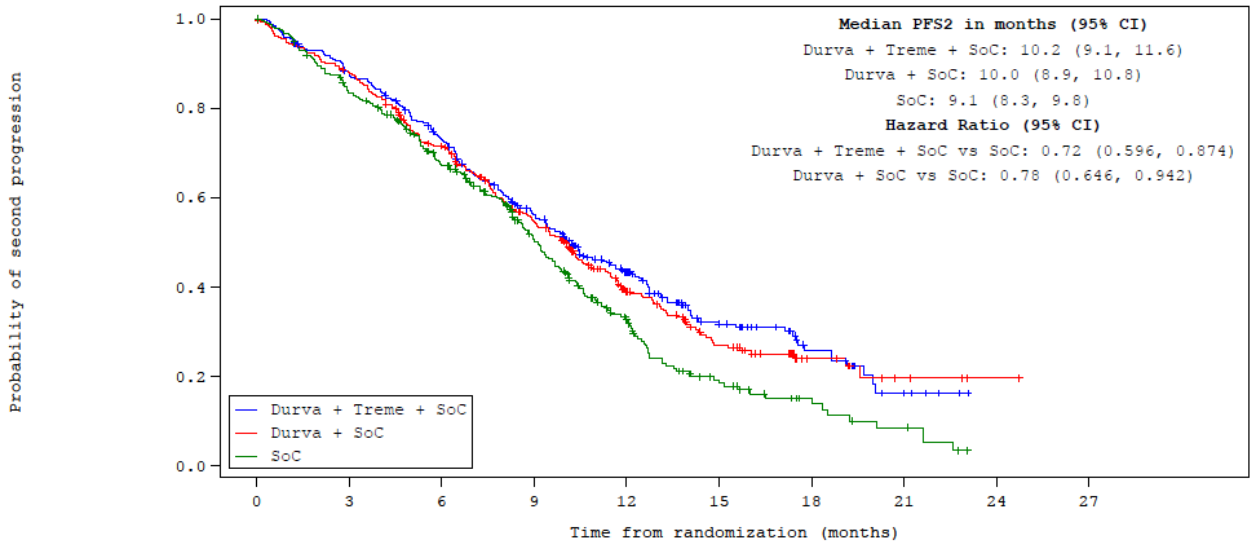
				Difference	
Progression	Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)	Durva + Treme + SoC vs SoC	Durva + SoC vs SoC
RECIST progression [a] declared by, n (%)					
Investigator and central review	151 (44.7)	169 (50.0)	179 (53.1)	NA	NA
Progression date agreement (within 2 weeks)	75 (22.2)	84 (24.9)	101 (30.0)	NA	NA
Progression date >= 2 weeks earlier by central review than by Investigator	58 (17.2)	67 (19.8)	60 (17.8)	NA	NA
Progression date >= 2 weeks earlier by Investigator than by central review	18 (5.3)	18 (5.3)	18 (5.3)	NA	NA
Investigator but not central review	40 (11.8)	31 (9.2)	44 (13.1)	NA	NA
Central review but not Investigator	23 (6.8)	24 (7.1)	25 (7.4)	NA	NA
No Progression by both, n (%)	124 (36.7)	114 (33.7)	89 (26.4)	NA	NA
Early Discrepancy Rate [b]	0.30	0.25	0.28	0.03	-0.03
Late Discrepancy Rate [c]	0.58	0.65	0.58	0.00	0.07

Secondary endpoint: PFS2 analysis (time to second progression)

Table 30. Time to second progression (by local clinical practice) in the ITT, DCO 24-JUL-2019

	Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)
Total events [a], n (%)	209 (61.8)	217 (64.2)	232 (68.8)
Second progression	65 (19.2)	70 (20.7)	88 (26.1)
Symptomatic progression	4 (1.2)	10 (3.0)	7 (2.1)
Objective radiological progression	61 (18.0)	59 (17.5)	81 (24.0)
Other	0	1 (0.3)	0
Death in the absence of second progression	144 (42.6)	147 (43.5)	144 (42.7)
Censored patients, n (%)	129 (38.2)	121 (35.8)	105 (31.2)
No second progression	123 (36.4)	117 (34.6)	96 (28.5)
Lost to follow-up	0	0	0
Withdrawn consent	4 (1.2)	2 (0.6)	8 (2.4)
Discontinued study [b]	2 (0.6)	2 (0.6)	1 (0.3)
Median time to second progression (months) [c]	10.2	10.0	9.1
95% CI for median time to second progression [c]	9.1, 11.6	8.9, 10.8	8.3, 9.8
Hazard ratio, Durva + Treme + SoC vs SoC [d]	0.72		
95% CI for hazard ratio	0.596, 0.874		
2-sided p-value [e]	<0.001		
Hazard ratio, Durva + SoC vs SoC [d]		0.78	
95% CI for hazard ratio		0.646, 0.942	
2-sided p-value [e]		0.010	

Figure 19. Time to second progression (by local clinical practice) in the ITT, Kaplan-Meier curve, DCO 24-JUL-2019



Number of patients at risk — Number of events/Number of randomized patients

Durva + Treme + SoC	338	287	232	166	96	49	22	6	0	0	209/338
Durva + SoC	338	292	229	165	85	47	16	5	1	0	217/338
SoC	337	271	207	134	63	26	12	6	0	0	232/337

Table 31. Subsequent anticancer therapy regimens in the ITT, DCO 12-MAR-2021

Anticancer therapy regimen[a]	Number (%) of patients			
	T+D+SoC (N=338)	D+SoC (N=338)	SoC (N=337)	Total (N=1013)
Number of patients with post-discontinuation anticancer therapy	138 (40.8)	150 (44.4)	203 (60.2)	491 (48.5)
Regimen category				
Systemic therapy	123 (36.4)	139 (41.1)	194 (57.6)	456 (45.0)
Cytotoxic chemotherapy	107 (31.7)	128 (37.9)	122 (36.2)	357 (35.2)
Single agent	76 (22.5)	95 (28.1)	87 (25.8)	258 (25.5)
Platinum doublet	37 (10.9)	31 (9.2)	24 (7.1)	92 (9.1)
Other combination	16 (4.7)	28 (8.3)	28 (8.3)	72 (7.1)
Immunotherapy	22 (6.5)	22 (6.5)	112 (33.2)	156 (15.4)
IO only	17 (5.0)	20 (5.9)	97 (28.8)	134 (13.2)
IO + chemo	1 (0.3)	0	9 (2.7)	10 (1.0)
IO + other	4 (1.2)	3 (0.9)	6 (1.8)	13 (1.3)
Targeted therapy	14 (4.1)	13 (3.8)	19 (5.6)	46 (4.5)
Other	4 (1.2)	2 (0.6)	6 (1.8)	12 (1.2)
Radiotherapy	48 (14.2)	57 (16.9)	65 (19.3)	170 (16.8)

[a] Therapies post discontinuation of study treatment.

1st subsequent therapy includes 2nd line therapy plus maintenance, 2nd subsequent therapy includes 3rd line therapy and ≥3rd subsequent therapy includes >3rd line therapies. Regimen categories manually identified from preferred terms combined by regimen number. Patients with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of patients in the full analysis set in that treatment arm. Data for 2 patients was not available. One patient received subsequent letrozole for breast cancer treatment.

Secondary endpoints: response rate and Duration of response

Table 32. ORR and DOR by BICR in patients with measurable disease at baseline, Durva + treme + chemo vs chemo, DCO 24-JUL-2019

	RECIST 1.1			
	Unconfirmed responses		Confirmed responses only	
	T + D + SoC (N = 335)	SoC (N = 332)	T + D + SoC (N = 335)	SoC (N = 332)
ORR				
ORR, n (%)	155 (46.3)	111 (33.4)	130 (38.8)	81 (24.4)
Odds ratio [a], T+D+SoC vs SoC	1.72		2.00	
95% CI for odds ratio	1.260, 2.367		1.428, 2.807	
2-sided p-value	<0.001		<0.001	
Best overall response, n (%)				
Complete response [b]	2 (0.6)	0	2 (0.6)	0
Partial response [b]	153 (45.7)	111 (33.4)	128 (38.2)	81 (24.4)
Stable disease ≥6 weeks [c]	120 (35.8)	150 (45.2)	120 (35.8)	150 (45.2)
Disease progression	48 (14.3)	61 (18.4)	48 (14.3)	61 (18.4)
Not evaluable	12 (3.6)	10 (3.0)	12 (3.6)	10 (3.0)
Duration of response				
Number of responders who subsequently progressed/died	87	84	65	60
DoR from onset of response (months)				
Median (25th, 75th percentiles) [d,e]	7.4 (3.5, NR)	4.2 (3.0, 6.9)	9.5 (5.0, NR)	5.1 (3.7, 7.5)
Percentage remaining in response [e]				
6 months	57.2	31.0	67.0	40.4
12 months	42.5	16.4	49.7	21.4
18 months	34.7	NR	40.7	NR

[n] An odds ratio >1 favors T + D + SoC compared to SoC chemotherapy alone.

[o] Response does not require confirmation.

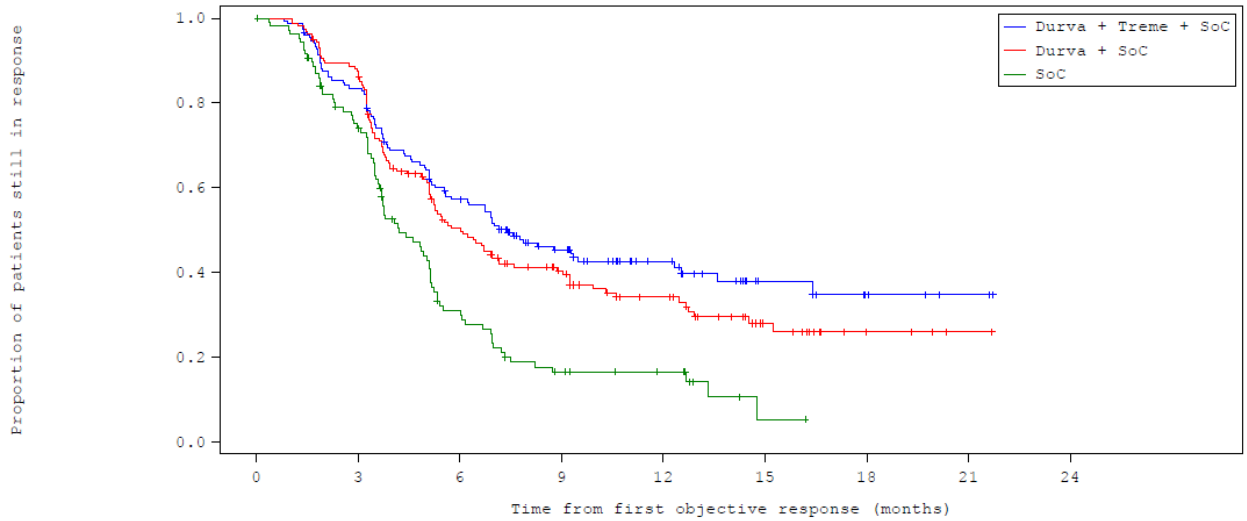
[p] In practice, considering '5 weeks' as threshold to allow for the 1-week permitted time-window.

[q] DoR is the time from the first documentation of complete response or partial response until the date of progression, death in absence of progression, or the last evaluable RECIST assessment for patients who progress or die after 2 or more missed visits.

[r] Calculated using the Kaplan-Meier technique.

The analysis was performed using logistic regression adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB), with the CI calculated using a profile likelihood approach and the p-value calculated based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model.
There was 1 patient who died 1 day prior to randomization and was censored at Day 1.

Figure 20. K-M plot of DOR by BICR in unconfirmed responders, DCO 24-JUL-2019



Number of patients at risk										Number of events/Number of patients with objective response
Durva + Treme + SoC	155	126	82	52	33	12	7	2	0	87/155
Durva + SoC	160	139	73	48	32	14	4	1	0	104/160
SoC	111	74	28	13	9	1	0	0	0	84/111

Secondary endpoints: Patient reported outcomes (PROs)

Overall compliance rates for EORTC QLQ-C30 and EORTC QLQ-L13 were 73.0% and 72.8% in the Durva + treme + chemo arm and 65.0% and 64.8% in the chemo arm.

Table 33: Baseline global health status, DCO 12-MAR-2021

Table 14.2.8.1
EORTC QLQ-C30 and QLQ-LC13 scales and items, absolute values, change from baseline and categories of change
Full analysis set

EORTC scale /item	Time point		Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)
QLQ-C30 Global Health Status / QoL	Baseline	Summary statistics			
		n	325	326	321
		Mean (SD)	59.21 (19.612)	59.07 (19.959)	59.74 (19.111)
		Median	58.33	58.33	58.33
		Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0

Table 34: Baseline physical functioning, DCO 12-MAR-2021

Table 14.2.8.1
EORTC QLQ-C30 and QLQ-LC13 scales and items, absolute values, change from baseline and categories of change
Full analysis set

EORTC scale /item	Time point		Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)
QLQ-C30 Physical Functioning	Baseline	Summary statistics			
		n	325	326	321
		Mean (SD)	75.69 (20.748)	75.60 (21.131)	75.22 (21.171)
		Median	80.00	80.00	80.00
		Min, Max	0.0, 100.0	0.0, 100.0	6.7, 100.0

Figure 21: Forest plot of time-to-deterioration (TTD) in EORTC QLQ-C30 and QLQ-L13 in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021

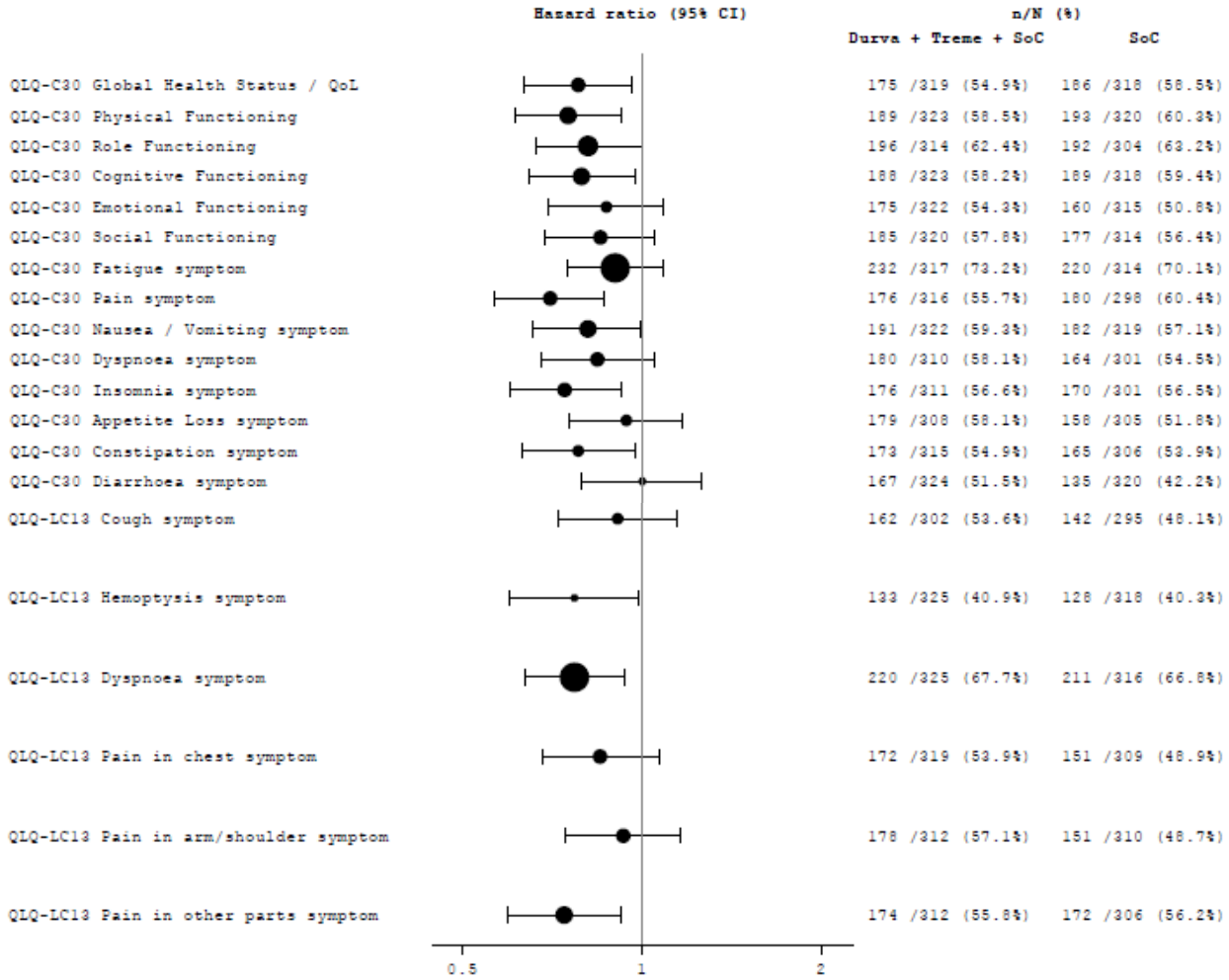
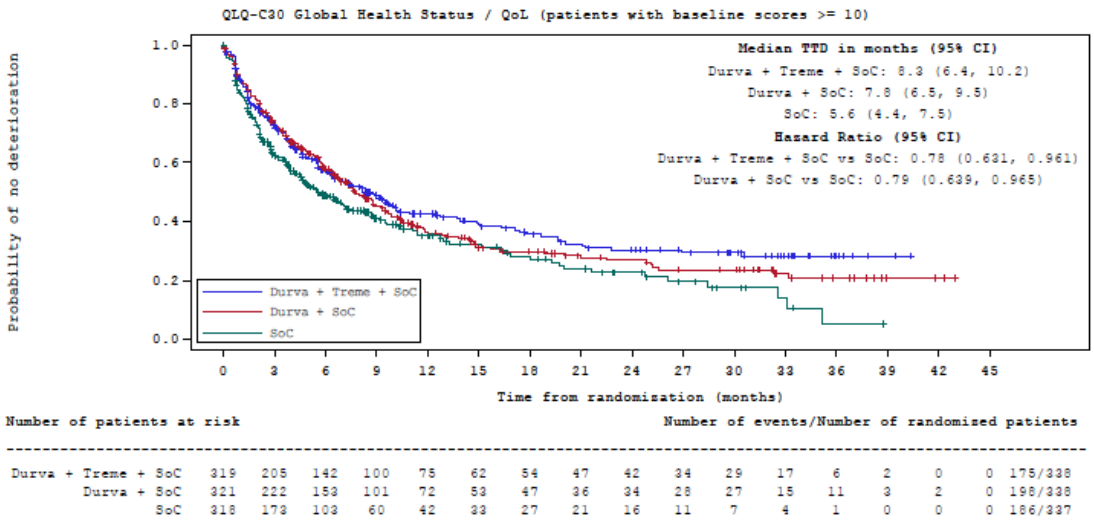


Figure 22: K-M plot of TTD in EORTC QLQ-C30 and QLQ-L13 in the ITT, DCO 12-MAR-2021



Ancillary analyses

Subgroup analyses:

Figure 23. Forest plot of OS in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021

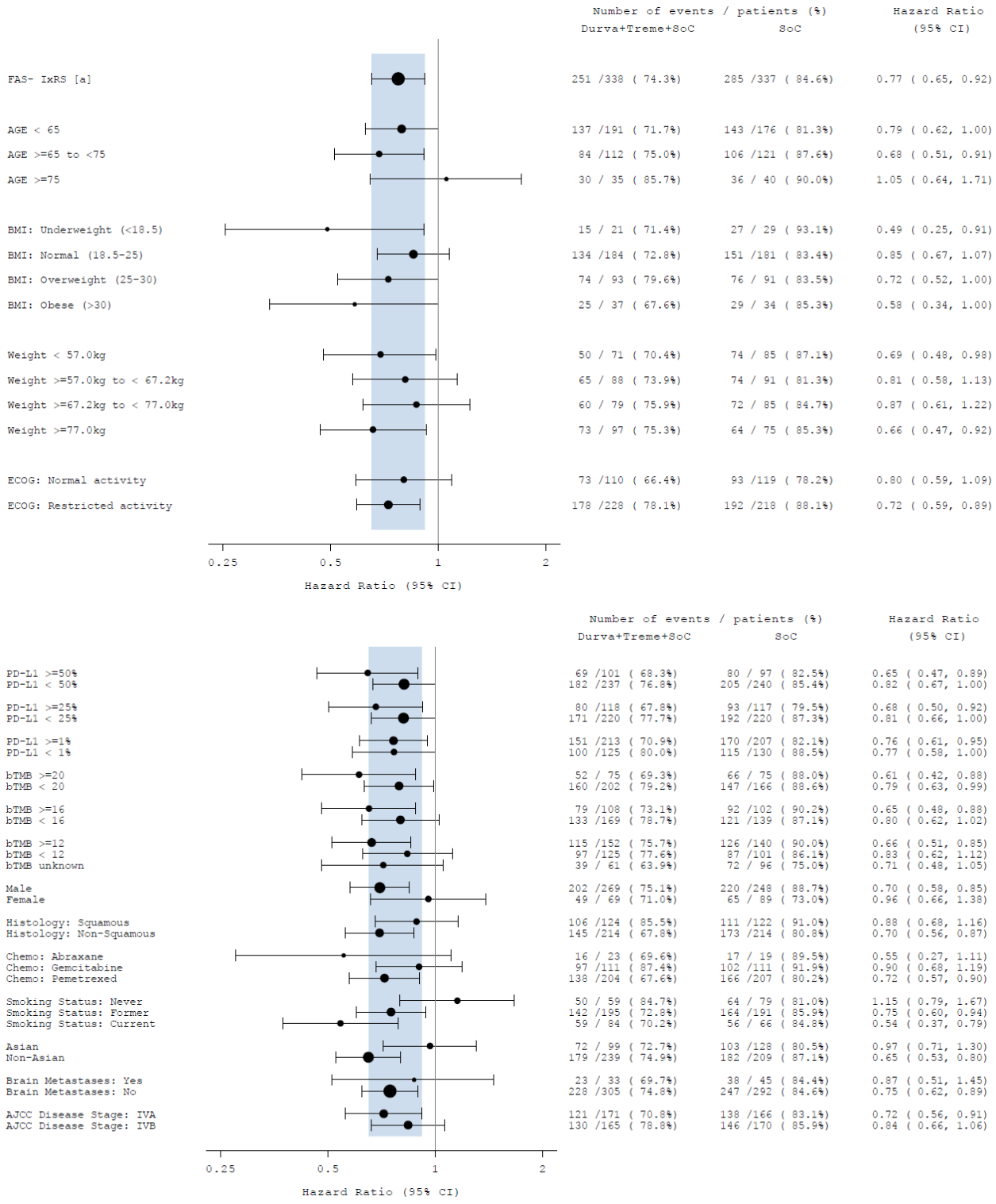
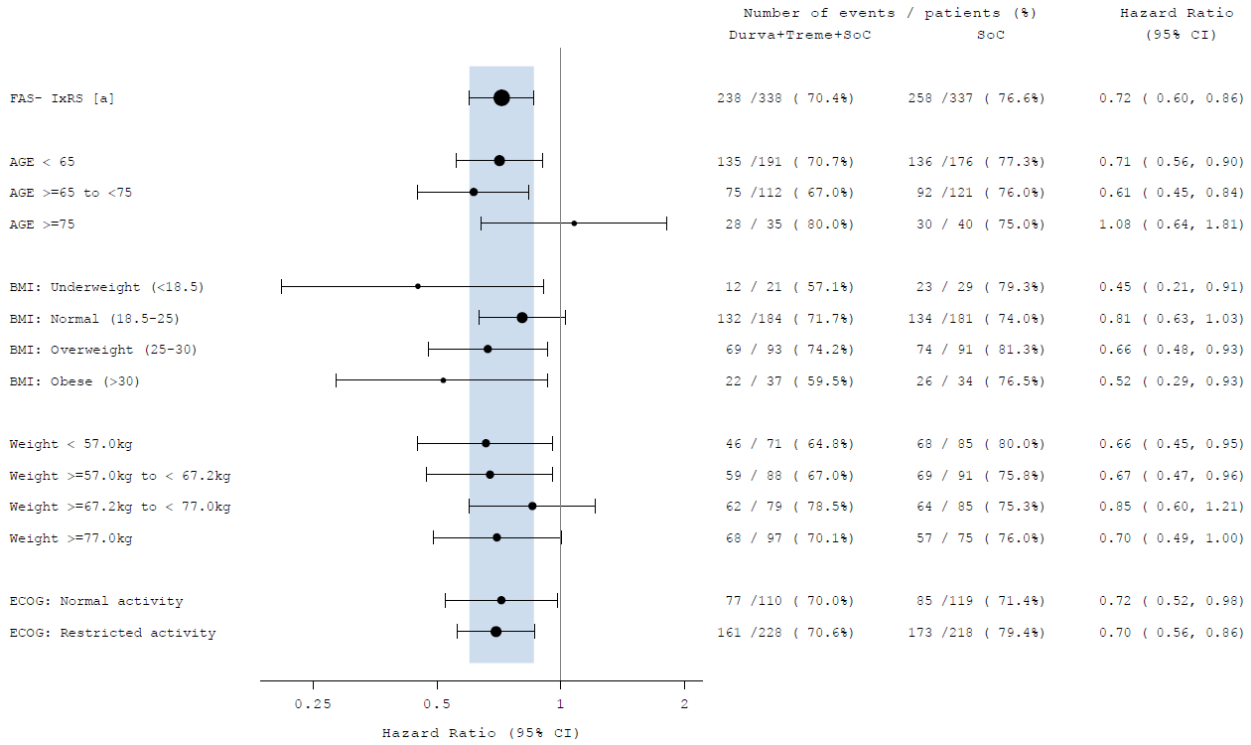
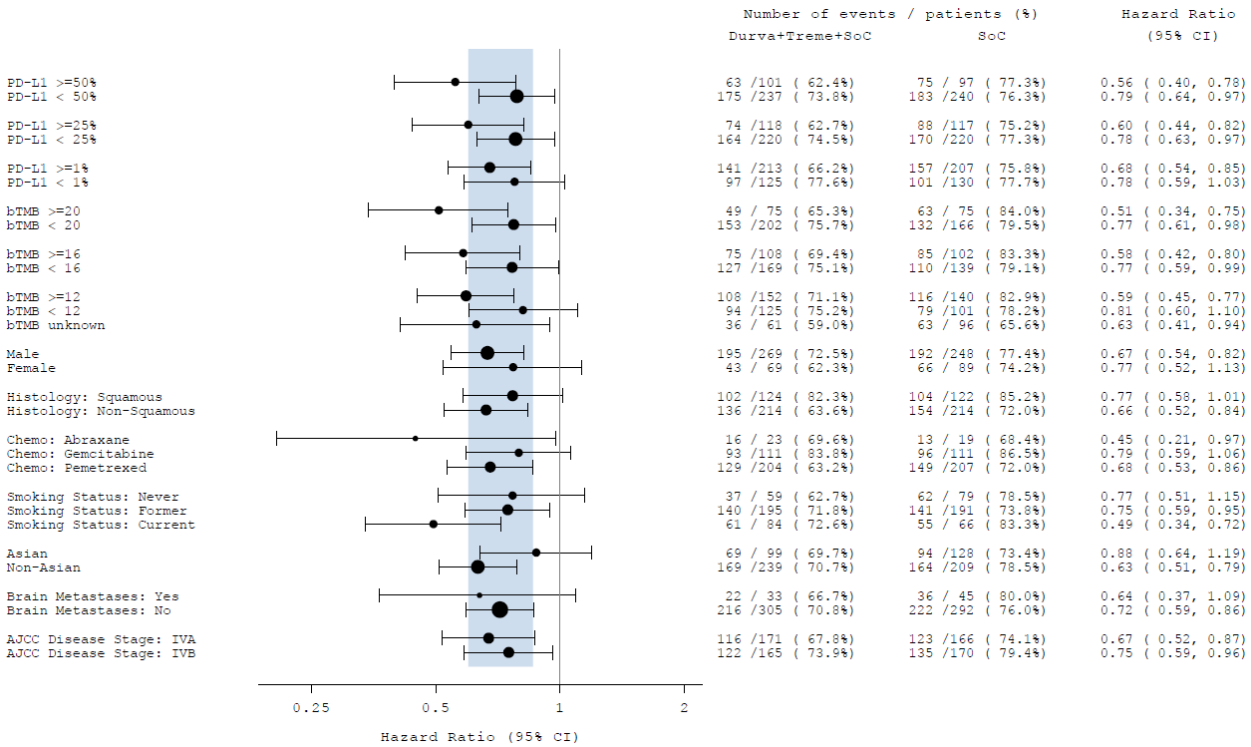


Figure 24. Forest plot of PFS by BICR in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021





Sensitivity analyses:

Table 35. Sensitivity analysis of OS adjusting for eCRF stratification variables

Group	N	Number (%) of patients with events	Median (months) [a]	Comparison with SoC: Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
Using eCRF-derived stratification variables [d]						
Durva + Treme + SoC	336	251 (74.7)	13.9	0.79	0.667, 0.940	0.008
Durva + SoC	335	262 (78.2)	13.3	0.86	0.728, 1.023	0.089
SoC	336	284 (84.5)	11.6			

Table 36. Sensitivity analysis of OS, effect of covariates in Cox proportional hazards model

Model/Group	N	Number (%) of patients with events	Comparison with SoC: Hazard ratio	95% CI	2-sided p-value
Model including treatment and stratification factors (primary) [a]					
Durva + Treme + SoC	338	251 (74.3)	0.78	0.658, 0.925	0.004
Durva + SoC	338	264 (78.1)	0.86	0.724, 1.014	0.072
SoC	337	285 (84.6)			
Primary model with additional covariates [b]					
Durva + Treme + SoC	338	251 (74.3)	0.76	0.635, 0.903	0.002
Durva + SoC	338	264 (78.1)	0.83	0.704, 0.986	0.034
SoC	336	284 (84.5)			

Table 37. Sensitivity analysis of OS, Max-Combo

Comparison	Test	Weight	p-value
Durva + Treme + SoC vs SoC	Fleming-Harrington	(0,0)	0.0030
		(0,1)	0.0015
		(1,1)	0.0050
	Max-Combo		0.0029
Durva + SoC vs SoC	Fleming-Harrington	(0,0)	0.0755
		(0,1)	0.1171
		(1,1)	0.0586
	Max-Combo		0.0969

Table 38. Sensitivity analysis of OS, RMST

Comparison	Max. Event Time (Months)	Treatment Arm	RMST Estimate (Months)	Difference between groups: Difference (Months) (95% CI)	p-value	Ratio between groups: Ratio (95% CI)	p-value
Durva + Treme + SoC vs SoC	37.32	Durva + Treme + SoC	17.86 (16.43, 19.28)	2.67 (0.75, 4.58)	0.00626	1.18 (1.05, 1.32)	0.00619
		SoC	15.19 (13.92, 16.47)				
Durva + SoC vs SoC	40.08	Durva + SoC	17.47 (15.99, 18.95)	1.93 (-0.07, 3.93)	0.05909	1.12 (1.00, 1.27)	0.05867
		SoC	15.54 (14.19, 16.89)				

Table 39. Sensitivity analyses of PFS by BICR in the ITT, Durva + treme + chemo vs. chemo, DCO 24-JUL-2019

	Number (%) of patients with events	Median PFS (months) [a]	HR [b]	95% CI [b]	2-sided p-value [c]
Analysis to assess possible evaluation-time bias [d, e, f]	T + D + SoC: 238/338 (70.4%)	5.5	0.72	0.600, 0.860	<0.001
	SoC chemotherapy: 258/337 (76.6%)	4.1			
Analysis to assess possible attrition bias [d, g]	T + D + SoC: 238/338 (70.4%)	6.3	0.74	0.614, 0.883	<0.001
	SoC chemotherapy: 248/337 (73.6%)	4.9			
Analysis to assess possible ascertainment bias [e, h]	T + D + SoC: 247/338 (73.1%)	6.4	0.66	0.552, 0.786	<0.001
	SoC chemotherapy: 284/337 (84.3%)	5.3			
Using eCRF-derived stratification variables [d, e, i]	T + D + SoC: 238/336 (70.8%)	6.2	0.72	0.603, 0.865	<0.001
	SoC chemotherapy: 258/336 (76.8%)	4.8			

a Calculated using the Kaplan-Meier technique.

b The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach. A hazard ratio <1 favors D +T + SoC or D + SoC to be associated with a longer PFS than SoC chemotherapy.

c P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.

[d] Progression is determined by BICR assessment, RECIST 1.1.

[e] Patients who have not progressed or died, or who progress or die after 2 or more missed visits, are censored at the latest evaluable RECIST assessment or at Day 1 if there are no evaluable visits or no baseline data and patient did not die within 2 visits of baseline.

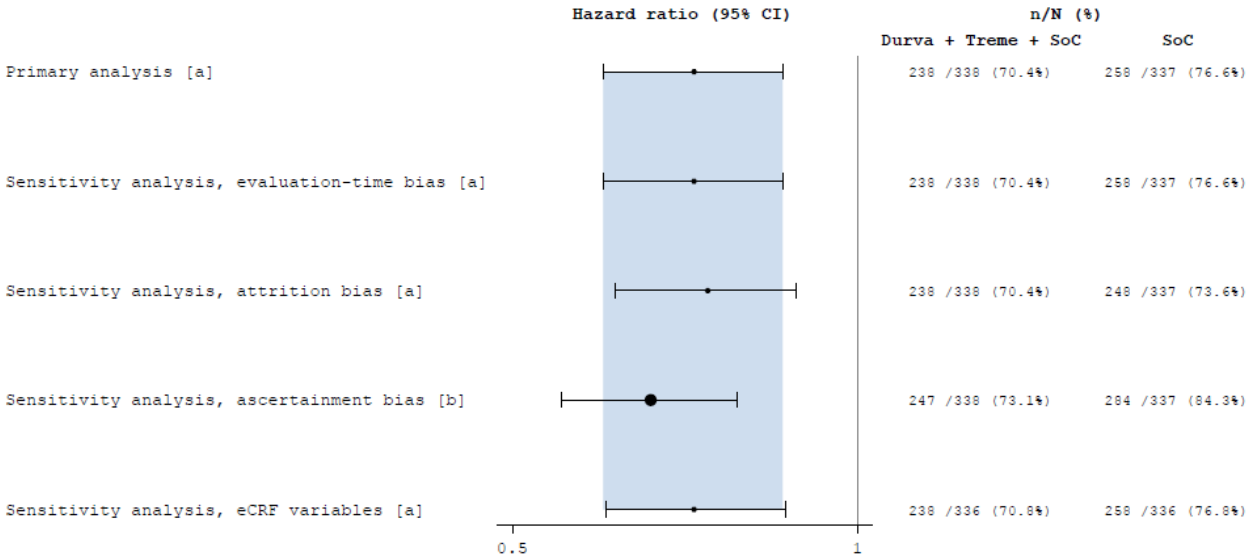
[f] The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) is analyzed.

[g] Patients who have not progressed or died will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment, or at Day 1 if there are no evaluable visits. In addition, patients initiating subsequent therapy prior to their last evaluable RECIST assessment, progression or death in absence of progression, will be censored at their last evaluable assessment prior to starting subsequent therapy.

[h] Progression is determined by site investigator assessment, RECIST 1.1.

[i] Covariates used in the statistical model are derived from eCRF data rather than using the values from IVRS.

Figure 25. Forest plot of primary and sensitivity analyses of PFS by BICR in the ITT, Durva + treme + chemo vs. chemo, DCO 24-JUL-2019



Exploratory analyses:

Contribution of each component:

Table 40. Contribution of components POSEIDON

Efficacy measure	Treatment arm		
	T + D + SoC	**D + SoC**	**SoC**
Overall survival [a]			
N	338	338	337
HR [b, c], T + D + SoC vs SoC (95% CI)	0.77 (0.650, 0.916)		
2-sided p-value [d]	0.00304		
HR [b, e], D + SoC vs SoC (95% CI)		0.86 (0.724, 1.016)	
2-sided p-value [d]		0.07581	
HR [b, f], T + D + SoC vs D + SoC (95% CI)	0.92 (0.776, 1.100)		
2-sided p-value [d]	0.373		
Death, n (%)	251 (74.3)	264 (78.1)	285 (84.6)
Median OS (months) [g] (95% CI) [g]	14.0 (11.7, 16.1)	13.3 (11.4, 14.7)	11.7 (10.5, 13.1)
Progression-free survival [h, i]			
N	338	338	337
HR [b, c], T + D + SoC vs SoC (95% CI)	0.72 (0.600, 0.860)		
2-sided p-value [d]	0.00031		
HR [b, e], D + SoC vs SoC (95% CI)		0.74 (0.620, 0.885)	
2-sided p-value [d]		0.00093	
HR [b, f], T + D + SoC vs D + SoC (95% CI)	0.97 (0.815, 1.166)		
2-sided p-value [d]	0.796		
Total events, n (%)	238 (70.4)	253 (74.9)	258 (76.6)

Efficacy measure	Treatment arm		
	T + D + SoC	**D + SoC**	**SoC**
Median (months) [g] (95% CI) [g]	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 5.8)
Objective response rate [h, i, j, k]			
N	**335**	**330**	**332**
Number (%) of patients with a confirmed response	130 (38.8)	137 (41.5)	81 (24.4)
Odds ratio [m], D + T + SoC vs D + SoC (95% CI)	0.89 (0.646, 1.218)		
2-sided p-value	0.461		
Duration of response (confirmed)			
N	**130**	**137**	**81**
Number of responders who subsequently progressed or died	65	83	60
Duration of response from onset of response (months) [g, k, n]			
Median (25th, 75th percentiles)	9.5 (5.0, NR)	7.0 (3.9, NR)	5.1 (3.7, 7.5)

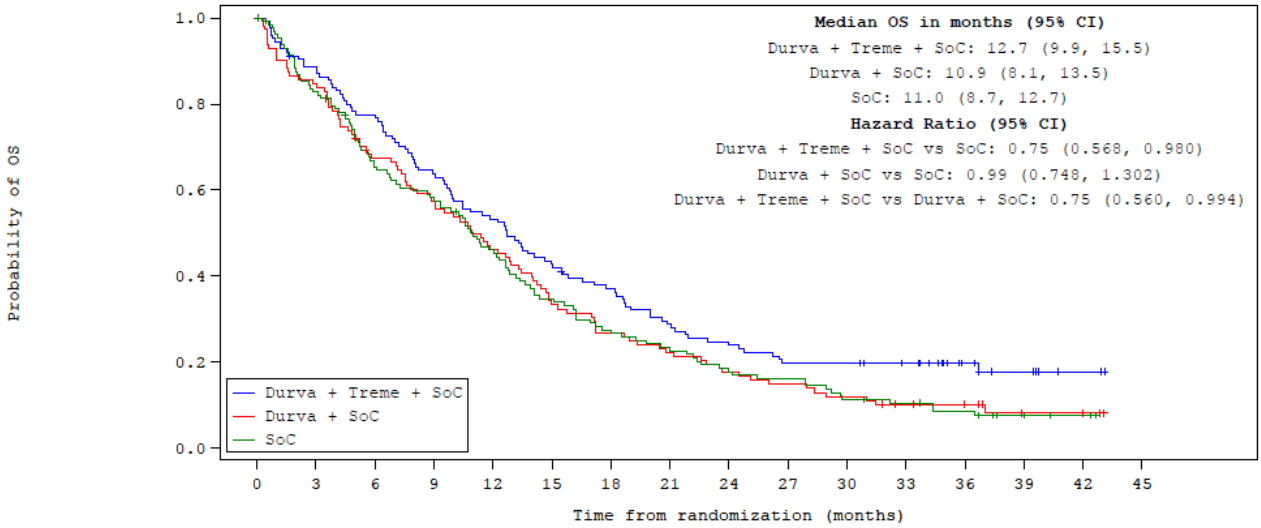
Efficacy according to PD-L1 subgroups

Table 41. OS according to PD-L1 subgroups in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021

	Number (%) of patients							
Analysis set	**Full analysis set**		**PD-L1 TC <50%**		**PD-L1 TC <25%**		**PD-L1 TC <1%**	
	T + D + SoC (N = 338)	**SoC (N = 337)**	**T + D + SoC (N = 237)**	**SoC (N = 240)**	**T + D + SoC (N = 220)**	**SoC (N = 220)**	**T + D + SoC (N = 125)**	**SoC (N = 130)**
HR, T+D+SoC vs SoC [a, b]	0.77		0.82		0.83		0.75	
95% CI for HR	0.650, 0.916		0.673, 1.006		0.674, 1.020		0.568, 0.980	
2-sided p-value	0.00304 [c]		0.057 [d]		0.077 [d]		0.035 [d]	
Death, n (%)	251 (74.3)	285 (84.6)	182 (76.8)	205 (85.4)	171 (77.7)	192 (87.3)	100 (80.0)	115 (88.5)
Censored patients, n (%)	87 (25.7)	52 (15.4)	55 (23.2)	35 (14.6)	49 (22.3)	28 (12.7)	25 (20.0)	15 (11.5)
Median OS (months) [g] (95% CI) [g]	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)	13.3 (10.3, 15.7)	12.0 (10.6, 14.1)	13.1 (10.0, 15.5)	12.2 (10.6, 14.4)	12.7 (9.9, 15.5)	11.0 (8.7, 12.7)

a The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.
b A HR <1 favors T + D + SoC chemotherapy to be associated with a longer OS than SoC chemotherapy alone.
c P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.
d P-values were generated using the stratified log-rank test adjusting for histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.
e Includes patients known to be alive at data cutoff.
f Includes patients with unknown survival status or patients who were lost to follow-up.
g Calculated using Kaplan-Meier technique.

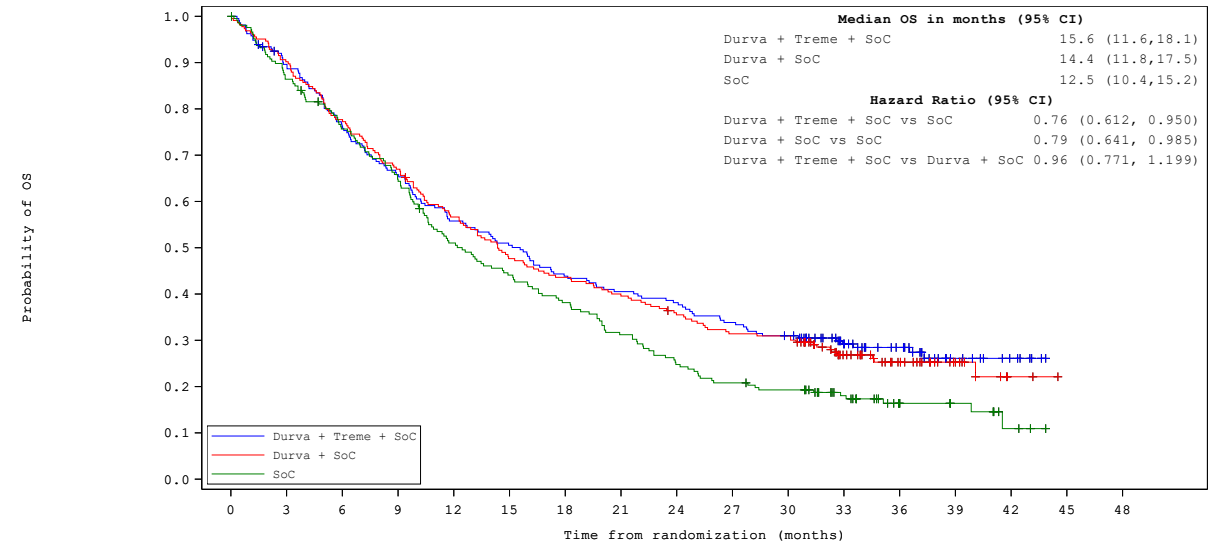
Figure 26. Overall survival in the PD-L1 TC<1% population, DCO 12-MAR-2021



Number of patients at risk — Number of events/Number of randomized patients

Durva + Treme + SoC	125	110	96	79	66	53	45	35	29	24	24	21	11	7	3	0	100/125
Durva + SoC	113	94	73	62	50	36	29	24	19	16	13	9	7	3	2	0	99/113
SoC	130	106	82	72	57	43	34	28	22	20	14	12	9	4	3	0	115/130

Figure 27. Overall survival in the PD-L1 TC≥1% population, DCO 12-MAR-2021



Number of patients at risk — Number of events/Number of randomized patients

Durva + Treme + SoC	213	188	160	138	117	106	92	85	80	71	64	43	30	13	6	0	0	151/213
Durva + SoC	224	202	174	150	126	106	97	88	78	69	68	42	26	12	3	0	0	165/224
SoC	207	178	154	132	103	89	77	63	50	42	38	26	12	9	3	0	0	170/207

Table 42: Progression-free survival (BICR; RECIST 1.1), full analysis set and PD-L1 analysis sets, T + D + SoC vs SoC, DCO 24-JUL-2019

Analysis set	Full analysis set		PD-L1 TC <50%		PD-L1 TC <25%		PD-L1 TC <1%	
	T + D + SoC (N = 338)	SoC (N = 337)	T + D + SoC (N = 237)	SoC (N = 240)	T + D + SoC (N = 220)	SoC (N = 220)	T + D + SoC (N = 125)	SoC (N = 130)
HR [a,b] vs T+D+SoC vs SoC	0.72 [a, b]		0.77 [b, c]		0.79 [b, c]		0.74 [b, c]	
95% CI	0.600, 0.860 [a]		0.627, 0.957 [c]		0.632, 0.978 [c]		0.554, 0.986 [c]	
2-sided p-value	0.00031 [d]		0.018 [e]		0.031 [e]		0.040 [e]	
Total events, n (%) [f]	238 (70.4)	258 (76.6)	175 (73.8)	183 (76.3)	164 (74.5)	170 (77.3)	97 (77.6)	101 (77.7)
Median PFS (months) [g] (95% CI) [g]	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)	6.0 (4.7, 6.5)	4.8 (4.6, 6.1)	6.0 (4.7, 6.5)	4.8 (4.6, 6.1)	6.1 (4.6, 6.5)	4.7 (4.6, 6.2)

[a] The HR and CI were estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.

[b] A HR <1 favors T + D + SoC chemotherapy to be associated with a longer PFS than SoC chemotherapy alone.

[c] The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.

[d] P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA s Stage IVB) and using the Breslow approach for handling ties.

[e] P-values were generated using the stratified log-rank test adjusting for histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.

[f] Patients who have not progressed or died, or who progress or die after 2 or more missed visits, are censored at the latest evaluable RECIST assessment or at Day 1 if there are no evaluable visits or no baseline data and patient did not die within 2 visits of baseline.

[g] Calculated using the Kaplan-Meier technique.

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).

Table 43. Summary of Efficacy for POSEIDON

A phase III, randomised, multicentre, open-label, comparative global study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic non-small-cell lung cancer (POSEIDON)		
Study identifier	EudraCT number 2017-000920-81; Study code D419MC00004; NCT03164616	
Design	Phase III, multicentre, open-label, three-arm, randomised 1:1:1, active control. Cross-over not allowed.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Not applicable, event driven Not applicable Not applicable
Hypothesis	Superiority	
Treatment groups	T + D + SoC chemotherapy (Treatment Arm 1)	SoC chemotherapy Q3W + tremelimumab 75 mg IV Q3W + durvalumab 1500 mg IV Q3W for 4 cycles. A fifth dose of tremelimumab 75 mg is to be given at Week 16 alongside durvalumab Dose 6. Post chemotherapy, durvalumab 1500 mg IV Q4W. n=338
	D + SoC chemotherapy (Treatment Arm 2)	SoC chemotherapy Q3W + durvalumab 1500 mg IV Q3W 4 cycles. Post chemotherapy, durvalumab 1500 mg IV Q4W. n=338
	SoC chemotherapy alone (Treatment Arm 3)	Up to 6 doses of histology-based SoC chemotherapy: abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin n=337

Endpoints and definitions	Primary	OS Arm 2 vs. 3	Time from date of randomisation until date of death by any cause.
	Primary	BICR-PFS Arm 2 vs. 3	Time from randomisation to the date of objective disease progression by RECIST 1.1 per blinded independent central review (BICR) assessment, or death due to any cause.
	Secondary	OS Arm 1 vs. 3	Time from date of randomisation until date of death by any cause.
	Secondary	BICR-PFS Arm 1 vs. 3	Time from randomisation to the date of objective disease progression by RECIST 1.1 per BICR assessment, or death due to any cause.
	Secondary	Confirmed BICR-ORR	Confirmed overall response rate per BICR (this is a post-hoc analysis, the predefined ORR was unconfirmed responses)
Database lock	18-SEP-2019 for final PFS analyses and 20-APR-2021 for final OS analyses		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	ITT (N=1013) Data cutoff for final analyses of PFS 24-JUL-2019 Data cutoff for final analyses of OS 12-MAR-2021		
Descriptive statistics and estimate variability	Treatment group	T + D + SoC chemotherapy (Treatment Arm 1)	SoC chemotherapy alone (Treatment Arm 3)
	Number of subjects	338	337
	OS, patients with event (%)	251 (74.3)	285 (84.6)
	Median OS[a], months	14.0	11.7
	95% CI	11.7, 16.1	10.5, 13.1
	BICR-PFS, patients with event (%)	238 (70.4)	258 (76.6)
	Median BICR-PFS[a], months	6.2	4.8
	95% CI	5.0, 6.5	4.6, 5.8
	Confirmed BICR ORR (n)	38.8 (130)	24.4 (81)
	95% CI	12.5, 21.1	3.8, 9.6

Effect estimate per comparison	OS	Comparison groups	T + D + SoC chemotherapy vs. SoC chemotherapy alone
		Stratified HR[b]	0.77
		95% CI	0.650, 0.916
		P-value[c]	0.00304
	BICR-PFS	Comparison groups	T + D + SoC chemotherapy vs. SoC chemotherapy alone
		Stratified HR[b]	0.72
		95% CI	0.600, 0.860
		P-value[c]	0.00031

Notes:
[a] Based on Kaplan-Meier method
[b] The HR and CI are estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) in the strata statement, and the CI calculated using a profile likelihood approach.
[c] P-values were generated using the stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB) and using the Breslow approach for handling ties.

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

N/A

Clinical studies in special populations

Table 44. Summary of Patient Age by Study (Full Analysis Set)

	Number (%) of Patients				
	Age < 65	Age 65 to 74	Age 75 to 84	Age ≥ 85	All Patients
Total Patients	1529 (51.8)	1104 (37.4)	314 (10.6)	7 (0.2)	2954
Controlled Trials					
POSEIDON (D419MC00004)	538 (53.1)	365 (36.0)	108 (10.7)	2 (0.2)	1013
MYSTIC (D419AC00001)	551 (49.3)	430 (38.5)	134 (12.0)	3 (0.3)	1118
NEPTUNE (D419AC00003)	440 (53.5)	309 (37.5)	72 (8.7)	2 (0.2)	823

In vitro biomarker test for patient selection for efficacy

As explained in the inclusion criteria of pivotal study POSEIDON, the collection of archival/residual diagnostic tumour tissue was mandatory, for potential analysis of various markers by IHC or other methods.

One of the exploratory objectives of the trial was to measure PD-L1 expression via the Ventana SP263 PD-L1 IHC assay and/or TMB to fully investigate the relationship between a patient's PD-L1 and/or TMB and efficacy outcomes with durvalumab, tremelimumab, and SoC regimens.

Data concerning PD-L1 expression were presented in the ancillary analyses section. Data concerning TMB expression and efficacy are not considered clinically relevant and are not presented in this report.

Supportive study(ies)

Table 45 depicts the main similarities and differences among pivotal study POSEIDON and supportive studies MYSTIC and NEPTUNE.

Table 45. Key similarities and differences among POSEIDON, MYSTIC and NEPTUNE.

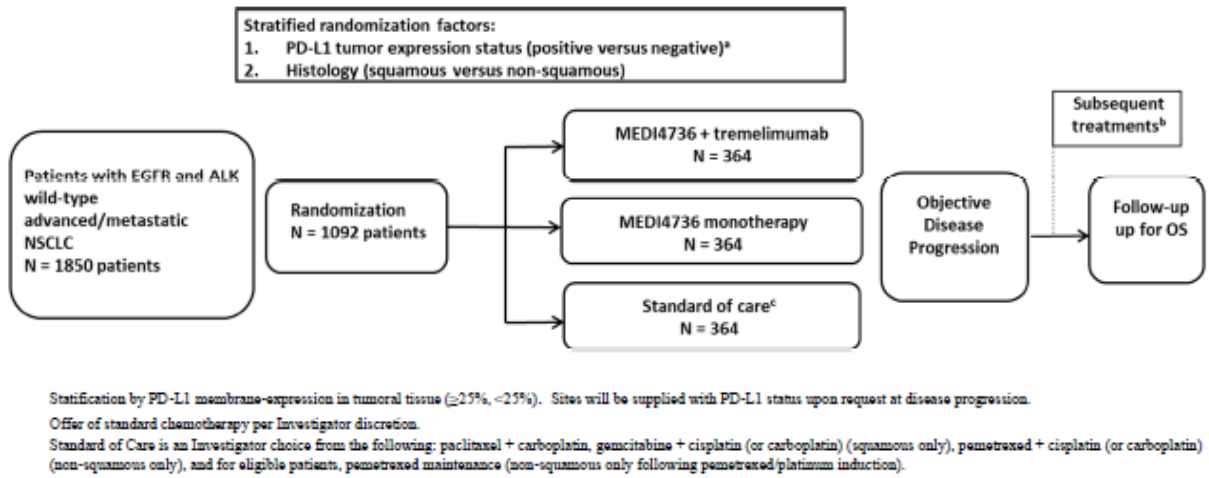
	POSEIDON	**MYSTIC**	**NEPTUNE**
Patient population	Advanced or metastatic NSCLC eligible for 1L treatment	Advanced or metastatic NSCLC eligible for 1L treatment	Advanced or metastatic NSCLC eligible for 1L treatment
Primary analysis set	All-comers	PD-L1 TC≥25%	bTMB>20 mut/megabase
Stratification	• Histology • PD-L1 (TC≥50%; TC<50%) • Disease stage	• Histology • PD-L1 (TC≥25%; TC<25%)	• Histology • PD-L1 (TC≥25%; TC<25%) • Smoking status
Treatment arm	• T + D + SoC • D + SoC • SoC	• T + D • D • SoC	• T + D • SoC

Study MYSTIC

MYSTIC (D419AC00001) is a randomized, open-label, multicenter, global, Phase III study to determine the efficacy and safety of treatment with durvalumab (MEDI4736) in combination with tremelimumab

(MEDI1123) or durvalumab monotherapy versus platinum-based standard of care (SoC) chemotherapy in the first-line treatment of patients with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type advanced or metastatic non-small cell lung cancer (NSCLC). A schematic diagram of the overall study design is shown in Figure 28. Table 46 summarises OS and PFS results in the primary efficacy dataset (PD-L1 ≥25%).

Figure 28. Overall study design of MYSTIC



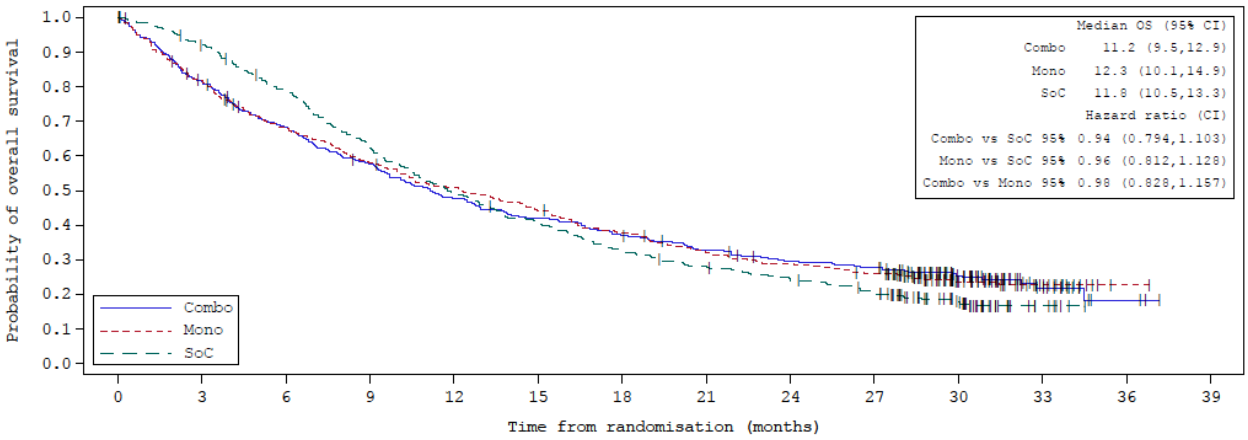
[a] Stratification by PD-L1 membrane-expression in tumoral tissue (≥25%, <25%). Sites will be supplied with PD-L1 status upon request at disease progression.
[b] Offer of standard chemotherapy per Investigator discretion.
[c] Standard of Care is an Investigator choice from the following: paclitaxel + carboplatin, gemcitabine + cisplatin (or carboplatin) (squamous only), pemetrexed + cisplatin (or carboplatin) (non-squamous only), and for eligible patients, pemetrexed maintenance (non-squamous only following pemetrexed/platinum induction).

Table 46. OS and PFS in the PD-L1 ⩾25% analysis dataset of study MYSTIC

Efficacy parameter	PD-L1 TC ≥25%		
	D + T	D	SoC
	N = 163	N = 163	N = 162
Overall survival			
HR [a, b, c], D + T vs SoC	0.85		
98.77% CI for HR	0.611, 1.173		
2-sided p-value	0.202		
HR [a, b, c], D vs SoC		0.76	
97.54% CI for HR		0.564, 1.019	
2-sided p-value		0.036	
Total events, n (%)	113 (69.3)	108 (66.3)	128 (79.0)
Median OS (95% CI), months [d]	11.9 (9.0, 17.7)	16.3 (12.2, 20.8)	12.9 (10.5, 15.0)
OS at 18 months (95% CI), % [d]	42.4 (34.7, 49.9)	47.8 (39.9, 55.3)	33.6 (26.4, 41.0)
OS at 24 months (95% CI), % [d]	35.4 (28.1, 42.8)	38.3 (30.7, 45.7)	22.7 (16.5, 29.5)
Progression-free survival			
HR [e, f, g], D + T vs SoC	1.05		
99.5% CI for HR	0.722, 1.534		
2-sided p-value	0.705		
HR [e, f, g], D vs SoC		0.87	
99.5% CI for HR		0.593, 1.285	
2-sided p-value		0.324	
Total events, n (%) [h]	118 (72.4)	106 (65.0)	112 (69.1)
Median PFS (95% CI), months [d]	3.9 (2.8, 5.0)	4.7 (3.1, 6.3)	5.4 (4.6, 5.8)
PFS at 12 months (95% CI) [d]	25.8 (18.9, 33.1)	32.3 (24.8, 39.9)	14.3 (8.4, 21.7)

a The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for histology (squamous vs non-squamous), with ties handled by the Breslow approach.
b The 2-sided p-value was calculated using a stratified log-rank test adjusting for histology (squamous vs non squamous), with ties handled by the Breslow approach.
c The adjusted alpha levels for the treatment comparison were derived based upon the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function.
d Calculated using the Kaplan-Meier technique.
e The analysis was performed using stratified log-rank test adjusting for histology (squamous vs non squamous), with ties handled by the Breslow approach.
f The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for histology (squamous vs non-squamous), with ties handled by the Breslow approach.
g An HR of <1 favors D + T or D to be associated with a longer PFS than SoC.
h Patients who have not progressed or died, or who progress or die after 2 or more missed visits, are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Patients with a RECIST progression within 2 visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at Day 1.
Data cutoff for OS: 04OCT2018.
Data cutoff: for PFS: 01JUN2017.
PFS is based on BICR assessment using RECIST 1.1.

Figure 29. Kaplan-Meier plot of OS in the ITT of MYSTIC, DCO 04-OCT-2018



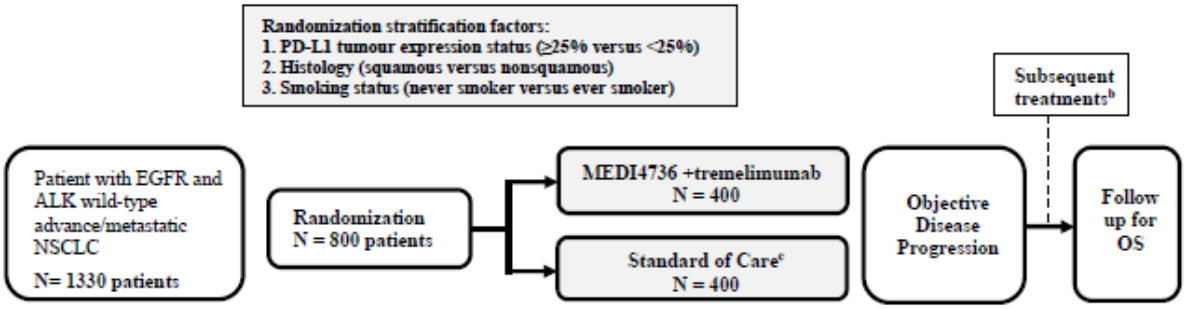
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Combo	372	303	253	212	175	154	136	119	104	98	55	16	3	0
Mono	374	303	249	212	185	161	136	115	103	92	41	14	1	0
SoC	372	336	287	227	180	148	118	100	85	71	37	6	0	0

Study NEPTUNE

NEPTUNE was a Phase III, randomized, open-label study to determine the efficacy and safety of durvalumab + tremelimumab combination therapy versus platinum-based SoC chemotherapy in the first-line treatment of patients with EGFR and ALK wild-type advanced or metastatic NSCLC. Crossover from SoC to durvalumab monotherapy or durvalumab + tremelimumab combination therapy was not permitted. The primary efficacy objective was to evaluate the OS benefits of durvalumab + tremelimumab vs. SoC used as 1L treatment. During the course of the study and based on the emerging results from MYSTIC study, the primary endpoint for NEPTUNE was amended after completion of enrolment to prospectively investigate OS in bTMB ≥20 mut/Mb population (results in Table 47). A schematic diagram of the overall study design is shown in Figure 30.

Figure 30. Overall study design of NEPTUNE



[a] The same study design was applied to the China cohort. The number of patients in Figure 1 reflects those for the Global cohort. Enrollment in China was to continue after the Global cohort enrollment was completed.

[b] Offer of standard chemotherapy per Investigator's discretion

[c] SoC is an Investigator choice from the following: paclitaxel + carboplatin, gemcitabine + cisplatin (or carboplatin) (squamous only), pemetrexed + cisplatin (or carboplatin) (non-squamous only), and for eligible patients, pemetrexed maintenance (non-squamous only following pemetrexed/platinum induction

Table 47. OS in the bTMB⩾20 analysis dataset of study NEPTUNE

	bTMB ≥20 analysis set	
	D + T	**SoC**
Efficacy parameter	**N = 69**	**N = 60**
HR (95% CI), D + T vs SoC	0.71 (0.485, 1.045) [a,b,c]	
2-sided p-value	0.0808	
Total events, n (%)	54 (78.3)	53 (88.3)
Median OS (95% CI), months [d]	11.7 (8.6, 15.2)	9.1 (7.8, 12.6)
OS at 12 months (95% CI), (%) [d]	49.3 (37.1, 60.4)	40.8 (28.3, 52.9)
OS at 18 months (95% CI), (%) [d]	36.2 (25.1, 47.4)	20.4 (11.3, 31.4)
OS at 24 months (95% CI), (%) [d]	26.1 (16.4, 36.8)	13.6 (6.4, 23.6)

[a] A HR <1 favors D + T combination therapy to be associated with a longer OS than SoC.

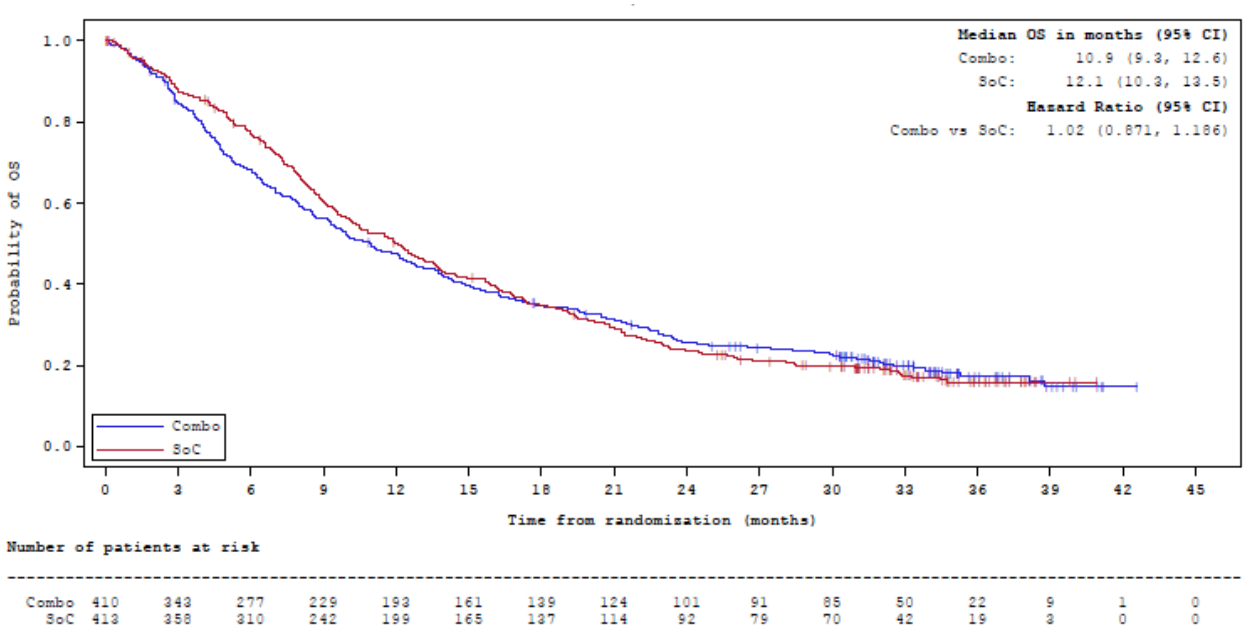
[b] The HR and CI were calculated using an unstratified Cox proportional hazards model, with ties handled by the Efron approach.

[c] The 2-sided p-value was calculated using an unstratified log-rank test.

[d] Calculated using the Kaplan-Meier technique.

Data cutoff: 24JUN2019.

Figure 31. Kaplan-Meier plot of OS in the ITT of NEPTUNE, DCO 24-JUN-2019



2.4.2. Discussion on clinical efficacy

The current application is based on efficacy data from POSEIDON, a pivotal phase III, three-arm, randomised, multi-centre, open-label study which compared durvalumab + chemotherapy (D+SoC, Arm 2) and tremelimumab + durvalumab + chemotherapy (T+D+SoC, Arm 1) to standard-of-care histology-specific platinum-based chemotherapy (SoC, Arm 3).

A total of 1013 patients were randomised between June 2017 and September 2018. The dual primary endpoints of BICR-PFS and OS were analysed in the ITT of the D+SoC vs. SoC arms, while identical secondary endpoints were evaluated in the ITT of the T+D+SoC vs. SoC arms.

Design and conduct of clinical studies

Scientific advice has not been sought from the CHMP.

Experimental and control arms: The overall design of POSEIDON resembles that of other recent landmark trials in the treatment-naïve setting of metastatic driver-negative NSCLC regardless of PD-L1 expression, with platinum-based chemotherapy as control arm. Currently, multiple regiments for these patients are approved and recommendable across Europe, most of them containing one or more immune checkpoint inhibitors (i.e., pembrolizumab or atezolizumab or nivolumab + ipilimumab) added to histology-selected platinum doublets. Even when this implies that platinum-based chemotherapy by itself has been long outdated as standard of care in this setting, it was still an appropriate choice of treatment at the time of design and conduct of POSEIDON.

The fact that crossover was not allowed to avoid confounding OS is understood. Noting that a significant number of patients from the control arm would likely receive immune checkpoint inhibitors at progression, an exploratory PFS2 analysis was planned.

There were 36 (10.9%) patients in the T+D+SoC arm and 33 (9.9%) in the D+SoC arm that continued treatment with durvalumab after confirmed disease progression. Of these, 18 (5.5%) and 20 (6.0%), respectively, received treatment more than 56 days post-progression. Overall, median duration of treatment post-progression was of 8.4 weeks in the T+D+SoC arm and 12.3 weeks in the D+SoC arm.

Considering the relatively low number of patients that received treatment beyond progression and that many of them received less than 8 weeks of treatment after progression (which corresponds to the imaging visits interval) it is not expected this may have impacted the results.

Induction vs. maintenance effect: In both experimental arms (D+SoC and T+D+SoC), after induction chemotherapy + durvalumab +/- tremelimumab, durvalumab was to be maintained Q4W until progressive disease. Although such design does not allow to disentangle effect magnitude of induction vs. maintenance immune checkpoint inhibition, this does not constitute an impediment to evaluate the B/R profile of the add-on products in this palliative setting.

Study participants: Inclusion/exclusion criteria in the POSEIDON trial did not suffer any major amendments along study conduct and appropriately reflect the target population as in the proposed therapeutic indication. Although the inclusion criteria declare that staging is to be determined per the IASLC staging manual in thoracic oncology 2016 by Rami-Porta et al, such parameters correspond to the AJCC 8th edition by Amin et al. The requirements for inclusion of patients with brain metastases are appropriate and in line with similar trials. PD-L1 testing by the SP263 IHC assay was centralised during the screening phase and before randomisation, which is endorsed.

Objectives/endpoints: The current application for durvalumab is based in efficacy results from the secondary objectives of this study. An improvement in survival is considered the most compelling

outcome of a pivotal trial in Oncology, especially when supported by a reciprocal prolongation of PFS. The definitions for OS and RECIST 1.1-based BICR-PFS according to the protocol and SAP are appropriate. The definitions for the other secondary endpoints of ORR, DoR, PFS2 and PROs are also endorsed.

Statistical methods: The planned sample size for the study was approximately 1000 patients. The study was primarily powered for showing a statistically significant improvement for durvalumab monotherapy compared to SoC in either OS or PFS or both. Sample size calculations are adequate. The stratification factors [PD-L1 tumour expression status (<50%; ≥50%), stage (IVA vs IVB) and histology (non-squamous vs squamous)] are clinically relevant and thus appropriate in this disease context. Censoring rules for PFS and OS are acceptable. The planned sensitivity and supplementary analyses to assess robustness of PFS and OS results are adequate, no additional analyses have been requested. Concerning interim analyses (one for PFS at approximately 80% of targeted events and three for OS at approximately 45%, 61% and 84%), an alpha spending function was used to account for multiplicity due to multiple looks, which is acceptable. Regarding the hierarchical testing procedure, if at least OS or PFS of D+SoC vs. SoC were statistically significant, the corresponding alpha portion was transferred to the T+D+SoC vs. SoC comparison. This strategy controls the type I error.

Participant flow and recruitment: 1807 patients were screened for eligibility. The screen failure rate (42%) is higher than expected, but understandable in view of stringent inclusion/exclusion criteria: the majority of patients failed screening because of EGFR/ALK status, missing PD-L1 status or investigator judgement. The proportion of patients who did not receive the assigned treatment across all three arms of POSEIDON is minimal and follows the characteristic attrition pattern in open-label trials: slightly more patients withdrew consent in the control arm. Recruitment of the whole study took approximately 1 year and 3 months. Median duration of follow-up of ~1 year in the ITT is considered borderline for assessment of B/R in the given clinical setting.

Conduct of the study: Important protocol deviations occurred in a small proportion of patients and are overall balanced among arms. A major amendment modified the dual primary endpoints as of protocol V 4.0 (25-SEP-2018), when all patients had already been recruited (last patient randomised 19-SEP-2018) and before the first interim analysis of PFS/OS on 07-JAN-2019. OS for the comparison of D+SoC vs. SoC was upgraded, while PFS of T+D+SoC vs. SoC was downgraded, establishing the comparisons of D+SoC vs. SoC in the first level (primary endpoints), while relegating the comparisons of T+D+SoC vs. SoC to secondary endpoints. According to the applicant, this change was justified on emerging external data from other immunotherapy trials. Since the statistical integrity of the trial could have been compromised due to changes in SAP, analyses according to original test hierarchy and study populations (first 804 patients randomised) were requested, which obtained successful results for PFS and OS testing of T+D+SoC vs. SoC.

Baseline data: The demographic characteristics of patients were relatively balanced among all three arms of treatment and correspond to what is expected within the clinical setting of advanced driver-negative NSCLC: median age was 64 years (27 to 87 years); 76% were male; 56% white, 35% Asian, 2% black; current/past smokers 78%; 33% had ECOG PS 0. Disease characteristics were also balanced among arms: 50% had stage IVA and 50% IVB; 63% had non-squamous tumours and 37% squamous; brain/CNS metastases were present in 10.5% of patients; presence of KRAS mutations was evaluated in ~15% (149/1013) of the ITT, and documented in 21% (31/149) of those tested. The distribution of patients according to tumour PD-L1 status across diverse thresholds (</≥50%, </≥25%, </≥1%) was balanced among all three arms of treatment and represents the global pattern of PD-L1 expression in advanced NSCLC.

Efficacy data and additional analyses

The primary OS endpoint (D+SoC vs SoC) in study POSEIDON did not meet statistical significance. However, the other primary PFS endpoint that compared the same arms showed statistical superiority and thus alpha was propagated to the next testing level, in which OS and PFS were evaluated as key secondary endpoints in the T+D+SoC vs. SoC arms.

OS: At data cutoff 12-MAR-2021 and with a median survival follow-up of 12.5 months, 800 deaths had occurred (79% of OS maturity) in the ITT population of study POSEIDON. Treatment with T+D+SoC showed a statistically significant survival benefit as compared with SoC: HR for OS was 0.77 (95% CI 0.65, 0.92), p-value 0.00304. K-M estimates of median OS were **14.0 months in the T+D+SoC arm** and 11.7 months in the SoC arm. Survival performance of the chemotherapy-only control arm in POSEIDON is comparable to other pivotal trials in a similar PD-L1 all-comer setting of metastatic NSCLC: range of 10.6 in KEYNOTE-189 to 13.9 months in IMpower130. The K-M curves of T+D+SoC vs. SoC separate as of the 10th month, noting a delayed treatment effect from added anti-CTLA-4/PD-L1 therapy. Important censoring occurs as of the 30th month of follow-up, but landmark analysis at 24 months (OS24) shows a considerably higher proportion of patients alive in the T+D+SoC (33%) as compared to the SoC (22%) arm.

Acknowledging differences in study design –particularly selection of squamous (SQ) or non-squamous (NSQ) histologies, or allowing both– and limitations from cross-trial comparisons, it is to note that longer median survival was observed in akin studies in which only anti-PD-1/PD-L1 agents were added to backbone platinum-based chemotherapy in the experimental arm: **22.0** months in the chemo + pembrolizumab arm in metastatic NSQ NSCLC (KEYNOTE-189; Rodríguez-Abreu et al, JCO 2020); **21.9** months in the chemo + cemiplimab arm in advanced SQ/NSQ NSCLC (EMPOWER-Lung3; Gogishvili et al, ESMO 2021); **19.5** months in the chemo + atezolizumab arm in metastatic SQ/NSQ NSCLC (IMpower150, Tecentriq SmPC); **18.6** months in the chemo + atezolizumab arm in metastatic NSQ NSCLC (IMpower130; Cappuzzo et al, Ann Onc 2018); **17.1** months in the chemo + pembrolizumab arm in metastatic SQ NSCLC (KEYNOTE-407; Paz-Ares et al, JTO 2020). Interestingly, however, the addition of both anti-CTLA-4 and anti-PD-1 agents to backbone platinum-based chemotherapy produced almost identical median OS results as those observed in POSEIDON: **14.1** months in the histology-based chemotherapy + nivolumab + ipilimumab arm in patients with metastatic SQ/NSQ NSCLC (CheckMate 9LA; Paz-Ares et al, Lancet Oncol 2021).

BICR-PFS: At data cutoff 24-JUL-2019, 749 PFS events (74% maturity) had occurred across the three arms of POSEIDON. K-M estimated median PFS was numerically higher in the T+D+SoC arm (6.2 months) as compared with the SoC arm (4.8 months), while HR for PFS outlines the statistical advantage from T+D+SoC vs. SoC: 0.72 (95% CI 0.60, 0.86), p-value 0.00031. The K-M curves separate as of the second month and remain separated, highlighting the PFS advantage of T+D+SoC. Overall, PFS results from the experimental (both T+D+SoC and D+SoC arms) and control arms of POSEIDON are comparable to those from other pivotal trials in the same setting. Results of PFS by investigator are overall comparable to BICR assessment and the HR for INV-PFS is consistent with that of BICR-PFS, discrepant declarations of the RECIST event occurred in a reasonably low number of instances.

BICR-ORR/DoR: Rather than using the ITT, the calculations of ORR were done using patients with measurable disease as the denominator. This is acceptable in a phase III trial since OS and PFS are prioritised in hierarchical testing. Both confirmed and unconfirmed responses (almost all of them partial) were numerically higher in the T+D+SoC arm as compared to the control SoC arm. However, the proportion of responders (unconfirmed responses) was nearly identical between both experimental arms: 46.3% in T+D+SoC vs. 48.5% in D+SoC. Responses (unconfirmed responses) were more

durable in the T+D+SoC arm (median DoR 7.4 months) as compared to the SoC arm (4.2 months), supporting the delayed treatment effect hypothesis portrayed in the OS analysis.

Subsequent treatment/PFS2: A notably higher proportion of patients received subsequent treatments in the SoC arm (60%) as compared to either of the experimental arms (41% in T+D+SoC, 44% in D+SoC). As expected, the proportion of second-line immunotherapy was higher in the immunotherapy-naïve SoC arm (49%, 95 out of 193) as compared to both T+D+SoC (9%, 11/121) and D+SoC (9%, 12/137). Across the three arms of POSEIDON, 66% (435/658) of the PFS2 events were deaths in the absence of second progression. Albeit the median time to second progression or death (PFS2) was comparable among all three arms (10.2 months in T+D+SoC, 10.0 in D+SoC and 9.1 in SoC), HR for PFS2 (0.72) suggests sustained benefit from T+D+SoC vs. SoC.

Ancillary analyses: OS and PFS benefits from T+D+SoC vs. SoC seem to be maintained across most of the prespecified subgroups. However, in elderly patients (≥75 years of age) a HR of 1.05 (95% CI: 0.64, 1.71) for OS was reported for T+D+SoC (n=35) vs. SoC (n=40). Due to the exploratory nature of this subgroup analysis no definitive conclusions can be drawn. This said, considering that an overall worse safety profile was observed in this subgroup of patients, a warning was included in section 4.4 of the SmPC stating that in elderly the combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis. Exploratory efficacy and safety results in this subgroup are outlined in sections 4.8 and 5.1 of the SmPC, respectively.

Importantly, the efficacious advantage –in terms of OS, PFS and ORR– of T+D+SoC vs. SoC is maintained regardless of PD-L1 expression status, i.e., above and below diverse PD-L1 cut-offs. Of note, a similar outcome regarding PD-L1 subgroups was observed in the CheckMate-9LA trial, when the nivolumab + ipilimumab + chemotherapy arm was compared against the chemotherapy arm in an akin population of advanced NSCLC (p. 99/157, EPAR EMEA/H/C/WS1783).

The sensitivity analyses of OS and PFS are consistent with the primary analysis of both variables.

Exploratory analysis of T+D+SoC vs. D+SoC: The survival K-M curves of the experimental arms remain close along the first year of follow-up, and subsequently show a wider separation, suggesting the benefit from added tremelimumab is established in the long term. This hypothesis is reinforced when looking at the duration of response data, as the K-M curves between T+D+SoC and D+SoC exhibit wider separation than those from OS or PFS. Importantly, OS subgroup analyses in the PD-L1 <1% population –about one third of the ITT– suggest the magnitude of survival benefit from T+D+SoC is particularly higher in this subgroup, as compared to that seen in across the other PD-L1 cut-offs, while the contribution of tremelimumab appears to be less clear as PD-L1 expression increases. However, these comparisons portray an exploratory nature –they were not statistically powered– and thus no firm conclusions can be drawn.

Supportive data from MYSTIC and NEPTUNE: Including POSEIDON, all three trials were open-label, randomised, had a similar metastatic NSCLC targeted population, and dual primary endpoints of OS and PFS. The essential difference was that MYSTIC and NEPTUNE did now allow a platinum-based backbone chemotherapy in the experimental arms, while POSEIDON did. The overall efficacy outcome of MYSTIC and NEPTUNE –none met their primary endpoints– was not different from other trials in which anti-PD-L1 monotherapy failed to show benefits for the ITT population, suggesting that the subgroup of patients who drive the beneficial trend for ICI-monotherapy were high-PD-L1 expressors (usually defined as PD-L1≥50%). Whether OS and PFS data from the ITT of either trial are supportive of efficacy benefits from adding tremelimumab to D+SoC is debatable, but in any case, it can be inferred that a detrimental OS/PFS effect is not evident.

2.4.3. Conclusions on the clinical efficacy

Although the primary OS endpoint for the comparison of durvalumab + chemotherapy vs. chemotherapy was not met in study POSEIDON, the favourable PFS comparison of these arms allowed testing of the secondary endpoints of OS and PFS in the tremelimumab + durvalumab + chemotherapy (T+D+SoC) vs. chemotherapy (SoC) arms. In the targeted population of patients with metastatic EGFR/ALK-negative NSCLC regardless of tumour PD-L1 expression, OS and PFS from treatment with T+D+SoC were statistically superior to SoC chemotherapy. Secondary endpoints of ORR, DoR and PFS2 endorsed such benefits, as did subgroup and sensitivity analyses.

2.5. Clinical safety

Introduction

The pivotal study to support this indication is POSEIDON, a phase III, randomised, multicentre, three-arm, open-label study, designed to compare the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (D+SoC) with that of SoC alone chemotherapy (SoC) for the first-line treatment in patients with metastatic NSCLC. Additionally, the study also planned to compare the efficacy and safety of tremelimumab, durvalumab and SoC chemotherapy combination (T+D+SoC) with that of SoC chemotherapy in the same patient population.

Safety dataset: The safety analysis set (SAS) of POSEIDON included all patients who received at least 1 dose of study treatment and comprised 997 patients: T + D + SoC (n = 330); D + SoC (n = 334); and SoC chemotherapy (n = 333). Of note, 1 patient who was randomized to the T + D + SoC arm and 1 patient who was randomized to the D + SoC arm only received SoC chemotherapy (see protocol deviations) and were included in the SoC chemotherapy arm of the safety analysis set.

For further support in the evaluation of the safety profile of durvalumab, the applicant provided data from a safety pool ("T + D pan-tumour pool") that included 2280 patients from 9 studies, who had received at least one dose of durvalumab at 1500 mg Q4W, 20 mg/kg Q4W or 10 mg/kg Q2W, in combination with tremelimumab at 75 mg Q4W or 1 mg/kg Q4W for any line of therapy across tumour types (Table 48). The main advantage of including the results from the T+D pan-tumour pool in the safety assessment report is to be able to elucidate the contribution of immunotherapy components to the combination safety profile as in the included studies patients only received T+D.

Table 48. Summary of clinical studies in T + D pan-tumour pool

Study 06 (D4190C00006) Phase I	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for 4 doses followed by durvalumab monotherapy 20 mg/kg Q4W for up to 9 doses in patients with advanced **NSCLC** (n = 355) DCO 19-NOV-2019
Study 10 (D4190C00010) Phase I	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 20 mg/kg Q4W for up to 12 months in patients with advanced **solid tumours** (n = 341) DCO 31-MAR-2018
Japan 02 (D4190C00002) Phase I	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 20 mg/kg Q4W for up to 12 months in patients with advanced **solid tumours** (n = 124) DCO 31-MAR-2018
Study 22 (D4190C00022) Phase I/II	Durvalumab 1500mg Q4W + tremelimumab 75 mg Q4W for up to 4 doses, followed by durvalumab 1500 mg Q4W until disease progression in patients with advanced **hepatocellular carcinoma** (n = 127) DCO 6-NOV-2020

ARCTIC (D4191C00004) Phase III	Sub-study B: Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 10 mg/kg Q2W for up to 18 doses in patients with advanced **NSCLC** (n = 173) DCO 9-FEB-2018
MYSTIC (D419AC00001) Phase III	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 20 mg/kg Q4W until disease progression in patients with advanced **NSCLC** (n = 371) DCO 4-OCT-2018
NEPTUNE (D419AC00003) Phase III	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 20 mg/kg Q4W until disease progression in patients with advanced **NSCLC** (n = 410) DCO 24-JUN-2019
CONDOR (D4193C00003) Phase II	Durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 10 mg/kg Q2W for up to 18 doses in patients with **squamous cell carcinoma of the head and neck** (n = 133) DCO 27-AUG-2018
EAGLE (D4193C00002) Phase III	Durvalumab 20mg/kg Q4W + tremelimumab 1 mg/kg Q4W for up to 4 doses followed by durvalumab monotherapy 10 mg/kg Q2W until disease progression in patients with **squamous cell carcinoma of the head and neck** (n = 246) DCO 10-SEP-2018

AEs: The integrated analysis of adverse events (AEs) for the safety pools was based on all treatment-emergent adverse events (TEAEs) as defined in each individual study. MedDRA v23.1 was used for coding of AE data. Data from studies originally reported in previous versions of MedDRA were upversioned to MedDRA v23.1 for the integrated safety database.

AESIs: Adverse events of special interest (AESIs) are defined as AEs with potential inflammatory or immune-mediated mechanism that may require frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (eg. therapies for hyperthyroidism include beta blockers [eg. propranolol], calcium channel blockers [eg. verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).

imAEs: Immune-mediated adverse events (imAEs) are AESIs (excluding infusion related/hypersensitivity/anaphylactic reaction) consistent with an immune-mediated mechanism that require treatment with systemic corticosteroids, high-dose steroids, immunosuppressants, or endocrine therapy.

The AESI categories include dermatitis/rash, pneumonitis, diarrhoea/colitis, endocrinopathies (adrenal insufficiency, hyperthyroid events, hypothyroid events, hypophysitis, thyroiditis, and Type I diabetes mellitus), hepatic events, intestinal perforations, myocarditis, myositis, renal events, pancreatic events, myasthenia gravis, Guillain-Barre syndrome and other rare/miscellaneous events. Infusion related reactions and hypersensitivity/anaphylactic reactions are AESIs; however, these are not assessed for imAE designation because they are common to mAb drugs in general and occur due to a mechanism of action different from that for imAEs.

Adjudication of imAEs: A suspected immune-mediated adverse event (imAE) was identified as AESI treated with systemic steroids, other immunosuppressants, and/or endocrine therapy, except pneumonitis AESIs, which are all suspected imAE. All suspected imAEs underwent medical review, which was performed in a blinded manner.

A confirmed imAE is a suspected imAE that, after medical review, is deemed consistent with an immune-mediated mechanism of action, and where there is no clear alternative etiology. The process for adjudicating imAEs starting from the study level AE reporting dataset through to confirmed imAE

included the steps depicted in Figure 32, and the process of adjudicating imAEs is presented in detail in the imAE Charter.

Figure 32 The process for adjudicating imAEs

Patient exposure

Table 49. Duration of overall exposure, SAS POSEIDON and pan-tumour pool

Exposure characteristic		POSEIDON			T + D pan-tumor pool (N = 2280)
		T + D + SoC (N = 330)	D + SoC (N=334)	SoC (N = 333)	
Total treatment duration (weeks)[a]	Mean (SD)	49.6 (48.15)	45.3 (44.7)	25.8 (29.00)	26.9 (30.52)
	Median (Min, Max)	29.9 (1, 190)	28.7 (0.1, 188)	18.0 (1, 184)	16.0 (1, 218)
	Total treatment years	313.8	289.9	164.9	1176.4

[a] Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1) / 7 . X is defined as the planned frequency in dosing (in days) - 1. X is based on the planned dosing frequency of the patient's last dose and defined as per the individual study's SAP.

Table 50. Exposure to durvalumab and tremelimumab, SAS POSEIDON and pan-tumour pool

Exposure characteristic		POSEIDON T + D + SoC		T + D Pan-tumor pool	
		Durvalumab (N = 330)	Tremelimumab (N = 330)	Durvalumab (N = 2280)	Tremelimumab (N = 2280)
Total number of infusions	Mean (SD)	12.5 (11.74)	4.3 (1.43)	7.3 (8.49)	3.0 (1.32)
	Median (Min, Max)	8.0 (1, 49)	5.0 (1, 9)	4.0 (1, 61)	3.0 (1, 9)
Total treatment duration (weeks) [a]	Mean (SD)	48.8 (47.98)	17.8 (7.36)	26.8 (30.47)	15.3 (11.79)
	Median (Min, Max)	29.8 (1, 190)	20.0 (1, 38)	16.0 (1, 218)	15.6 (1, 100)
	Total treatment years	308.8	112.4	1171.9	670.0

[a] Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1) / 7 . X is defined as the planned frequency in dosing (in days) - 1. X is based on the planned dosing frequency of the patient's last dose and defined as per the individual study's SAP.

Table 51. Exposure to chemotherapy, SAS POSEIDON

	Number of (%) patients			
	T+D+SoC (N=330)	D+SoC (N=334)	SoC (N=333)	Total (N=997)
Received SoC in combination stage	329[a]	334	333	996
Pemetrexed doublet	198 (60.2)	198 (59.3)	204 (61.3)	600 (60.2)
Pemetrexed + cisplatin	31 (9.4)	29 (8.7)	33 (9.9)	93 (9.3)
Pemetrexed + carboplatin	167 (50.8)	169 (50.6)	171 (51.4)	507 (50.9)
Gemcitabine doublet	107 (32.5)	107 (32.0)	112 (33.6)	326 (32.7)
Gemcitabine + cisplatin	15 (4.6)	17 (5.1)	20 (6.0)	52 (5.2)
Gemcitabine + carboplatin	92 (28.0)	90 (26.9)	92 (27.6)	274 (27.5)
Abraxane doublet (Abraxane + carboplatin)	24 (7.3)	29 (8.7)	17 (5.1)	70 (7.0)
Received pemetrexed doublet in maintenance stage	149	159	131	439
Pemetrexed maintenance[b]	149 (75.3)	159 (80.3)	131 (64.2)	439 (73.2)

[a] One patient was randomized to the T + D + SoC treatment arm but did not receive SoC. This was not considered a protocol deviation (the patient was included in the T + D + SoC treatment arm).

[b] Percentages calculated using the number of patients who received pemetrexed doublet in the combination stage.

Percentages are calculated from number of patients in the safety analysis set in that treatment arm that received at least one dose of the chemotherapy regimen in the combination stage.

Patients who received chemotherapy during re-treatment are also included.

Chemotherapy exposure for patients who switched from cisplatin to carboplatin (N=12) is summarized based on the chemotherapy regimen received at the start of treatment.

Table 52. Duration of chemotherapy exposure, SAS POSEIDON

	T+D+SoC (N=330)	D+SoC (N=334)	SoC (N=333)
	(n=329)	(n=334)	(n=333)
Total treatment duration (weeks)[a]			
Mean (SD)	35.35 (41.733)	32.70 (39.346)	25.83 (29.004)
Median (Min, Max)	15.00 (1.1, 189.6)	15.50 (0.1, 187.3)	18.00 (0.7, 184.4)
Total treatment years	222.9	209.3	164.9
Number of infusions			
Mean (SD)	10.7 (9.77)	10.1 (9.16)	9.1 (8.33)
Median (Min, Max)	8.0 (1, 49)	8.0 (1, 48)	8.0 (1, 57)
Number of cycles received[b]			
Mean (SD)	9.3 (10.31)	8.7 (9.66)	7.6 (8.42)
Median (Min, Max)	4.0 (1, 49)	4.0 (1, 48)	6.0 (1, 57)
Number of patients that switched treatment n (%)	4 (1.2)	1 (0.3)	7 (2.1)

[a] Total treatment duration = minimum of (last infusion/dose date of the last cycle + 20 days [if last infusion/dose date was during combination]/last infusion/dose date of the last cycle + 27 days [if last infusion/dose date was in maintenance], date of death, date of DCO) – first infusion/dose date of first cycle + 1.

[b] At least one dose of any study treatment must be administered for a cycle to be considered to have taken place.

Twelve patients switched from cisplatin to carboplatin.

Percentages are calculated from number of patients in the safety analysis set in that treatment arm.

Chemotherapy of a patient who received it during re-treatment is included in this table also.

Adverse events

Overview of all AEs:

Table 53. Overview of adverse events in SAS POSEIDON and pan-tumour pool

Category of AE	Number (%) of patients [a]			
	POSEIDON			
	T + D + SoC (N = 330)	D + SoC (N = 334)	SoC (N = 333)	T + D Pan-tumor pool (N = 2280)
Any AE	321 (97.3)	321 (96.1)	320 (96.1)	2160 (94.7)
Any AE of maximum CTCAE Grade 3 or Grade 4 [b]	176 (53.3)	183 (54.8)	172 (51.7)	1127 (49.4)
Any AE with outcome = death	41 (12.4)	34 (10.2)	30 (9.0)	153 (6.7)
Any SAE (including events with outcome = death) [c]	146 (44.2)	134 (40.1)	117 (35.1)	1020 (44.7)
Any AE leading to discontinuation of any study treatment	73 (22.1)	68 (20.4)	51 (15.3)	367 (16.1)
Any AE leading to discontinuation of durvalumab or tremelimumab	57 (17.3)	0	0	367 (16.1)
Any AE leading to dose modification of any study treatment [d]	206 (62.4)	197 (59.0)	179 (53.8)	622 (27.3)
Any AE leading to dose modification of durvalumab or tremelimumab [d]	174 (52.7)	172 (51.5)	0	622 (27.3%)
AEs leading to dose delay/interruption of any study treatment [e]	189 (57.3)	186 (55.7)	143 (42.9)	622 (27.3)
AEs leading to dose reduction of chemotherapy [f]	38 (11.5)	32 (9.6)	54 (16.2)	0
Infusion reaction AEs [g]	14 (4.2)	10 (3.0)	7 (2.1)	45 (2.0)

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 Maximum CTCAE grade per patient is considered.
c Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.
d Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
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). Disease progression AEs reported in Study 06 and Study 10 are not included in this summary.
e AEs on the AE eCRF page with Action taken="Drug interrupted" for at least one treatment or with Treatment cycle delayed = "Yes" on any exposure eCRF page.
f AEs on the AE eCRF page with Action taken="Dose reduced" for at least one chemotherapy.
g As assessed by the investigator.

Table 54. Overview of most common AEs (incidence ⩾10% in any arm) in SAS POSEIDON and pan-tumour pool

Preferred term	Number (%) of patients [a]		
	POSEIDON		
	T + D + SoC (N = 330)	SoC (N = 333)	T + D Pan-tumor pool (N = 2280)
Patients with any AE	**321 (97.3)**	**320 (96.1)**	**2160 (94.7)**
Anaemia	164 (49.7)	163 (48.9)	365 (16.0)
Nausea	137 (41.5)	122 (36.6)	449 (19.7)
Neutropenia	99 (30.0)	78 (23.4)	27 (1.2)
Decreased appetite	93 (28.2)	82 (24.6)	499 (21.9)
Fatigue	81 (24.5)	74 (22.2)	537 (23.6)
Diarrhoea	71 (21.5)	51 (15.3)	526 (23.1)
Rash	64 (19.4)	22 (6.6)	298 (13.1)
Constipation	63 (19.1)	79 (23.7)	382 (16.8)
Thrombocytopenia	60 (18.2)	57 (17.1)	41 (1.8)
Vomiting	60 (18.2)	45 (13.5)	268 (11.8)
Asthenia	56 (17.0)	41 (12.3)	302 (13.2)
Pyrexia	53 (16.1)	23 (6.9)	326 (14.3)
Pneumonia	47 (14.2)	32 (9.6)	208 (9.1)
Alanine aminotransferase increased	46 (13.9)	44 (13.2)	182 (8.0)
Aspartate aminotransferase increased	42 (12.7)	38 (11.4)	193 (8.5)
Leukopenia	42 (12.7)	39 (11.7)	15 (0.7)
Arthralgia	41 (12.4)	21 (6.3)	270 (11.8)
Hypothyroidism	39 (11.8)	4 (1.2)	248 (10.9)
Neutrophil count decreased	39 (11.8)	59 (17.7)	22 (1.0)
Headache	37 (11.2)	25 (7.5)	160 (7.0)
Pruritus	36 (10.9)	15 (4.5)	424 (18.6)
Alopecia	33 (10.0)	20 (6.0)	23 (1.0)
Cough	33 (10.0)	22 (6.6)	306 (13.4)
Dyspnoea	32 (9.7)	26 (7.8)	348 (15.3)
Back pain	25 (7.6)	15 (4.5)	235 (10.3)
Weight decreased	23 (7.0)	20 (6.0)	242 (10.6)

a Number (%) of patients with AEs, sorted in decreasing frequency of PT
Patients with multiple AEs are counted once for each 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). Disease progression AEs reported in Study 06 and Study 10 are not included in this summary.
COVID-19 events only apply to POSEIDON and Study 22.
MedDRA version 23.1.

Table 55. AEs by maximum reported CTCAE grade, SAS POSEIDON and pan-tumour pool

Category of AE	Number (%) of patients [a]			
	POSEIDON			T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	D + SoC (N=334)	SoC (N = 333)	
Any AE	**321 (97.3)**	**321 (96.1)**	**320 (96.1)**	**2160 (94.7)**
Grade 1	21 (6.4)	17 (5.1)	26 (7.8)	241 (10.6)
Grade 2	83 (25.2)	87 (26.0)	92 (27.6)	638 (28.0)
Grade 3	135 (40.9)	140 (41.9)	136 (40.8)	927 (40.7)
Grade 4	41 (12.4)	43 (12.9)	36 (10.8)	200 (8.8)
Grade 5	41 (12.4)	34 (10.2)	30 (9.0)	153 (6.7)
Grade 3 or higher	217 (65.8)	183 (54.8)	202 (60.7)	1280 (56.1)
Grade 3 or 4	176 (53.3)	217 (65.0)	172 (51.7)	1127 (49.4)

Table 56. G3/4 AEs with incidence ⩾2%, SAS POSEIDON and pan-tumour pool

Preferred term	Number (%) of patients [a]		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
Patients with any AE of maximum CTCAE Grade 3 or 4	**176 (53.3)**	**172 (51.7)**	**1127 (49.4)**
Anaemia	68 (20.6)	75 (22.5)	112 (4.9)
Neutropenia	56 (17.0)	41 (12.3)	4 (0.2)
Neutrophil count decreased	25 (7.6)	25 (7.5)	3 (0.1)
Pneumonia	23 (7.0)	10 (3.0)	109 (4.8)
Thrombocytopenia	18 (5.5)	17 (5.1)	11 (0.5)
Lipase increased	13 (3.9)	6 (1.8)	100 (4.4)
Amylase increased	12 (3.6)	6 (1.8)	57 (2.5)
Asthenia	12 (3.6)	8 (2.4)	64 (2.8)
Leukopenia	9 (2.7)	12 (3.6)	1 (<0.1)
Platelet count decreased	9 (2.7)	17 (5.1)	9 (0.4)
White blood cell count decreased	9 (2.7)	9 (2.7)	1 (<0.1)
Fatigue	8 (2.4)	9 (2.7)	50 (2.2)
Hypertension	8 (2.4)	2 (0.6)	40 (1.8)
Febrile neutropenia	7 (2.1)	2 (0.6)	0
Hypokalaemia	7 (2.1)	6 (1.8)	53 (2.3)
Hyponatraemia	6 (1.8)	12 (3.6)	85 (3.7)
Nausea	6 (1.8)	7 (2.1)	31 (1.4)
Alanine aminotransferase increased	5 (1.5)	7 (2.1)	40 (1.8)
Diarrhoea	5 (1.5)	5 (1.5)	60 (2.6)
Gamma-glutamyl transferase increased	5 (1.5)	1 (0.3)	56 (2.5)
Aspartate aminotransferase increased	2 (0.6)	1 (0.3)	51 (2.2)
Dyspnoea	2 (0.6)	5 (1.5)	72 (3.2)

a Each patient has only been represented with the maximum reported CTCAE grade at either the start of AE or after increasing in severity for each system organ class / preferred term.

AESIs:

Table 57. Adverse Events of Special Interest - Categories Reported for >2% Patients in POSEIDON (Safety Analysis Set)

AESI Category	Number (%) of Patients					
	T + D + SoC (N = 330)		D + SoC (N = 334)		SoC (N = 333)	
	Any grade	Maximum CTCAE Grade 3 or 4	Any Grade	Maximum CTCAE Grade 3 or 4	Any Grade	Maximum CTCAE Grade 3 or 4
Dermatitis/ rash	116 (35.2)	7 (2.1)	82 (24.6)	5 (1.5)	45 (13.5)	2 (0.6)
Diarrhoea/ colitis	81 (24.5)	13 (3.9)	63 (18.9)	6 (1.8)	51 (15.3)	6 (1.8)
Hepatic events	77 (23.3)	16 (4.8)	66 (19.8)	14 (4.2)	56 (16.8)	9 (2.7)
Other Rare/ miscellaneous	47 (14.2)	4 (1.2)	34 (10.2)	5 (1.5)	23 (6.9)	2 (0.6)
Pancreatic events	45 (13.6)	23 (7.0)	31 (9.3)	13 (3.9)	20 (6.0)	12 (3.6)
Hypothyroid events	44 (13.3)	0 (0.0)	27 (8.1)	0 (0.0)	7 (2.1)	0 (0.0)
Renal events	24 (7.3)	1 (0.3)	17 (5.1)	4 (1.2)	17 (5.1)	0 (0.0)
Hyperthyroid events	22 (6.7)	0 (0.0)	26 (7.8)	1 (0.3)	3 (0.9)	0 (0.0)
Pneumonitis	16 (4.8)	4 (1.2)	13 (3.9)	4 (1.2)	2 (0.6)	2 (0.6)
Infusion/ hypersensitivity reactions	15 (4.5)	2 (0.6)	10 (3.0)	2 (0.6)	8 (2.4)	0
Adrenal insufficiency	8 (2.4)	2 (0.6)	4 (1.2)	1 (0.3)	0 (0.0)	0 (0.0)

Pancreatic events:

Table 58: Adverse Events of Special Interest/Immune-mediated Adverse Events - Category of Pancreatic Events - Reported for Patients in POSEIDON (Safety Analysis Set)

Category/ Subcategory MedDRA Preferred Term	Number (%) of Patients [a]					
	T + D + SoC (N = 330)		D + SoC (N = 334)		SoC (N = 333)	
	Any Grade	Maximum CTCAE Grade 3 or 4	Any Grade	Maximum CTCAE Grade 3 or 4	Any Grade	Maximum CTCAE Grade 3 or 4
Pancreatic events						
AESI	7 (2.1)	1 (0.3)	4 (1.2)	0	2 (0.6)	0
Autoimmune pancreatitis	1 (0.3)	0	0	0	0	0
Pancreatitis	6 (1.8)	1 (0.3)	4 (1.2)	0	2 (0.6)	0
AEPI	39 (11.8)	22 (6.7)	27 (8.1)	13 (3.9)	19 (5.7)	12 (3.6)
Amylase increased	28 (8.5)	12 (3.6)	24 (7.2)	8 (2.4)	16 (4.8)	6 (1.8)
Hyperamylasaemia	2 (0.6)	1 (0.3)	0	0	0	0
Hyperlipasaemia	1 (0.3)	1 (0.3)	0	0	0	0
Lipase increased	21 (6.4)	13 (3.9)	12 (3.6)	7 (2.1)	7 (2.1)	6 (1.8)
imAE	6 (1.8)	4 (1.2)	3 (0.9)	2 (0.6)	0	0
Amylase increased	1 (0.3)	0	1 (0.3)	0	0	0
Autoimmune pancreatitis	1 (0.3)	0	0	0	0	0
Lipase increased	3 (0.9)	3 (0.9)	2 (0.6)	2 (0.6)	0	0
Pancreatitis	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0

Source: Responses to D150 LoOI, Module 1.

imAEs:

Table 59. ImAEs in SAS POSEIDON and pan-tumour pool

AE Category	Number (%) of patients [a]		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N=330)	SoC (N=333)	
Any AE	105 (31.8)	14 (4.2)	628 (27.5)
Any AE of maximum CTCAE Grade 3 or 4	32 (9.7)	4 (1.2)	223 (9.8)
Any SAE (including events with outcome of death) [b]	30 (9.1)	3 (0.9)	224 (9.8)
Any AE with outcome of death	1 (0.3)	0 (0.0)	9 (0.4)
Received systemic corticosteroids	78 (23.6)	10 (3.0)	458 (20.1)
Received high-dose steroids	60 (18.2)	5 (1.5)	343 (15.0)
Received endocrine therapy	39 (11.8)	4 (1.2)	234 (10.3)
Received other immunosuppressants	3 (0.9)	0 (0.0)	36 (1.6)
Any AE leading to discontinuation of study treatment	17 (5.2)	2 (0.6)	148 (6.5)
Event outcome resolved	54 (16.4)	10 (3.0)	337 (14.8)
Event outcome not resolved	50 (15.2)	4 (1.2)	282 (12.4)

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 Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.
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 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).
Percentages are calculated from number of patients in the treatment group (N).
Reasons of NOT RECOVERED/NOT RESOLVED, RECOVERING/RESOLVING, and UNKNOWN map to an outcome of Not Resolved.
Reasons of RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE map to an outcome of Resolved.

Table 60. imAEs that occurred in ⩾2% of patients in SAS POSEIDON

	Number (%) of patients [a]					
	T + D + SoC (N=330)		D + SoC (N=334)		SoC (N=333)	
imAE Category	Any grade	CTCAE Grade 3 or 4	Any grade	CTCAE Grade 3 or 4	Any grade	CTCAE Grade 3 or 4
Hypothyroid events	27 (8.2)	0	19 (5.7)	0	3 (0.9)	0
Dermatitis/rash	23 (7.0)	4 (1.2)	8 (2.4)	2 (0.6)	7 (2.1)	2 (0.6)
Diarrhea/colitis	14 (4.2)	5 (1.5)	6 (1.8)	2 (0.6)	1 (0.3)	0
Hepatic events	11 (3.3)	6 (1.8)	10 (3.0)	7 (2.1)	0	0
Pneumonitis	14 (4.2)	4 (1.2)	9 (2.7)	3 (0.9)	2 (0.6)	2 (0.6)
Hyperthyroid events	9 (2.7)	0	4 (1.2)	1 (0.3)	1 (0.3)	0
Adrenal insufficiency	8 (2.4)	2 (0.6)	4 (1.2)	1 (0.3)	0	0

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 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). Percentages are calculated from number of patients in the treatment group (N).

In the combined safety database with Imfinzi in combination with tremelimumab:

- immune-mediated pneumonitis occurred in 86 (3.8%) patients, including Grade 3 in 30 (1.3%) patients, Grade 4 in 1 (< 0.1%) patient, and Grade 5 (fatal) in 7 (0.3%) patients. The median time to onset was 57 days (range: 8 - 912 days). All patients received systemic corticosteroids and 79 of the 86 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients also received other immunosuppressants. Treatment was discontinued in 39 patients. Resolution occurred in 51 patients.

- immune-mediated hepatitis occurred in 80 (3.5%) patients, including Grade 3 in 48 (2.1%) patients, Grade 4 in 8 (0.4%) patients and Grade 5 (fatal) in 2 (< 0.1%) patients. The median time to onset was 36 days (range: 1 - 533 days). All patients received systemic corticosteroids and 68 of the 80 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients also received other immunosuppressants. Treatment was discontinued in 27 patients. Resolution occurred in 47 patients.

- immune-mediated colitis or diarrhoea occurred in 167 (7.3%) patients, including Grade 3 in 76 (3.3%) patients and Grade 4 in 3 (0.1%) patients. The median time to onset was 57 days (range: 3 - 906 days). All patients received systemic corticosteroids and 151 of the 167 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-two patients also received other immunosuppressants. Treatment was discontinued in 54 patients. Resolution occurred in 141 patients.

Intestinal perforation and large intestine perforation were uncommonly reported in patients receiving Imfinzi in combination with tremelimumab.

- immune-mediated hypothyroidism occurred in 209 (9.2%) patients, including Grade 3 in 6 (0.3%) patients. The median time to onset was 85 days (range: 1 - 624 days). Thirteen patients received systemic corticosteroids and 8 of the 13 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment discontinued in 3 patients. Resolution occurred in 52 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 25 patients or immune-mediated thyroiditis in 2 patients.

- immune-mediated hyperthyroidism occurred in 62 (2.7%) patients, including Grade 3 in 5 (0.2%) patients. The median time to onset was 33 days (range: 4 - 176 days). Eighteen patients received

systemic coticosteroids, and 11 of the 18 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Fifty-three patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker or beta-blocker), One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 47 patients.

- immune-mediated thyroiditis occurred in 15 (0.7%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 57 days (range: 22 - 141 days). Five patients received systemic corticosteroids and 2 of the 5 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Thirteen patients required other therapy including, hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. No patients discontinued treatment due to immune-mediated thyroiditis. Resolution occurred in 5 patients.

- immune-mediated adrenal insufficiency occurred in 33 (1.4%) patients, including Grade 3 in 16 (0.7%) patients and Grade 4 in 1 (< 0.1%) patient. The median time to onset was 105 days (range: 20-428 days). Thirty-two patients received systemic corticosteroids, and 10 of the 32 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in one patient. Resolution occurred in 11 patients.

- immune-mediated type 1 diabetes mellitus occurred in 6 (0.3%) patients, including Grade 3 in 1 (< 0.1%) patient and Grade 4 in 2 (< 0.1%) patients. The median time to onset was 58 days (range: 7 - 220 days). All patients required insulin. Treatment was discontinued for 1 patient. Resolution occurred in 1 patient.

- immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset for the events was 123 days (range: 63 - 388 days). All patients received systemic corticosteroids and 8 of the 16 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy. Treatment was discontinued in 2 patients. Resolution occurred in 7 patients.

- immune-mediated nephritis occurred in 9 (0.4%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 79 days (range: 39 - 183 days). All patients received systemic corticosteroids and 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 3 patients. Resolution occurred in 5 patients.

- immune-mediated rash or dermatitis (including pemphigoid) occurred in 112 (4.9%) patients, including Grade 3 in 17 (0.7%) patients. The median time to onset was 35 days (range: 1 - 778 days). All patients received systemic corticosteroids, and 57 of the 112 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 10 patients. Resolution occurred in 65 patients.

Infusion-related and hypersensitivity/anaphylaxis reactions:
In POSEIDON, AESIs of infusion related reactions (grouped term) were reported in 13 patients (3.9%) in the T + D + SoC arm and 5 patients (1.5%) in the SoC alone arm. The majority of the events were of CTCAE Grade 1 or 2 in severity with 1 patient (0.3%) in the T + D + SoC arm experiencing a CTCAE Grade 3 event. In the T + D + Chemo pool and the T + D pan tumour pool, AESIs of infusion related reaction were reported in 17 patients (2.9%) and 45 patients (2.0%), respectively. There were no Grade 4 or 5 events.

In POSEIDON, AESIs of hypersensitivity/anaphylactic reactions (grouped term) were reported in 3 patients (0.9%) each in the T + D + SoC arm and the SoC alone arm. In the D + T + Chemo pool and the T + D pan-tumor pool, AESIs of hypersensitivity/anaphylactic reactions were reported in 5 patients (0.8%) and 22 patients (1.0%), respectively.

ADRs:

Table 61. Adverse Drug Reactions in the three arms of the POSEIDON trial

ADR system organ class/ ADR term	Number (%) of Patients [a]								
	POSEIDON								
	T + D + SoC (N = 330)			D + SoC (N = 334)			SoC (N = 333)		
	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4
Blood and lymphatic system disorders									
Anaemia [c]	164 (49.7)	Very common	68 (20.6)	151 (45.2)	Very common	59 (17.7)	163 (48.9)	Very common	75 (22.5)
Febrile neutropenia [c]	10 (3.0)	Common	7 (2.1)	7 (2.1)	Common	6 (1.8)	5 (1.5)	Common	2 (0.6)
Immune thrombocytopenia	1 (0.3)	Uncommon	0	0	Not known	0	0	Not known	0
Leukopenia [c]	64 (19.4)	Very common	18 (5.5)	54 (16.2)	Very common	18 (5.4)	64 (19.2)	Very common	20 (6.0)
Neutropenia [c]	136 (41.2)	Very common	79 (23.9)	122 (36.5)	Very common	70 (21.0)	134 (40.2)	Very common	66 (19.8)
Pancytopenia [c]	6 (1.8)	Common	2 (0.6)	7 (2.1)	Common	6 (1.8)	3 (0.9)	Uncommon	2 (0.6)
Thrombocytopenia [c]	81 (24.5)	Very common	27 (8.2)	64 (19.2)	Very common	27 (8.1)	83 (24.9)	Very common	34 (10.2)
Cardiac disorders									
Myocarditis	1 (0.3)	Uncommon	0	0	Not known	0	0	Not known	0
Endocrine disorders									
Adrenal insufficiency	7 (2.1)	Common	2 (0.6)	4 (1.2)	Common	1 (0.3)	0	Not known	0
Diabetes insipidus	1 (0.3)	Uncommon	1 (0.3)	0	Not known	0	0	Not known	0
Hyperthyroidism	22 (6.7)	Common	0	26 (7.8)	Common	1 (0.3)	3 (0.9)	Uncommon	0
Hypopituitarism/ Hypophysitis	5 (1.5)	Common	1 (0.3)	2 (0.6)	Uncommon	1 (0.3)	0	Not known	0
Hypothyroidism	44 (13.3)	Very common	0	26 (7.8)	Common	0	7 (2.1)	Common	0
Thyroiditis	4 (1.2)	Common	0	4 (1.2)	Common	0	1 (0.3)	Uncommon	0
Type 1 diabetes mellitus	1 (0.3)	Uncommon	1 (0.3)	1 (0.3)	Uncommon	1 (0.3)	0	Not known	0
Gastrointestinal disorders									
Abdominal pain	24 (7.3)	Common	0	31 (9.3)	Common	2 (0.6)	18 (5.4)	Common	0
Amylase increased [d]	28 (8.5)	Common	12 (3.6)	24 (7.2)	Common	8 (2.4)	16 (4.8)	Common	6 (1.8)
Colitis	18 (5.5)	Common	7 (2.1)	4 (1.2)	Common	1 (0.3)	1 (0.3)	Uncommon	1 (0.3)
Constipation [c]	63 (19.1)	Very common	0	72 (21.6)	Very common	0	79 (23.7)	Very common	2 (0.6)
Diarrhoea	71 (21.5)	Very common	5 (1.5)	60 (18.0)	Very common	5 (1.5)	51 (15.3)	Very common	5 (1.5)
Intestinal perforation [d]	0	Not known	0	0	Not known	0	0	Not known	0
Large intestine perforation [d]	0	Not known	0	0	Not known	0	0	Not known	0
Lipase increased [d]	21 (6.4)	Common	13 (3.9)	12 (3.6)	Common	7 (2.1)	7 (2.1)	Common	6 (1.8)
Nausea [c]	137 (41.5)	Very common	6 (1.8)	121 (36.2)	Very common	2 (0.6)	122 (36.6)	Very common	7 (2.1)
Pancreatitis	7 (2.1)	Common	1 (0.3)	4 (1.2)	Common	0	2 (0.6)	Uncommon	0
Stomatitis [c]	32 (9.7)	Common	0	31 (9.3)	Common	1 (0.3)	20 (6.0)	Common	1 (0.3)
Vomiting [c]	60 (18.2)	Very common	4 (1.2)	52 (15.6)	Very common	4 (1.2)	45 (13.5)	Very common	5 (1.5)
General disorders and administration site conditions									
Fatigue [c]	119 (36.1)	Very common	17 (5.2)	109 (32.6)	Very common	17 (5.1)	106 (31.8)	Very common	15 (4.5)
Oedema peripheral	28 (8.5)	Common	0	23 (6.9)	Common	2 (0.6)	30 (9.0)	Common	0
Pyrexia	53 (16.1)	Very common	0	31 (9.3)	Common	0	23 (6.9)	Common	0

Hepatobiliary disorders									
AST increased/ALT increased	58 (17.6)	Very common	7 (2.1)	52 (15.6)	Very common	10 (3.0)	51 (15.3)	Very common	8 (2.4)
Hepatitis	13 (3.9)	Common	3 (0.9)	7 (2.1)	Common	3 (0.9)	2 (0.6)	Uncommon	0
Infections and infestations									
Dental and oral soft tissue infections	2 (0.6)	Uncommon	1 (0.3)	4 (1.2)	Common	1 (0.3)	3 (0.9)	Uncommon	0
Influenza	11 (3.3)	Common	0	10 (3.0)	Common	1 (0.3)	4 (1.2)	Common	0
Oral candidiasis	8 (2.4)	Common	1 (0.3)	2 (0.6)	Uncommon	0	6 (1.8)	Common	0
Pneumonia	49 (14.8)	Very common	24 (7.3)	34 (10.2)	Very common	16 (4.8)	33 (9.9)	Common	10 (3.0)
Upper respiratory tract infections	51 (15.5)	Very common	2 (0.6)	33 (9.9)	Common	0	29 (8.7)	Common	3 (0.9)
Injury, poisoning and procedural complications									
Infusion related reaction	13 (3.9)	Common	1 (0.3)	7 (2.1)	Common	0	5 (1.5)	Common	0
Metabolism and nutrition disorders									
Decreased appetite [c]	93 (28.2)	Very common	5 (1.5)	72 (1.6)	Very common	2 (0.6)	82 (24.6)	Very common	4 (1.2)
Musculoskeletal and connective tissue disorders									
Myalgia	14 (4.2)	Common	0	15 (4.5)	Common	0	9 (2.7)	Common	0
Myositis	1 (0.3)	Uncommon	1 (0.3)	0	Not known	0	1 (0.3)	Uncommon	0
Polymyositis	1 (0.3)	Uncommon	1 (0.3)	0	Not known	0	0	Not known	0

ADR system organ class/ ADR term	Number (%) of Patients [a]								
	POSEIDON								
	T + D + SoC (N = 330)			D + SoC (N = 334)			SoC (N = 333)		
	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4	Any CTCAE Grade	CIOMS III Category [b]	Max Grade 3 or 4
Nervous system disorders									
Encephalitis	2 (0.6)	Uncommon	2 (0.6)	0	Not known	0	0	Not known	0
Myasthenia gravis	0	Not known	0	0	Not known	0	0	Not known	0
Neuropathy peripheral [e]	21 (6.4)	Common	0	32 (9.6)	Common	1 (0.3)	30 (9.0)	Common	1 (0.3)
Guillain-Barre syndrome	0	Not known	0	0	Not known	0	0	Not known	0
Meningitis	0	Not known	0	0	Not known	0	0	Not known	0
Renal and urinary disorders									
Blood creatinine increased	21 (6.4)	Common	1 (0.3)	12 (3.6)	Common	0	12 (3.6)	Common	0
Dysuria	5 (1.5)	Common	0	7 (2.1)	Common	0	7 (2.1)	Common	0
Nephritis	2 (0.6)	Uncommon	0	3 (0.9)	Uncommon	3 (0.9)	0	Not known	0
Respiratory, thoracic and mediastinal disorders									
Cough/ Productive cough	40 (12.1)	Very common	0	49 (14.7)	Very common	0	28 (8.4)	Common	1 (0.3)
Dysphonia	8 (2.4)	Common	0	8 (2.4)	Common	0	3 (0.9)	Uncommon	0
Interstitial lung disease	2 (0.6)	Uncommon	0	0	Not known	0	1 (0.3)	Uncommon	1 (0.3)
Pneumonitis	14 (4.2)	Common	4 (1.2)	13 (3.9)	Common	4 (1.2)	1 (0.3)	Uncommon	1 (0.3)
Skin and subcutaneous tissue disorders									
Alopecia [c]	33 (10.0)	Very common	0	36 (10.8)	Very common	0	20 (6.0)	Common	0
Dermatitis	2 (0.6)	Uncommon	0	9 (2.7)	Common	0	2 (0.6)	Uncommon	0
Night sweats	2 (0.6)	Uncommon	0	0	Not known	0	1 (0.3)	Uncommon	0
Pemphigoid	1 (0.3)	Uncommon	1 (0.3)	1 (0.3)	Uncommon	1 (0.3)	0	Not known	0
Pruritus	36 (10.9)	Very common	0	30 (9.0)	Common	0	15 (4.5)	Common	0
Rash	85 (25.8)	Very common	5 (1.5)	57 (17.1)	Very common	4 (1.2)	29 (8.7)	Common	2 (0.6)

[a] Number (%) of patients with AEs, sorted in alphabetical order by ADR system organ class and ADR PT.

[b] CIOMS III convention is defined as: (1) very common (≥1/10); (2) common (≥1/100 to < 1/10); (3) uncommon (≥ 1/1,000 to < 1/100); (4) rare (≥ 1/10,000 to < 1/1,000); (5) very rare (< 1/10,000); and (6) not known (cannot be estimated from available data).

[c] Only applies to chemotherapy ADRs in CASPIAN and POSEIDON studies.

[d] Only applies to D + T combination ADRs.

[e] Only applies to chemotherapy ADRs in the POSEIDON study.

A patient can have one or more PTs reported under a given SOC.

Maximum CTCAE grade per patient is considered.

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).

ADR terms are grouped PTs. Grouped term included multiple PTs.

Table 62. Adverse Drug Reactions in the T + D Pan tumor Pool

ADR system organ class/ ADR term	Number (%) of patients [a] T + D Pan-tumor pool (N = 2280)		
	Any CTCAE Grade CIOMS III category [b]		Max CTCAE Grade 3 or 4
Blood and lymphatic system disorders			
Immune thrombocytopenia	0	Not known	0

ADR system organ class/ ADR term	Number (%) of patients [a] T + D Pan-tumor pool (N = 2280) Any CTCAE Grade CIOMS III category [b]		Max CTCAE Grade 3 or 4
Cardiac disorders			
Myocarditis	2 (<0.1)	Rare	2 (<0.1)
Endocrine disorders			
Adrenal insufficiency	33 (1.4)	Common	13 (0.6)
Diabetes insipidus	0	Not known	0
Hyperthyroidism	179 (7.9)	Common	7 (0.3)
Hypopituitarism/Hypophysitis	16 (0.7)	Uncommon	7 (0.3)
Hypothyroidism	268 (11.8)	Very common	5 (0.2)
Thyroiditis	24 (1.1)	Common	1 (<0.1)
Type 1 diabetes mellitus	6 (0.3)	Uncommon	1 (<0.1)
Gastrointestinal disorders			
Abdominal pain	279 (12.2)	Very common	36 (1.6)
Amylase increased [c]	136 (6.0)	Common	57 (2.5)
Colitis	87 (3.8)	Common	46 (2.0)
Diarrhoea	526 (23.1)	Very common	60 (2.6)
Intestinal perforation [c]	2 (<0.1)	Rare	2 (<0.1)
Large intestine perforation [c]	3 (0.1)	Uncommon	2 (<0.1)
Lipase increased [c]	152 (6.7)	Common	100 (4.4)
Pancreatitis	23 (1.0)	Common	11 (0.5)
General disorders and administration site conditions			
Oedema peripheral	211 (9.3)	Common	7 (0.3)
Pyrexia	326 (14.3)	Very common	9 (0.4)
Hepatobiliary disorders			
AST increased/ALT increased	247 (10.8)	Very common	68 (3.0)
Hepatitis	37 (1.6)	Common	29 (1.3)
Infections and infestations			
Dental and oral soft tissue infections	19 (0.8)	Uncommon	1 (<0.1)
Influenza	28 (1.2)	Common	7 (0.3)
Oral candidiasis	41 (1.8)	Common	0
Pneumonia	218 (9.6)	Common	113 (5.0)
Upper respiratory tract infections	216 (9.5)	Common	6 (0.3)
Injury, poisoning and procedural complications			
Infusion related reaction	45 (2.0)	Common	2 (<0.1)
Musculoskeletal and connective tissue disorders			
Myalgia	96 (4.2)	Common	4 (0.2)
Myositis	4 (0.2)	Uncommon	3 (0.1)
Polymyositis	2 (<0.1)	Rare	1 (<0.1)
Nervous system disorders			
Myasthenia gravis	1 (<0.1)	Rare	0
Encephalitis	1 (<0.1)	Rare	0
Guillain-Barre syndrome	1 (<0.1)	Rare	1 (<0.1)
Meningitis	1 (<0.1)	Rare	0
Renal and urinary disorders			
Blood creatinine increased	80 (3.5)	Common	3 (0.1)
Dysuria	28 (1.2)	Common	0
Nephritis	4 (0.2)	Uncommon	1 (<0.1)
Respiratory, thoracic and mediastinal disorders			
Cough/Productive cough	381 (16.7)	Very common	3 (0.1)
Dysphonia	44 (1.9)	Common	0
Interstitial lung disease	20 (0.9)	Uncommon	4 (0.2)
Pneumonitis	92 (4.0)	Common	28 (1.2)
Skin and subcutaneous tissue disorders			
Dermatitis	19 (0.8)	Uncommon	1 (<0.1)
Night sweats	31 (1.4)	Common	0
Pemphigoid	7 (0.3)	Uncommon	1 (<0.1)
Pruritus	424 (18.6)	Very common	9 (0.4)
Rash	490 (21.5)	Very common	18 (0.8)

ADR system organ class/ ADR term	Number (%) of patients [a]	
	T + D Pan-tumor pool (N = 2280)	
	Any CTCAE Grade CIOMS III category [b]	Max CTCAE Grade 3 or 4

[a] Number (%) of patients with AEs, sorted in alphabetical order by ADR system organ class and ADR PT.

[b] The CIOMS III category applies to any CTCAE Grade events. CIOMS III convention and is defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1,000 to < 1/100); (4) rare (≥ 1/10,000 to < 1/1,000); (5) very rare (< 1/10,000); and (6) not known (cannot be estimated from available data).

[c] Only applies to D + T combination ADRs.

Chemotherapy ADRs are not included in this table as they are not relevant to T + D pan-tumor pool.
A patient can have one or more PT reported under a given SOC.
Maximum CTCAE grade per patient is considered.
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).
ADR terms are grouped PTs. Grouped term included multiple PTs.
MedDRA version 23.1.
Urticaria events in the Infusion related reaction ADR term include Urticaria starting on same day or 1 day after latest dose.
Disease progression AEs reported in Study 6 and Study 10 are not included in this summary.
AE, adverse events; ADR, adverse drug reaction; ALT, alanine transaminase; AST, aspartate transaminase; CIOMS, Council for International Organizations of Medical Sciences; D, durvalumab; Max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; SoC, standard of care; T, tremelimumab

Serious adverse event/deaths/other significant events

SAEs:

Table 63. SAEs with incidence ⩾1% SAS POSEIDON and pan-tumour pool

Preferred term	Number (%) of patients [a]		
	POSEIDON		
	T + D + SoC (N = 330)	SoC (N = 333)	T + D Pan-tumor pool (N = 2280)
Any SAE [b]	**146 (44.2)**	**117 (35.1)**	**1020 (44.7)**
Pneumonia	36 (10.9)	16 (4.8)	132 (5.8)
Anaemia	18 (5.5)	21 (6.3)	22 (1.0)
Diarrhoea	8 (2.4)	2 (0.6)	56 (2.5)
Pyrexia	8 (2.4)	1 (0.3)	42 (1.8)
Thrombocytopenia	8 (2.4)	3 (0.9)	4 (0.2)
Febrile neutropenia	7 (2.1)	4 (1.2)	0
Acute kidney injury	6 (1.8)	1 (0.3)	18 (0.8)
Pneumonitis	6 (1.8)	1 (0.3)	45 (2.0)
Colitis	5 (1.5)	0	39 (1.7)
Pulmonary embolism	5 (1.5)	9 (2.7)	34 (1.5)
Sepsis	5 (1.5)	2 (0.6)	21 (0.9)
Cerebrovascular accident	4 (1.2)	1 (0.3)	8 (0.4)
Neutropenia	4 (1.2)	3 (0.9)	2 (<0.1)
Death	3 (0.9)	1 (0.3)	10 (0.4)
Dyspnoea	3 (0.9)	2 (0.6)	42 (1.8)
Hyponatraemia	3 (0.9)	1 (0.3)	18 (0.8)
Dehydration	2 (0.6)	2 (0.6)	23 (1.0)
Enterocolitis	2 (0.6)	0	9 (0.4)
Vomiting	2 (0.6)	0	27 (1.2)
Pleural effusion	0	2 (0.6)	27 (1.2)
Abdominal pain	0	0	24 (1.1)
Back pain	0	0	24 (1.1)

Based on the data presented by the Applicant, the contribution of tremelimumab in the occurrence of SAEs is evident and cannot be disregarded: tremelimumab was involved in 8 of the 14 fatal SAEs.

Deaths:

Table 64. All deaths (full analysis set - POSEIDON)

Category	Number (%) of patients		
	T+D+SoC (N=338)	D+SoC (N=338)	SoC (N=337)
Total number of deaths	251 (74.3)	265 (78.4)	285 (84.6)
Death related to disease under investigation only[a]	202 (59.8)	224 (66.3)	246 (73.0)
Death related to disease under investigation[a] and an AE with outcome of death	17 (5.0)	9 (2.7)	13 (3.9)
AE onset prior to subsequent therapy[b]	15 (4.4)	9 (2.7)	12 (3.6)
AE onset after start of subsequent therapy[c]	2 (0.6)	0	1 (0.3)
AE with outcome of death only	28 (8.3)	26 (7.7)	17 (5.0)
AE onset prior to subsequent therapy[b]	26 (7.7)	26 (7.7)	17 (5.0)
AE onset after start of subsequent therapy[c]	2 (0.6)	0	0
Death after end of safety follow up period and not due to disease under investigation[d]	2 (0.6)	5 (1.5)	6 (1.8)
Unknown reason for death	2 (0.6)	0	3 (0.9)
Other deaths[e]	0	1 (0.3)	0

a Death related to disease under investigation was determined by the investigator.
b Includes adverse events with an onset date, or pre-treatment AEs that increased in severity, on or after the date of first dose and up to and including 90 days following the date of last dose of study treatment or up to the date of initiation of the first subsequent anticancer therapy (whichever occurred first).
c AE start date ≤90 days following the last dose of study treatment and AE start date > the date of initiation of the first subsequent anticancer therapy (whichever occurred first).
d Death not due to disease progression or a treatment emergent AE
e Patients who died and are not captured in the earlier categories. Patient E780804 had a date of death prior to randomization (discovered after randomization). As such this patient is included in the FAS but their death does not fall under any of the other categories.

Table 65. AEs with outcome of death by preferred term (incidence ⩾2 patients) in SAS POSEIDON and pan-tumour pool

Preferred term	Number (%) of patients [a]		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
Patients with any AE with outcome of death	**41 (12.4)**	**30 (9.0)**	**153 (6.7)**
Pneumonia	7 (2.1)	7 (2.1)	14 (0.6)
Sepsis	3 (0.9)	1 (0.3)	7 (0.3)
Septic shock	0	0	6 (0.3)
Febrile neutropenia	1 (0.3)	2 (0.6)	0
Pancytopenia	0	1 (0.3)	0
Cerebrovascular accident	2 (0.6)	1 (0.3)	3 (0.1)
Depressed level of consciousness	0	0	2 (< 0.1)
Ischaemic stroke	1 (0.3)	0	2 (<0.1)
Acute coronary syndrome	1 (0.3)		3 (0.1)
Cardiac arrest	0	0	4 (0.2)
Cardiac failure	2 (0.6)	1 (0.3)	5 (0.2)
Cardiopulmonary failure	2 (0.6)	1 (0.3)	0
Acute respiratory failure	0	0	4 (0.2)
Asphyxia	0	0	2 (< 0.1)

Preferred term	Number (%) of patients [a]		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)	2 (<0.1)
Dyspnoea	1 (0.3)	0	3 (0.1)
Interstitial lung disease	0	0	2 (< 0.1)
Pneumonia aspiration	0	0	4 (0.2)
Pneumonitis	1 (0.3)	0	7 (0.3)
Pulmonary embolism	1 (0.3)	5 (1.5)	10 (0.4)
Pulmonary haemorrhage	0	2 (0.6)	2 (<0.1)
Respiratory failure	0	0	3 (0.1)
Acute kidney injury	2 (0.6)	0	3 (0.1)
Death	3 (0.9)	1 (0.3)	10 (0.4)
Multiple organ dysfunction syndrome	0	0	3 (0.1)
Sudden cardiac death	0	0	3 (0.1)
Sudden death	0	0	5 (0.2)

Laboratory findings

Table 66. Changes in Haematology parameters, SAS POSEIDON and pan-tumour pool

Parameter	n/N (%) of patients					
	POSEIDON				T + D Pan-tumor pool (N = 2280)	
	T + D + SoC (N = 330)		SoC (N = 333)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	120/326 (36.8)	77/326 (23.6)	120/323 (37.2)	81/323 (25.1)	127/2167 (5.9)	110/2167 (5.1)
Leukocytes	166/326 (50.9)	70/326 (21.5)	167/323 (51.7)	59/323 (18.3)	62/2167 (2.9)	19/2167 (0.9)
Lymphocytes (low)	140/326 (42.9)	64/326 (19.6)	117/323 (36.2)	60/323 (18.6)	443/2137 (20.7)	289/2137 (13.5)
Neutrophils	197/326 (60.4)	120/326 (36.8)	186/323 (57.6)	102/323 (31.6)	81/2114 (3.8)	20/2114 (0.9)
Platelets	61/326 (18.7)	35/326 (10.7)	54/323 (16.7)	38/323 (11.8)	47/2161 (2.2)	24/2161 (1.1)

Table 67. Changes in chemistry parameters, SAS POSEIDON and pan-tumour pool

Parameter	n/N (%) of patients					
	POSEIDON				T + D Pan-tumor pool (N = 2280)	
	T + D + SoC (N = 330)		SoC (N = 333)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
ALT	45/324 (13.9)	20/324 (6.2)	37/321 (11.5)	15/321 (4.7)	164/2158 (7.6)	93/2158 (4.3)
Albumin	45/324 (13.9)	6/324 (1.9)	29/ 319 (9.1)	3/319 (0.9)	310/2146 (14.4)	36/2146 (1.7)
Alkaline phosphatase	16/323 (5.0)	11/323 (3.4)	4/ 321 (1.2)	4/321 (1.2)	99/2151 (4.6)	77/2151 (3.6)
Amylase	54/307 (17.6)	29/307 (9.4)	31/308 (10.1)	18/308 (5.8)	140/1460 (9.6)	90/1460 (6.2)
AST	31/324 (9.6)	17/324 (5.2)	23/321 (7.2)	7/321 (2.2)	145/2151 (6.7)	101/2151 (4.7)

Parameter	n/N (%) of patients					
	POSEIDON				T + D Pan-tumor pool (N = 2280)	
	T + D + SoC (N = 330)		SoC (N = 333)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Corrected calcium	17/317 (5.4)	6/317 (1.9)	18/316 (5.7)	5/316 (1.6)	122/1997 (6.1)	66/1997 (3.3)
Low	10/317 (3.2)	3/317 (0.9)	11/316 (3.5)	3/316 (0.9)	46/1997 (2.3)	15/1997 (0.8)
High	7/317 (2.2)	3/317 (0.9)	7/316 (2.2)	2/316 (0.6)	78/1997 (3.9)	52/1997 (2.6)
Creatinine	87/324 (26.9)	13/324 (4.0)	61/321 (19.0)	6/321 (1.9)	160/2039 (7.8)	15/2039 (0.7)
GGT	3/45 (6.7)	1/45 (2.2)	4/43 (9.3)	2/43 (4.7)	236/1935 (12.2)	231/1935 (11.9)
Glucose	59/322 (18.3)	20/322 (6.2)	47/319 (14.7)	12/319 (3.8)	240/2020 (11.9)	114/2020 (5.6)
Low	8/322 (2.5)	0/322	4/319 (1.3)	3/319 (0.9)	29/2020 (1.4)	7/2020 (0.3)
High	55/322 (17.1)	20/322 (6.2)	43/319 (13.5)	10/319 (3.1)	215/2020 (10.6)	108/2020 (5.3)
Lipase	59/301 (19.6)	41/301 (13.6)	24/291 (8.2)	15/291 (5.2)	212/1445 (14.7)	176/1445 (12.2)
Magnesium	3/49 (6.1)	2/49 (4.1)	1/48 (2.1)	0/48	42/1955 (2.1)	37/1955 (1.9)
Low	3/49 (6.1)	2/49 (4.1)	1/48 (2.1)	0/48	22/1955 (1.1)	17/1955 (0.9)
High	0/49	0/49	0/48	0/48	22/1955 (1.1)	22/1955 (1.1)
Potassium	56/323 (17.3)	28/ 323 (8.7)	36/ 320 (11.3)	18/320 (5.6)	183/2037 (9.0)	107/2037 (5.3)
Low	21/323 (6.5)	21/323 (6.5)	8/320 (2.5)	9/320 (2.8)	69/2037 (3.4)	70/2037 (3.4)
High	36/323 (11.1)	7/323 (2.2)	29/320 (9.1)	9/320 (2.8)	114/2037 (5.6)	38/2037 (1.9)
Sodium	43/323 (13.3)	41/323 (12.7)	35/319 (11.0)	35/319 (11.0)	238/2039 (11.7)	219/2039 (10.7)
Low	40/323 (12.4)	41/323 (12.7)	34/319 (10.7)	35/319 (11.0)	209/2039 (10.3)	211/2039 (10.3)
High	4/323 (1.2)	0/323	1/319 (0.3)	0/319	30/2039 (1.5)	8/2039 (0.4)
Total bilirubin	13/323 (4.0)	3/323 (0.9)	5/321 (1.6)	1/321 (0.3)	90/2154 (4.2)	37/2154 (1.7)

Table 68. Abnormal thyroid tests, SAS POSEIDON and pan-tumour pool

Category	Number (%) of patients		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
On-treatment elevated TSH > ULN	103 (31.2)	80 (24.0)	727 (31.9)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline	77 (23.3)	45 (13.5)	455 (20.0)
with at least one T_3 free/T_4 free < LLN	61 (18.5)	23 (6.9)	454 (19.9)
with all T_3 free/T_4 free ≥ LLN	35 (10.6)	44 (13.2)	223 (9.8)
with all T_3 free/T_4 free missing	7 (2.1)	13 (3.9)	50 (2.2)
On-treatment low TSH < LLN	115 (34.8)	50 (15.0)	622 (27.3)
On-treatment low TSH < LLN with TSH ≥ LLN at baseline	102 (30.9)	40 (12.0)	530 (23.2)
with at least one T_3 free/T4 free > ULN	41 (12.4)	7 (2.1)	301 (13.2)
with all T_3 free/T_4 free ≤ ULN	61 (18.5)	37 (11.1)	274 (12.0)
With all T_3 free/T_4 free missing	13 (3.9)	6 (1.8)	47 (2.1)
Number of patients with at least one baseline and post-baseline TSH result	310 (93.9)	298 (89.5)	2070 (90.8)

Category	Number (%) of patients		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
On-treatment elevated TSH > ULN and above baseline	96 (29.1)	68 (20.4)	643 (28.2)
On-treatment decreased TSH < LLN and below baseline	113 (34.2)	47 (14.1)	585 (25.7)

Safety in special populations

Age:

Table 69. AEs by category and age group, SAS POSEIDON and pan-tumour pool

AEs by Category	Age Group	Number (%) of Patients a				
		POSEIDON		T + D + Chemo pool	Chemo pool	T + D Pan-tumor pool
		T + D + SoC (N1=29) (N2=158) (N3=108) (N4=35)	SoC (N1=31) (N2=143) (N3=120) (N4=39)	(N1=45) (N2=295) (N3=198) (N4=58)	(N1=51) (N2=279) (N3=209) (N4=60)	(N1=259) (N2=1041) (N3=774) (N4=206)
Patients with AE	<50	26 (89.7)	30 (96.8)	42 (93.3)	49 (96.1)	245 (94.6)
	⩾50 - <65	155 (98.1)	136 (95.1)	291 (98.6)	268 (96.1)	984 (94.5)
	⩾65 - <75	105 (97.2)	115 (95.8)	194 (98.0)	201 (96.2)	733 (94.7)
	⩾75	35 (100.0)	39 (100.0)	58 (100.0)	60 (100.0)	198 (96.1)
Patients with SAEs b	<50	11 (37.9)	3 (9.7)	15 (33.3)	7 (13.7)	97 (37.5)
	⩾50 - <65	57 (36.1)	45 (31.5)	114 (38.6)	90 (32.3)	451 (43.3)
	⩾65 - <75	52 (48.1)	47 (39.2)	98 (49.5)	85 (40.7)	360 (46.5)
	⩾75	26 (74.3)	22 (56.4)	40 (69.0)	32 (53.3)	112 (54.4)
Patients with any AE of CTCAE Grade 3 or Grade 4 c	< 50	13 (44.8)	13 (41.9)	22 (48.9)	24 (47.1)	135 (52.1)
	⩾50 - <65	97 (61.4)	76 (53.1)	197 (66.8)	156 (55.9)	544 (52.3)
	⩾65 - <75	68 (63.0)	75 (62.5)	131 (66.2)	136 (65.1)	405 (52.3)
	⩾75	25 (71.4)	25 (64.1)	40 (69.0)	40 (66.7)	130 (63.1)
Patients with any AE leading to outcome of death	<50	1 (3.4)	2 (6.5)	1 (2.2)	2 (3.9)	10 (3.9)
	⩾50 - <65	11 (7.0)	10 (7.0)	18 (6.1)	16 (5.7)	67 (6.4)
	⩾65 - <75	15 (13.9)	12 (10.0)	30 (15.2)	19 (9.1)	52 (6.7)
	⩾75	14 (40.0)	6 (15.4)	19 (32.8)	8 (13.3)	24 (11.7)
Patients with any AE leading to discontinuation of any study treatment	<50	1 (3.4)	4 (12.9)	5 (11.1)	5 (9.8)	31 (12.0)
	⩾50 - <65	26 (16.5)	18 (12.6)	47 (15.9)	26 (9.3)	149 (14.3)
	⩾65 - <75	29 (26.9)	20 (16.7)	53 (26.8)	32 (15.3)	136 (17.6)
	⩾75	17 (48.6)	9 (23.1)	25 (43.1)	13 (21.7)	51 (24.8)

a Percentages are calculated from N1, N2, N3, and N4 for <50 years, ≥50 - <65 years, ≥65 - <75 years, and ≥75 years, respectively. Number of patients with events divided by the total number of patients in the age group, multiplied by 100.
b Seriousness, as assessed by the Investigator. An Ae with missing seriousness is considered serious.
N1 = Total number of <50 years patients, N2 = Total number of ≥50 - <65 years patients, N3 = Total number of ≥65 - <75 years patients, N4 = Total number of ≥ 75 years patients.
Patients with multiple AEs are counted once for the PT.

Table 70. Adverse Events by Age Group in POSEIDON T + D + SoC Arm (Safety Analysis Set)

AE Group	Number (%) of Patients [a]			
	Age < 65 n = 187	Age 65-74 n = 108	Age 75-84 n = 33	Age ≥ 85 n = 2
Total AEs	181 (96.8)	105 (97.2)	33 (100.0)	2 (100.0)
Total serious AEs	68 (36.4)	52 (48.1)	24 (72.7)	2 (100.0)
Fatal	12 (6.4)	15 (13.9)	12 (36.4)	2 (100.0)
Hospitalisation/prolong existing hospitalisation	60 (32.1)	48 (44.4)	21 (63.6)	1 (50.0)
Life-threatening	14 (7.5)	17 (15.7)	6 (18.2)	1 (50.0)
Disability/incapacity	5 (2.7)	2 (1.9)	1 (3.0)	0
Other (medically significant)	25 (13.4)	18 (16.7)	7 (21.2)	1 (50.0)
AE leading to drop-out	27 (14.4)	29 (26.9)	16 (48.5)	1 (50.0)
Psychiatric disorders	25 (13.4)	21 (19.4)	5 (15.2)	0
Nervous system disorders	62 (33.2)	44 (40.7)	10 (30.3)	1 (50.0)

	Number (%) of Patients [a]			
AE Group	Age < 65 n = 187	Age 65-74 n = 108	Age 75-84 n = 33	Age ≥ 85 n = 2
Accident and injuries	13 (7.0)	10 (9.3)	5 (15.2)	0
Cardiac disorders	16 (8.6)	12 (11.1)	5 (15.2)	0
Vascular disorders	21 (11.2)	22 (20.4)	7 (21.2)	0
Central nervous system vascular disorders	9 (4.8)	8 (7.4)	0	1 (50.0)
Infections and infestations	88 (47.1)	54 (50.0)	17 (51.5)	2 (100.0)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	19 (10.2)	18 (16.7)	8 (24.2)	0
Other AEs [b]				
Lipase increased	11 (5.9)	5 (4.6)	4 (12.1)	1 (50.0)
Amylase increased	16 (8.6)	8 (7.4)	4 (12.1)	0
Back pain	15 (8.0)	6 (5.6)	4 (12.1)	0
Dehydration	3 (1.6)	6 (5.6)	4 (12.1)	0
Dyspepsia	6 (3.2)	2 (1.9)	4 (12.1)	0
Mucosal inflammation	6 (3.2)	7 (6.5)	4 (12.1)	0
Pain in extremity	6 (3.2)	7 (6.5)	4 (12.1)	0

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.
AEs by PTs with a ≥ 3% higher incidence in patients ≥ 75 years compared with patients < 65 years or 65-74 years and occurring in ≥ 10% of patients that are ≥ 75 years..
Includes AEs with an onset date or pre-treatment AEs that increase in severity on or after the date of first dose and up to and including the earlier of 90 days following the date of last dose of study treatment or the date of initiation of the first subsequent therapy (whichever occurred first).

Sex:

Table 71. Adverse Events by Category and Sex (Safety Analysis Set)

AEs by Category	Sex	Number (%) of Patients a				
		POSEIDON				
		T + D + SoC (N1=264) (N2=66)	SoC (N1=247) (N2=86)	T + D + Chemo pool (N1=464) (N2=132)	Chemo pool (N1=428) (N2=171)	T + D Pan-tumor pool (N1=1585) (N2=695)
Patients with any AE	Male	256 (97.0)	235 (95.1)	454 (97.8)	410 (95.8)	1497 (94.4)
	Female	65 (98.5)	85 (98.8)	131 (99.2)	168 (98.2)	663 (95.4)
Patients with any SAE b	Male	114 (43.2)	92 (37.2)	203 (43.8)	151 (35.3)	706 (44.5)
	Female	32 (48.5)	25 (29.1)	64 (48.5)	63 (36.8)	314 (45.2)
Patients with any AE of CTCAE G3 or G4 c	Male	158 (59.8)	138 (55.9)	295 (63.6)	253 (59.1)	815 (51.4)
	Female	45 (68.2)	51 (59.3)	95 (72.0)	103 (60.2)	399 (57.4)
Patients with any AE leading to outcome of death	Male	35 (13.3)	27 (10.9)	59 (12.7)	37 (8.6)	122 (7.7)
	Female	6 (9.1)	3 (3.5)	9 (6.8)	8 (4.7)	31 (4.5)
Patients with any AE leading to discontinuation of any study treatment	Male	58 (22.0)	43 (17.4)	97 (20.9)	59 (13.8)	253 (16.0)
	Female	15 (22.7)	8 (9.3)	33 (25.0)	17 (9.9)	114 (16.4)

Percentages are calculated from N1 and N2 for male and female, respectively. Number of patients with events divided by the total number of patients in the sex group, multiplied by 100.
Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.

Weight quartiles:

Table 72: Treatment-emergent Adverse Events with Maximum Grade 3 or 4 – Incidence ≥ 5% of Patients in any Weight Group (Safety Analysis Set)

Preferred term	Weight group [b]	Number (%) of patients [a]		
		T + D + SoC (N1 = 68) (N2 = 87) (N3 = 77) (N4 = 95)	D + SoC (N1 = 84) (N2 = 82) (N3 = 80) (N4 = 88)	SoC (N1 = 85) (N2 = 90) (N3 = 83) (N4 = 75)
Any AE of maximum CTCAE grade 3 or 4	< Q1	45 (66.2)	51 (60.7)	44 (51.8)
	≥ Q1 to < Q2	43 (49.4)	42 (51.2)	45 (50.0)
	≥ Q2 to < Q3	43 (55.8)	39 (48.8)	40 (48.2)
	≥ Q3	45 (47.4)	51 (58.0)	43 (57.3)
Alanine aminotransferase increased	< Q1	2 (2.9)	1 (1.2)	2 (2.4)
	≥ Q1 to < Q2	1 (1.1)	0	0
	≥ Q2 to < Q3	0	3 (3.8)	3 (3.6)
	≥ Q3	2 (2.1)	5 (5.7)	2 (2.7)
Amylase increased	< Q1	4 (5.9)	4 (4.8)	1 (1.2)
	≥ Q1 to < Q2	4 (4.6)	2 (2.4)	1 (1.1)
	≥ Q2 to < Q3	1 (1.3)	1 (1.3)	3 (3.6)
	≥ Q3	3 (3.2)	1 (1.1)	1 (1.3)
Anaemia	< Q1	16 (23.5)	20 (23.8)	25 (29.4)
	≥ Q1 to < Q2	18 (20.7)	16 (19.5)	20 (22.2)
	≥ Q2 to < Q3	19 (24.7)	11 (13.8)	15 (18.1)
	≥ Q3	14 (14.7)	12 (13.6)	15 (20.0)
Asthenia	< Q1	2 (2.9)	2 (2.4)	2 (2.4)
	≥ Q1 to < Q2	4 (4.6)	1 (1.2)	2 (2.2)
	≥ Q2 to < Q3	2 (2.6)	0	0
	≥ Q3	4 (4.2)	2 (2.3)	4 (5.3)
Fatigue	< Q1	1 (1.5)	4 (4.8)	3 (3.5)
	≥ Q1 to < Q2	3 (3.4)	5 (6.1)	2 (2.2)
	≥ Q2 to < Q3	2 (2.6)	0	2 (2.4)
	≥ Q3	2 (2.1)	3 (3.4)	2 (2.7)
Febrile neutropenia	< Q1	4 (5.9)	2 (2.4)	1 (1.2)
	≥ Q1 to < Q2	1 (1.1)	2 (2.4)	0
	≥ Q2 to < Q3	1 (1.3)	1 (1.3)	1 (1.2)
	≥ Q3	1 (1.1)	1 (1.1)	0
Hypertension	< Q1	4 (5.9)	1 (1.2)	0
	≥ Q1 to < Q2	0	0	2 (2.2)
	≥ Q2 to < Q3	1 (1.3)	0	0
	≥ Q3	3 (3.2)	1 (1.1)	0
Hypokalaemia	< Q1	4 (5.9)	4 (4.8)	3 (3.5)
	≥ Q1 to < Q2	1 (1.1)	1 (1.2)	1 (1.1)
	≥ Q2 to < Q3	1 (1.3)	0	2 (2.4)
	≥ Q3	0	0	0
Hyponatraemia	< Q1	2 (2.9)	5 (6.0)	4 (4.7)
	≥ Q1 to < Q2	3 (3.4)	0	3 (3.3)
	≥ Q2 to < Q3	1 (1.3)	1 (1.3)	4 (4.8)
	≥ Q3	0	1 (1.1)	1 (1.3)
Leukopenia	< Q1	1 (1.5)	1 (1.2)	6 (7.1)
	≥ Q1 to < Q2	2 (2.3)	4 (4.9)	2 (2.2)
	≥ Q2 to < Q3	3 (3.9)	1 (1.3)	2 (2.4)
	≥ Q3	3 (3.2)	2 (2.3)	2 (2.7)
Lipase increased	< Q1	3 (4.4)	1 (1.2)	0
	≥ Q1 to < Q2	9 (10.3)	2 (2.4)	4 (4.4)
	≥ Q2 to < Q3	0	2 (2.5)	0
	≥ Q3	1 (1.1)	2 (2.3)	2 (2.7)
Neutropenia	< Q1	9 (13.2)	5 (6.0)	12 (14.1)
	≥ Q1 to < Q2	15 (17.2)	15 (18.3)	10 (11.1)
	≥ Q2 to < Q3	14 (18.2)	9 (11.3)	9 (10.8)
	≥ Q3	18 (18.9)	17 (19.3)	10 (13.3)
Neutrophil count decreased	< Q1	5 (7.4)	10 (11.9)	8 (9.4)
	≥ Q1 to < Q2	6 (6.9)	4 (4.9)	8 (8.9)
	≥ Q2 to < Q3	10 (13.0)	5 (6.3)	6 (7.2)
	≥ Q3	4 (4.2)	6 (6.8)	3 (4.0)
Platelet count decreased	< Q1	3 (4.4)	4 (4.8)	5 (5.9)
	≥ Q1 to < Q2	2 (2.3)	3 (3.7)	3 (3.3)
	≥ Q2 to < Q3	2 (2.6)	3 (3.8)	3 (3.6)

Preferred term	Weight group [b]	Number (%) of patients [a]		
		T + D + SoC (N1 = 68) (N2 = 87) (N3 = 77) (N4 = 95)	**D + SoC (N1 = 84) (N2 = 82) (N3 = 80) (N4 = 88)**	**SoC (N1 = 85) (N2 = 90) (N3 = 83) (N4 = 75)**
	≥ Q3	2 (2.1)	1 (1.1)	6 (8.0)
Pneumonia	< Q1	8 (11.8)	7 (8.3)	4 (4.7)
	≥ Q1 to < Q2	7 (8.0)	3 (3.7)	3 (3.3)
	≥ Q2 to < Q3	4 (5.2)	3 (3.8)	1 (1.2)
	≥ Q3	4 (4.2)	2 (2.3)	2 (2.7)
Thrombocytopenia	< Q1	4 (5.9)	1 (1.2)	7 (8.2)
	≥ Q1 to < Q2	4 (4.6)	8 (9.8)	3 (3.3)
	≥ Q2 to < Q3	3 (3.9)	3 (3.8)	3 (3.6)
	≥ Q3	7 (7.4)	4 (4.5)	4 (5.3)
White blood cell count decreased	< Q1	3 (4.4)	5 (6.0)	4 (4.7)
	≥ Q1 to < Q2	2 (2.3)	2 (2.4)	1 (1.1)
	≥ Q2 to < Q3	3 (3.9)	1 (1.3)	3 (3.6)
	≥ Q3	1 (1.1)	2 (2.3)	1 (1.3)

[s] Patients are counted once for each preferred term. Number (%) of patients with AEs, sorted by alphabetical order for preferred term. Each patient has only been represented with the maximum reported CTCAE grade at either the start of AE or after increasing in severity for each system organ class/preferred term.

[t] The boundaries for the weight quartiles are derived from the overall POSEIDON population with known baseline weight (n = 1009) and are Q1 = 57.0 kg, Q2 = 67.2 kg and Q3 = 77.0 kg, respectively.

Percentages calculated from number of patients in the safety analysis set in that weight group in that treatment group.

Race:

Table 73. Adverse Events by Category and Race (Safety Analysis Set)

AEs by Category	Race	Number (%) of Patients a				
		POSEIDON		T + D + Chemo pool (N1=144) (N2=452)	Chemo pool (N1=167) (N2=432)	T + D Pan-tumor pool (N1=581) (N2=1699)
		T + D + SoC (N1=97) (N2=233)	SoC (N1=127) (N2=206)			
Patients with any AE	Asian	96 (99.0)	123 (96.9)	143 (99.3)	163 (97.6)	553 (95.2)
	Non-Asian	225 (96.6)	197 (95.6)	442 (97.8)	415 (96.1)	1607 (94.6)
Patients with any SAE b	Asian	56 (57.7)	53 (41.7)	84 (58.3)	73 (43.7)	270 (46.5)
	Non-Asian	90 (38.6)	64 (31.1)	183 (40.5)	141 (32.6)	750 (44.1)
Patients with any AE of CTCAE G3 or G4 c	Asian	72 (74.2)	77 (60.6)	108 (75.0)	108 (64.7)	289 (49.7)
	Non-Asian	131 (56.2)	112 (54.4)	282 (62.4)	248 (57.4)	925 (54.4)
Patients with any AE leading to outcome of death	Asian	13 (13.4)	9 (7.1)	21 (14.6)	10 (6.0)	38 (6.5)
	Non-Asian	28 (12.0)	21 (10.2)	47 (10.4)	35 (8.1)	115 (6.8)
Patients with any AE leading to discontinuation of any study treatment	Asian	18 (18.6)	16 (12.6)	35 (24.3)	20 (12.0)	92 (15.8)
	Non-Asian	55 (23.6)	35 (17.0)	95 (21.0)	56 (13.0)	275 (16.2)

Percentages are calculated from N1 and N2 for Asian and Non-Asian, respectively. Number of patients with events divided by the total number of patients in the race group, multiplied by 100.
Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.

Geographic region:

Table 74: Adverse Events by Category and Geographic Region (Safety Analysis Set)

AEs by Category	Geographic Region	Number (%) of Patients a				
		POSEIDON		T + D + Chemo pool (N1=137) (N2=357) (N3=62) (N4=40)	Chemo pool (N1=162) (N2=335) (N3=56) (N4=46)	T + D Pan-tumor pool (N1=547) (N2=1005) (N3=667) (N4=61)
		T + D + SoC (N1=94) (N2=160) (N3=42) (N4=34)	SoC (N1=123) (N2=130) (N3=39) (N4=41)			
Patients with any AE	Asia	93 (8.9)	119 (96.7)	136 (99.3)	158 (97.5)	519 (94.9)
	Europe	153 (95.6)	123 (94.6)	348 (97.5)	320 (95.5)	928 (92.3)
	North America	41 (97.6)	37 (94.9)	61 (98.4)	54 (96.4)	655 (98.2)
	South America	34 (100.0)	41 (100.0)	40 (100.0)	46 (100.0)	58 (95.1)
Patients with any SAE b	Asia	54 (57.4)	50 (40.7)	81 (59.1)	69 (42.6)	250 (45.7)
	Europe	60 (37.5)	47 (36.2)	141 (39.5)	114 (34.0)	410 (40.8)
	North America	18 (42.9)	10 (25.6)	27 (43.5)	18 (32.1)	331 (49.6)
	South America	14 (41.2)	10 (24.4)	18 (45.0)	13 (28.3)	29 (47.5)
Patients with any AE of CTCAE G3 or G4 c	Asia	70 (74.5)	74 (60.2)	105 (76.6)	104 (64.2)	265 (48.4)
	Europe	85 (53.1)	78 (60.0)	216 (60.5)	199 (59.4)	492 (49.0)
	North America	24 (57.1)	15 (38.5)	41 (66.1)	27 (48.2)	425 (63.7)
	South America	24 (70.6)	22 (53.7)	28 (70.0)	26 (56.5)	32 (52.5)
Patients with any AE leading to outcome of death	Asia	11 (11.7)	9 (7.3)	19 (13.9)	9 (5.6)	36 (6.6)
	Europe	21 (13.1)	17 (13.1)	37 (10.4)	30 (9.0)	92 (9.2)
	North America	5 (11.9)	2 (5.1)	7 (11.3)	4 (7.1)	15 (2.2)
	South America	4 (11.8)	2 (4.9)	5 (12.5)	2 (4.3)	10 (16.4)
Patients with any AE leading to discontinuation of any study treatment	Asia	16 (17.0)	16 (13.0))	32 (23.4)	19 (11.7)	83 (15.2)
	Europe	37 (23.1)	24 (18.5)	73 (20.4)	45 (13.4)	180 (17.9)
	North America	13 (31.0)	4 (10.3)	16 (25.8)	5 (8.9)	93 (13.9)
	South America	7 (20.6)	7 (17.1)	9 (22.5)	7 (15.2)	11 (18.0)

Percentages are calculated from N1, N2, N3, and N4 for Asia, Europe, North America, and South America, respectively. Number of patients with events divided by the total number of patients in the geographic region group, multiplied by 100.
Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.

ECOG performance status:

Table 75. Adverse Events by Category and ECOG/WHO Performance Status (Safety Analysis Set)

AEs by Category	Baseline ECOG/WHO Performance Status	Number (%) of Patients a				
		POSEIDON		T + D + Chemo pool (N1=215) (N2=381)	Chemo pool (N1=206) (N2=393)	T + D Pan-tumor pool (N1=825) (N2=1455)
		T + D + SoC (N1=108) (N2=222)	SoC (N1=117) (N2=216)			
Patients with any AE	0	104 (96.3)	114 (97.4)	211 (98.1)	199 (96.6)	791 (95.9)
	≥1	217 (97.7)	206 (95.4)	374 (98.2)	379 (96.4)	1369 (94.1)
Patients with any SAE b	0	43 (39.8)	39 (33.3)	91 (42.3)	72 (35.0)	327 (39.6)
	≥1	103 (46.4)	78 (36.1)	176 (46.2)	142 (36.1)	693 (47.6)
Patients with any AE of CTCAE G3 or G4 c	0	60 (55.6)	58 (49.6)	136 (63.3)	107 (51.9)	406 (49.2)
	≥1	143 (64.4)	131 (60.6)	254 (66.7)	249 (63.4)	808 (55.5)
Patients with any AE leading to outcome of death	0	10 (9.3)	11 (9.4)	19 (8.8)	14 (6.8)	39 (4.7)
	≥1	31 (14.0)	19 (8.8)	49 (12.9)	31 (7.9)	114 (7.8)
Patients with any AE leading to discontinuation of any study treatment	0	23 (21.3)	21 (17.9)	48 (22.3)	24 (11.7)	138 (16.7)
	≥1	50 (22.5)	30 (13.9)	82 (21.5)	52 (13.2)	229 (15.7)

Percentages are calculated from N1 and N2, for baseline ECOG/WHO Performance Status=0 and baseline ECOG/WHO Performance Status≥1, respectively. Number of patients with events divided by the total number of patients in the baseline ECOG/WHO Performance Status group, multiplied by 100.
Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.

Immunological events

POSEIDON: Of the 278 tremelimumab ADA-evaluable patients in the T + D + SoC arm, 44 (15.8%) tested positive for tremelimumab ADA at any visit. Of the 286 durvalumab evaluable patients in the same arm, 42 (14.7%) tested positive for durvalumab at any visit. The overall safety and tolerability profile of patients with ADAs was similar to those without ADAs.

T + D pan-tumour pool: Of the 1337 tremelimumab ADA-evaluable patients, 171 (12.8%) tested positive for tremelimumab at any visit. Of the 1379 durvalumab-evaluable patients, 86 (6.2%) tested positive for durvalumab at any visit.

Safety related to drug-drug interactions and other interactions

Durvalumab and tremelimumab are immunoglobulins, therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

Table 76: AEs leading to discontinuation of any study treatment in ⩾2 patients, SAS POSEIDON and pan-tumour pool

Preferred term	Number (%) of patients [a]		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 333)	SoC (N = 330)	
Any AE leading to discontinuation of any study treatment [b]	**73 (22.1)**	**51 (15.3)**	**367 (16.1)**
Pneumonia	8 (2.4)	7 (2.1)	9 (0.4)
Anaemia	5 (1.5)	4 (1.2)	1 (<0.1)
Acute kidney injury	4 (1.2)	1 (0.3)	4 (0.2)
Blood creatinine increased	4 (1.2)	0	1 (<0.1)
Pneumonitis	3 (0.9)	1 (0.3)	35 (1.5)
Sepsis	3 (0.9)	0	6 (0.3)
Pulmonary embolism	2 (0.6)	4 (1.2)	6 (0.3)
Colitis	2 (0.6)	0	23 (1.0)
Diarrhoea	2 (0.6)	0	26 (1.1)
Nausea	2 (0.6)	1 (0.3)	2 (<0.1)
Drug-induced liver injury	2 (0.6)	0	5 (0.2)
Autoimmune nephritis	2 (0.6)	0	0
Fatigue	2 (0.6)	1 (0.3)	5 (0.2)
Neutrophil count decreased	2 (0.6)	1 (0.3)	0

a Number (%) of patients with an AE leading to discontinuation of any study treatment, sorted by international order for SOC and alphabetically for PT.
b Action taken, study treatment permanently discontinued.
Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.

Table 77: AEs leading to discontinuation of tremelimumab or durvalumab in ⩾2 patients, SAS POSEIDON (Arm 1) and pan-tumour pool.

Preferred term	Number (%) of patients [a]	
	POSEIDON	T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	
Any AE leading to discontinuation of tremelimumab or durvalumab [b]	**57 (17.3)**	**367 (16.1)**
Pneumonia	7 (2.1)	9 (0.4)
Anaemia	3 (0.9)	1 (<0.1)
Acute kidney injury	3 (0.9)	4 (0.2)
Blood creatinine increased	3 (0.9)	1 (<0.1)
Pneumonitis	3 (0.9)	35 (1.5)
Sepsis	3 (0.9)	6 (0.3)
Pulmonary embolism	2 (0.6)	6 (0.3)
Colitis	2 (0.6)	23 (1.0)

Preferred term	Number (%) of patients [a]	
	POSEIDON	
	T + D + SoC (N = 330)	T + D Pan-tumor pool (N = 2280)
Drug-induced liver injury	2 (0.6)	5 (0.2)
Autoimmune nephritis	2 (0.6)	0

a Number (%) of patients with an AE leading to discontinuation of any study treatment, sorted by international order for SOC and alphabetically for PT.
b Action taken, study treatment permanently discontinued.
Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.

Post marketing experience

Durvalumab (IMFINZI) was first approved by the US FDA on 01 May 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

IMFINZI was further approved by the US FDA on 16 February 2018 for the treatment of patients with unresectable Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. On 21 September 2018, IMFINZI was approved in the EU for the treatment of patients with locally advanced unresectable NSCLC in adults whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2021, IMFINZI for the treatment of Stage III NSCLC has been approved in over 70 countries (including EU countries).

IMFINZI was first approved for the first-line treatment of patients with ES-SCLC in combination with etoposide and either carboplatin or cisplatin in Singapore on 28 February 2020. On 27 March 2020, IMFINZI was additionally approved in the US for the indication cited above. As of 12 July 2021, IMFINZI has been approved in over 53 countries for ES-SCLC (including EU countries).

In February 2021, the US supplemental BLA for IMFINZI has been voluntarily withdrawn for the locally-advanced or metastatic urothelial carcinoma indication, following consultation with the FDA; however, this was not due to any safety concerns, new safety data and the benefit/risk profile in this setting remains consistent per historical evaluation of provided clinical data.

The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) since launch to 30 June 2021 has been estimated to be 52006 patient-years. No new safety concern was identified based on the post-marketing safety reports.

2.5.1. Discussion on clinical safety

Safety results were provided for all three arms of POSEIDON (T+D+SoC, D+SoC and SoC), a "T+D+chemo pool" and a "T+D pan-tumour pool". The supportive pooled data have been used to try to elucidate the contribution of T + D to the safety profile of the proposed combination. The size and content of the presented safety database are deemed sufficient for B/R assessment in the targeted advanced NSCLC population.

Out of the entire pipeline of phase I, II and III trials where tremelimumab was given in monotherapy or in combination at multiple doses/regimens for diverse cancers, the latter was established by selecting 8 trials (2 in solid tumours, 4 NSCLC, 2 HNSCC) in which tremelimumab was administered at 1 mg/kg Q4W x 4 in combination with durvalumab, and 1 single trial (HCC) in which tremelimumab was administered at the flat 75 mg dose. The selection of these trials and exclusion of others (e.g. DANUBE) has been well justified.

The "T+D+chemo pool" included the T+D+SoC chemotherapy arms of POSEIDON (NSCLC) and CASPIAN (ES-SCLC). There is at least another ongoing trial with a T+D+chemo arm (NILE, patients with advanced urothelial carcinoma), but results are not expected until 2023.

Adjudication of imAEs in the POSEIDON study was done programmatically (following a prespecified algorithm, without independent review), which is acceptable.

Exposure: According to the protocol of POSEIDON, tremelimumab as part of the T+D+SoC arm was to be administered for up to 5 doses (C1-4, C6). About 66% of patients in the T+D+SoC arm of POSEIDON received 5 or more tremelimumab doses, roughly comparable to 61% in CASPIAN. Durvalumab was instead to be given along induction chemotherapy (Q3W x 4 cycles), and then maintained Q4W until patients met any of the discontinuation criteria. Durvalumab exposure was appropriate overall (mean of 12 cycles in both experimental arms, more than half patients receiving 8). Chemotherapy could be given for a maximum of 4 cycles in the experimental arms and 6 cycles in the control arm. Across the three arms, the majority of patients received 4 or more cycles of chemotherapy (80% in T+D+SoC, 82% D+SoC and 75% SoC), implying that added immunotherapy did not have an impact on chemotherapy exposure. The distribution of the 5 histology-specific chemotherapy doublets permitted in the study was balanced among the three arms and reflects global trends in physician's choice for this setting.

Overall, exposure parameters of chemotherapy, durvalumab and tremelimumab across the different arms of study POSEIDON are considered appropriate for the assessment of B/R.

AEs occurred in almost all patients across the three arms of POSEIDON. While high-grade (G3/4) AEs occurred in about half of the patients from each arm, G5 AEs were slightly more frequent in the experimental arms (12% in T+D+SoC, 10% D+SoC, 9% SoC), as were SAEs (44%, 40% and 35%, respectively) and AEs leading to discontinuation of any treatment (22%, 24% and 15%, respectively).

25 out the 26 most frequent AEs (incidence ≥10% in any arm) exhibited numerically higher incidence in the T+D+SoC arm as compared to the SoC arm, while the opposite occurred only for neutrophil count decreased. Typical chemotherapy-related AEs (anaemia, nausea, neutropenia, decreased appetite and fatigue) were the five most frequent AEs across the three arms of POSEIDON, with slightly higher incidence in the T+D+SoC arm as compared to the SoC arm. Diarrhoea and rash, with potentially immune-related pathophysiology, were considerably more frequent in the T+D+SoC arm than in the SoC arm (22% and 19% vs. 15% and 7%, respectively). Of note, comparable incidence of both AEs was observed in similar arms from the Checkmate-9LA trial: 20% and 18% vs. 12% and 3% (EPAR WS-1783, p. 125/157), noting that patients only received two chemotherapy cycles in this trial.

The incidence of hypothyroidism, a well-known imAE, was noticeably higher in the T+D+SoC arm (12%) than in the D+SoC (6%) or SoC (1%) arms. In line with these data, the incidence of this AE was 11% across both T+D+chemo and T+D pan-tumour pools.

High-grade (≥G3) AEs: Since the proportions of G3/4 AEs were similar in both T+D+SoC and SoC arms (53% and 52%, respectively), it can be inferred that the higher incidence of G≥3 AEs in the T+D+SoC arm (66% vs. 61% in SoC) is driven by G5 AEs (12.4% and 9%, respectively), which is worrisome. Noting that G5 AEs occurred in 10.2% of the D+SoC arm, it becomes apparent that the addition of tremelimumab increases the risk for toxic death.

The proportions of the most frequent G3/4 AEs were overall similar across the three arms of POSEIDON, highlighting events of chemotherapy-related myelotoxicity, increases in pancreatic and hepatic enzymes and pneumonia. Of note, high-grade imAEs were not among the most frequently observed events in the experimental arms.

AESIs/imAEs:

AESIs included imAEs and infusion-related reactions (IRRs) or hypersensitivity/ anaphylaxis reactions.

The proportion of patients with imAEs was 32% in the T+D+SoC arm, 17% in the D+SoC and 4% in the SoC arm. The distribution of G3/4 imAEs (10%, 6% and 1%, respectively), serious imAEs (9%, 5% and 1%) and imAEs leading to discontinuation (5%, 4% and 1%) were similar. The distribution of specific imAEs in the D+SoC arm is typical for PD-L1 inhibition, with predominance of hypothyroidism (6%), hepatotoxicity (3%), pneumonitis (3%) and dermatitis/rash (2%).

Endocrinopathies, hepatotoxicity and rash/dermatitis are overall more manageable than other imAEs, have less impact in morbidity, and less likelihood for becoming serious events or worsening the overall outcome of a patient. 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 and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

On the other hand, diarrhoea/colitis and pneumonitis might present as challenges since they imply a symptomatic burden and often require hospitalisation. The T+D+SoC arm presented twice as many cases of immune-mediated diarrhoea/colitis than the D+SoC arm (14 vs. 6) and more cases of pneumonitis (14 vs. 9).

Despite an unexpected proportion of pancreatic events was reported as AESIs in the T+D+SoC arm (any-grade 14%, G3/4 1.2%), most of these correspond to laboratorial anomalies (elevations of amylase and lipase, among others).

Of note, there was one death related to multiple imAEs: pancreatitis, hepatitis, myocarditis and nephritis: these events took place shortly after the second treatment cycle. Patients should be monitored for abnormal liver tests prior to and periodically during treatment with Imfinzi in combination with tremelimumab, and as indicated based on clinical evaluation. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment. Patients should also be monitored for signs and symptoms of immune-mediated pancreatitis and myocarditis. Immune mediated hepatitis, nephritis, pancreatitis and myocarditis should be managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

There was one death due to haemophagocytic lymphohistiocytosis in the D+SoC arm.

Given the mechanism of action of tremelimumab in combination with durvalumab, other potential immune mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with tremelimumab in combination with durvalumab: myasthenia gravis, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia and cystitis noninfective. Patients should be monitored for signs and symptoms and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

IRRs and hypersensitivity/anaphylaxis reactions were rare across the three arms of POSEIDON, and nearly all were G1/2: there was only one patient who presented a G3 IRR in the T+D+SoC arm, and nobody presented ≥G4 events. Patients should be monitored for signs and symptoms of IRRs. IRRs should be managed through dose interruption, treatment discontinuation, prophylaxis and appropriate treatment (see sections 4.2 and 4.4 of the SmPC).

ADRs: The most common (> 20%) adverse reactions observed in patients treated with T+D+SoC (n=330) in the POSEIDON trial were anaemia (49.7%), nausea (41.5%), neutropenia (41.2%), fatigue (36.1%), rash (25.8%) thrombocytopenia (24.5%), and diarrhoea (21.5%). The most common (> 2%) Grade ≥ 3 adverse reactions were neutropenia (23.9%), anaemia (20.6%), pneumonia (9.4%),

thrombocytopenia (8.2%), leukopenia (5.5%), fatigue (5.2%), lipase increased (3.9%), amylase increased (3.6%), febrile neutropenia (2.4%), colitis (2.1%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.1%).

SAEs: Pneumonia was the most frequent SAE in the trial, and its incidence in the T+D+SoC arm doubled that of the control arm SoC (11% vs. 5%). As expected, myelotoxic events (anaemia, thrombocytopenia, febrile neutropenia, neutropenia, pancytopenia), likely related to chemotherapy, were also frequent in all three arms of the trial, with comparable incidence among them.

Noting that diarrhoea and colitis are important identified risks of anti-CTLA-4 agent ipilimumab, it is of no surprise that the number of patients with serious diarrhoea was higher in the T+D+SoC arm (8 patients), as compared to the other two arms (1 each) of the pivotal trial, pointing out the potential pathophysiologic role of CTLA-4 block in the development of serious immune-mediated diarrhoea/colitis. To support this hypothesis, the incidence of this SAE was nearly identical across the T+D+SoC arm (2.4%), and the T+D+chemo and T+D pools (2.5% in each). Data for colitis, slightly less prevalent, mimics this pattern. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Serious pneumonitis, with a likely immune-mediated background –known imAE from durvalumab– occurred almost exclusively in the experimental arms (6 cases in T+D+SoC, 5 in D+SoC, 1 in SoC). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed through dose interruption, treatment discontinuation and corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Deaths: Regardless of causality, there were 41 AEs leading to death in the T+D+SoC arm, 34 in the D+SoC arm and 30 in the SoC arm. The most frequent category (system organ class) of AEs leading to death across all three arms of POSEIDON was infections and infestations (15, 8 and 9, respectively), with 7 events of fatal pneumonia in each arm (although there was another event of fatal respiratory tract infection in the T+D+SoC arm). Cardiac disorders followed in frequency as AEs with outcome of death, again with almost twice as many occurrences in the T+D+SoC arm, as compared to the other two arms: 8, 4 and 5, respectively. On the other hand, fatal events of pulmonary embolism occurred much frequently in the control arm: 1, 3 and 5, respectively.

Laboratory findings: Shifts in haematological parameters were comparable between the T+D+SoC and SoC arms of the pivotal trial. Increases of ALT/AST/bilirubin were noticeably higher in the T+D+SoC arm across different categories. This parallels the overall higher incidence of hepatobiliary disorders (8.2% patients in the T+D+SoC arm vs. 3.3% in the SoC arm). Paradoxically, a potential Hy's law definition was met in more patients from the SoC arm (9) as compared to the T+D+SoC arm (3).

Incidence of AE of hypothyroidism was declared in 11.8% in the T+D+SoC arm, 6.3% in the D+SoC arm and 1.2% in the SoC arm (p. 190/9160 ISS), highlighting likely immune-mediated pathophysiology in relationship to the addition of immune checkpoint inhibitors. The true incidence of subclinical –likely immune-mediated– hypothyroidism is probably higher, as the table on abnormal thyroid tests suggest, elevated TSH was evident in 31% of patients from the T+D+SoC arm, vs. 28 in the D+SoC arm, and 24% in the SoC arm. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed through dose interruption, symptomatic treatment or thyroid hormone replacement as clinically indicated (see sections 4.2 and 4.4 of the SmPC).

Immune mediated adrenal insufficiency occurred in patients receiving Imfinzi in combination with tremelimumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed through dose interruption, corticoisteroid treatment and hormone replacement (see sections 4.2 and 4.4 of the SmPC).

Immune mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving tremelimumab in combination with durvalumab and chemotherapy. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed via treatment with insulin as clinically indicated (see sections 4.2, 4.4 and 4.8 of the SmPC).

Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended through dose interruption and corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Individual patient listings of ECG values have been provided. The risk of QT prolongation in relationship to tremelimumab appears low.

AEs by age subgroups: In the POSEIDON study in patients treated with tremelimumab in combination with Imfinzi and platinum-based chemotherapy, some differences in safety were reported between elderly (≥ 65 years) and younger patients. The safety data from patients 75 years of age or older are limited to a total of 74 patients. There was a higher frequency of serious adverse reactions and discontinuation of any study treatment due to adverse reactions in 35 patients aged 75 years of age or older treated with Imfinzi and tremelimumab and platinum-based chemotherapy (45.7% and 28.6%, respectively) relative to 39 patients aged 75 years of age or older who received platinum-based chemotherapy only (35.9% and 20.5%, respectively). Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended (see sections 4.4 and 4.8 of the SmPC).

Overview of AEs by subgroups of other intrinsic and extrinsic characteristics does not show a specific pattern of safety concerns in a subgroup of considerable size. Data on safety by weight quartiles does not suggest major differences except for a higher incidence of maximum CTCAE Grade 3 or 4 in the subgroup of patients with the lowest body weight (i.e. <57 kg). However, a particular toxicity trend for the occurrence of high-grade events was not observed.

AEs by ADA status: The proportions of patients with anti-tremelimumab antibodies in the T+D+SoC arm and T+D pan-tumour pool were similar (16% and 13%, respectively), but those for anti-durvalumab antibodies were higher in POSEIDON (15% and 6%, respectively). The incidence of AEs across the diverse categories did not differ significantly for patients defined as ADA+ or ADA- (durvalumab in both experimental arms and tremelimumab in arm T+D+SoC).

AEs leading to discontinuation: The overall proportion of patients that discontinued any treatment in the context of an AE was higher in the experimental arms (22% in T+D+SoC, 20% in D+SoC) than in the control arm (15%). The main AEs leading to discontinuation of any treatment across the three arms of POSEIDON were pneumonia, anaemia and acute kidney injury. The addition of tremelimumab or durvalumab does not translate into a higher rate of AEs leading to dose reduction of chemotherapy.

2.5.2. Conclusions on clinical safety

Regardless of causality, all AEs categories (high-grade, serious, AEs leading to death or to treatment discontinuation, AESIs/imAEs) occurred in a numerically higher proportion of patients from the T+D+SoC arm as compared to the other two arms of pivotal trial POSEIDON.

Undoubtedly, the addition of double checkpoint inhibition (PD-L1 and CTLA-4) to a backbone platinum doublet imposes higher overall toxicity in the targeted population, which must be considered in the context of frail patients, particularly those of advanced age or multiple comorbidities. Immune-mediated events are the main concern from the combination of tremelimumab and durvalumab: although most were manageable and did not considerably impact long-term clinical outcome (e.g. endocrinopathies, hepatotoxicity and rash/dermatitis), others constitute serious entities with a significant symptomatic burden (diarrhoea/colitis, pneumonitis), representing a considerable hazard to the wellbeing of patients in this palliative setting.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 succession 1 is acceptable.

The CHMP endorsed the Risk Management Plan version 8 succession 1 with the following content:

Safety concerns

There are no safety concerns.

Pharmacovigilance plan

There are no safety concerns, so only routine pharmacovigilance activities are required.

Risk minimisation measures

Not applicable as there are no safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template version 10.2, which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The wording in the PL is similar to the text previously tested during the IMFINZI MAA. IMFINZI is administered as an IV infusion by a medical professional therefore that the changes are not significant

enough to warrant an additional user consultation for this new indication.

2.7.2. 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 and it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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

3.1.1. Disease or condition

The approved therapeutic indication is:

IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitizing EGFR mutations or ALK positive mutations.

3.1.2. Available therapies and unmet medical need

The first line (1L) treatment of metastatic NSCLC has evolved from cytotoxic chemotherapies based on physician's preference to a hallmark of personalized medicine, with subsets of patients treated according to the genetic alterations of their tumour and PD-L1 status, which predict for benefit from targeted therapies or immune checkpoint inhibitors (ICIs), respectively.

For patients without genetic drivers (e.g. EGFR, ALK, ROS1), treatment selection in clinical practice is usually based on PD-L1 expression or histology. For patients with high PD-L1 expression (i.e., PD-L1 expressed in ≥50% of tumour cells), monotherapy with either pembrolizumab or atezolizumab or cemiplimab are acceptable approved. Conversely, regardless of PD-L1 expression, a series of combinations of immunotherapy with histology-selected platinum-based chemotherapy have also shown survival benefits, which led to EMA approval:

- Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel for squamous histology
- Pembrolizumab + carboplatin + pemetrexed for non-squamous histology
- Atezolizumab + bevacizumab + carboplatin + paclitaxel for non-squamous histology
- Atezolizumab + carboplatin + nab-paclitaxel for non-squamous histology
- Nivolumab + ipilimumab + 2 cycles of platinum-doublet, regardless of histology

Although immunochemotherapy treatments are the 1L standard-of-care in patients with advanced metastatic NSCLC whose tumours do not harbour driver mutations, new treatment options are required that can explore the potential of immunotherapy strategies and benefit a broader patient population.

3.1.3. Main clinical studies

POSEIDON is a phase III, three-arm, randomised, multi-centre, open-label study in patients with metastatic NSCLC without EGFR or ALK aberrations, which compared durvalumab + chemotherapy (D+SoC, n=338) and tremelimumab + durvalumab + chemotherapy (T+D+SoC, n=338) to standard-of-care histology-specific platinum-based chemotherapy (SoC, n=337).

The dual primary endpoints of BICR-PFS and OS were analysed in the ITT of the D+SoC vs. SoC arms, while identical secondary endpoints were evaluated in the ITT of the T+D+SoC vs. SoC arms.

3.2. Favourable effects

The primary OS endpoint (D+SoC vs SoC) in study POSEIDON did not meet statistical significance. However, the other primary PFS endpoint that compared the same arms showed statistical superiority and thus alpha was propagated to the next testing level, in which OS and PFS were evaluated as key secondary endpoints in the T+D+SoC vs. SoC arms.

- At data cutoff 12-MAR-2021 and with median survival follow-up of 12.5 months, 800 deaths had occurred (79% of OS maturity) in the ITT population. Treatment with T+D+SoC showed a statistically significant survival benefit as compared with SoC: HR for OS was 0.77 (95% CI 0.65, 0.92), p-value 0.00304. K-M estimates of median OS were 14.0 months in the T+D+SoC arm and 11.7 months in the SoC arm.
- At data cutoff 24-JUL-2019, 749 PFS events (74% maturity) had occurred across the three arms of the trial. K-M estimated median PFS was numerically higher in the T+D+SoC arm (6.2 months) than in the SoC arm (4.8 months), while HR for PFS outlines the statistical advantage from T+D+SoC vs. SoC: 0.72 (95% CI 0.60, 0.86), p-value 0.00031.
- Secondary endpoints of ORR, DoR and PFS2 endorsed the advantage of T+D+SoC over SoC, as did subgroup and diverse sensitivity analyses.
- The benefit of T+D+SoC vs. SoC –in terms of OS, PFS and ORR– is maintained regardless of PD-L1 expression status, i.e., above and below various PD-L1 cutoffs (1%, 25%, 50%).

3.3. Uncertainties and limitations about favourable effects

- Acknowledging differences in study design –particularly selection of squamous (SQ) or non-squamous (NSQ) histologies or allowing both– and limitations from cross-trial comparisons, it is noted that longer median survival was observed in akin studies in which only anti-PD-1/PD-L1 agents were added to backbone platinum-based chemotherapy in the experimental arm.
- Even if the combination of T+D+SoC has demonstrated an improvement in OS, PFS and ORR compared with the SoC alone, the contribution of tremelimumab to this effect appears marginal in view of the results of a descriptive comparison with D+SoC. Since these analyses were not statistically powered, firm conclusions cannot be drawn.
- The OS benefit of T+D+SoC over SoC seems minimal in Asian patients and non-smokers. Of note, the smaller effect in the subgroup of non-smoker patients has already been observed in prior studies with immunotherapy. However, both subgroups were less represented in the T+D+SoC arm compared with the SoC arm.

- In elderly patients (≥75 years of age) a HR of 1.05 (95% CI: 0.64, 1.71) for OS was reported for T+D+SoC (n=35) vs. SoC (n=40). The uncertainty regarding efficacy (and safety) in this subgroup of patients is reflected in the SmPC.

3.4. Unfavourable effects

- AEs occurred in almost all patients across the three arms of POSEIDON. While high-grade (G3/4) AEs occurred in about half of the patients from each arm, G5 AEs were slightly more frequent in the experimental arms (12% in T+D+SoC, 10% D+SoC, 9% SoC), as were SAEs (44%, 40% and 35%, respectively) and AEs leading to discontinuation of any treatment (22%, 24% and 15%, respectively).
- Typical chemotherapy-related AEs (anaemia, nausea, neutropenia, decreased appetite and fatigue) were the five most frequent AEs across the three arms of the trial, with slightly higher incidence in the T+D+SoC arm as compared to the SoC arm. Diarrhoea and rash, with potentially immune-related pathophysiology, were considerably more frequent in the T+D+SoC arm than in the SoC arm (22% and 19% vs. 15% and 7%, respectively).
- The higher incidence of G≥3 AEs in the T+D+SoC arm (66% vs. 61% in SoC) is driven by G5 AEs (12.4% and 9%, respectively). The proportions of the most frequent G3/4 AEs were overall similar across the three arms of the trial, highlighting events of chemotherapy-related myelotoxicity, increases in pancreatic and hepatic enzymes and pneumonia.
- Regarding causality of AEs, it is difficult to elucidate which events could be caused by the chemotherapy component and which ones could be related to tremelimumab and/or durvalumab. Incidence of AEs reported with a ≥5% difference between both arms were: neutropenia (30.0% vs 23.4%), diarrhoea (21.5% vs. 15.3%), rash (19.4% vs. 6.6%), pyrexia (16.1% vs. 6.9%), arthralgia (12.4% vs. 6.3%), hypothyroidism (11.8% vs. 1.2%), pruritus (10.9% vs. 4.5%), and hyperthyroidism (5.8% vs. 0.6%).
- There were 41 AEs leading to death (G5 AEs) in the T+D+SoC arm, 34 in the D+SoC arm and 30 in the SoC arm. Most of these events were related to infections and cardiac disorders, noting that twice as many toxic deaths from infections occurred in the T+D+SoC arm, as compared to the other two arms (15, 8 and 9, respectively).
- The proportion of patients with imAEs was 32% in the T+D+SoC arm, 17% in the D+SoC and 4% in the SoC arm. The distribution of specific imAEs in the D+SoC arm is typical for PD-L1 inhibition, with predominance of hypothyroidism (6%), hepatotoxicity (3%), pneumonitis (3%) and dermatitis/rash (2%). The T+D+SoC arm presented twice as many cases of immune-mediated diarrhoea/colitis than the D+SoC arm (14 vs. 6) and more cases of pneumonitis (14 vs. 9). Hypothyroidism was more frequent in the T+D+SoC arm (12%) than in the D+SoC (6%) or SoC (1%) arms.
- Pneumonia was the most frequent SAE in the trial, and its incidence in the T+D+SoC arm doubled that of the control arm SoC (11% vs. 5%). Serious myelotoxic events, likely related to chemotherapy, were also frequent in all three arms of the trial, with comparable incidence among them. Serious pneumonitis and colitis/diarrhoea were more prevalent in the T+D+SoC arm than in the other two arms.
- The overall proportion of patients that discontinued any treatment in the context of an AE was higher in the experimental arms (22% in T+D+SoC, 20% in D+SoC) than in the control arm (15%). The main AEs leading to discontinuation of any treatment across the three arms of POSEIDON were pneumonia, anaemia and acute kidney injury.

- Patients who were 75 years or older (11% from the pivotal trial) presented a significantly higher proportion of SAEs (74% in T+D+SoC vs. 56% SoC), high-grade AEs (71% vs. 64%), G5 AEs (40% vs. 14%) and AEs leading to treatment discontinuation (49% vs. 23%) as compared to their younger counterparts. Caution should be exerted when considering treatment of tremelimumab + durvalumab + chemotherapy in patients older than 75 years. A specific warning in sections 4.4 and 4.8 was inserted.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable

3.6. Effects Table

Table 78 . Effects Table for Imfinzi in combination with tremelimumab and platinum-based chemotherapy for the 1L treatment of adults with metastatic NSCLC without EGFR or ALK aberrations. Data cut-off 12-MAR-2021 for OS and 24-JUL-20 for PFS

Effect	Short description	Unit	Arm 1 T+D+SoC n=338	Arm 2 D+SoC n=338	Arm 3 SoC chemo n=337	Uncertainties / Strength of evidence
Favourable Effects						
OS	Median overall survival	Months (95% CI)	14.0 (11.7, 16.1)	13.3 (11.4, 14.7)	11.7 (10.5, 13.1)	At 79% OS events HR T+D+SoC vs. SoC 0.77 (95% CI 0.65, 0.92) p-value 0.00304
BICR-PFS	Median progression free survival by BICR	Months (95% CI)	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 4.8)	At 74% PFS events HR T+D+SoC vs. SoC 0.72 (95% CI 0.60, 0.86) p-value 0.00031
BICR-ORR-	Overall response rate (confirmed) by BICR	% (n)	130 (38.8)	137 (41.5)	81 (24.4)	Denominator for calculations was patients with measurable disease, not ITT
Unfavourable Effects						
			Arm 1 T+D+SoC n=330	**Arm 2 D+SoC n=334**	**Arm 3 SoC chemo n=333**	
≥G3 AEs	High-grade (severe) AEs	%	66	55	61	SCS
G5 AEs	AEs leading to death	n (%)	41 (12.4)	34 (10.2)	30 (9.0)	SCS
SAEs	Serious AEs	%	44	40	35	SCS
AEs disc.	AEs leading to discontinuation of any treatment	%	22	20	15	SCS
imAEs	Immune-mediated AEs	%	32	17	4	SCS
	Diarrhoea/ colitis	n (%)	14 (4.2)	6 (1.8)	2 (0.6)	SCS
	Pneumonitis	n (%)	14 (4.2)	9 (2.7)	1 (0.3)	SCS

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The addition of immune checkpoint inhibition (PD-1, PD-L1 or CTLA-4) to a platinum doublet has proven successful at prolonging survival in advanced driver-negative NSCLC: a series of trials conducted concurrently in the last few years –the majority depicting add-on design with platinum-based chemotherapy as control– have shown improved efficacy outcomes of the experimental arms. Indeed, current guidelines across the globe highlight a plethora of immunochemotherapy regimens that are recommended for the initial approach in a treatment-naïve setting. While most of these combinations are appropriate regardless of tumoral PD-L1 expression, PD-1/PD-L1 inhibitors as monotherapy are also adequate choices for high-expressors (≥50% of tumour cells).

Albeit strictly unsuccessful for its primary OS endpoint in the D+SoC vs. SoC arms, the overall efficacy outcome of pivotal trial POSEIDON parallels results of other similar studies, noting statistically improved OS and PFS for the T+D+SoC vs. SoC comparisons. Upon appropriate maturity of the database, beneficial effects were observed across different PD-L1 cut-offs. Importantly, however, the exploratory comparisons between the experimental arms seem to suggest a borderline efficacious advantage of the addition of tremelimumab to durvalumab and chemotherapy, challenging the clinical relevance of double immune checkpoint inhibition, especially in the light of added immune toxicity risks.

As thoroughly depicted in the safety section, all the categories of adverse events present numerically higher incidence in the experimental arms, particularly in the 4-drug combination implied in the therapeutic indication of tremelimumab. As expected, immune-mediated events prevailed in both experimental arms, and although the majority were low-grade and manageable (e.g. hypothyroidism, rash), potentially symptomatic events (e.g. diarrhoea/colitis, pneumonitis) occurred predominantly in the tremelimumab arm. Undeniably, if dual PD-L1 and CTLA-4 inhibition plus chemotherapy are considered for advanced NSCLC, toxicity and tolerability concerns are to be taken into account, particularly for more frail or elderly patients.

3.7.2. Balance of benefits and risks

Efficacy data from the POSEIDON trial are sufficiently mature: it seems unlikely that updated results would alter the current conclusions.

Although the combination of tremelimumab, durvalumab and platinum-based does not seem to fill an unmet medical need in the current therapeutic paradigm of advanced NSCLC, it could be considered another appropriate chemoimmunotherapy regimen in this palliative setting.

The addition of tremelimumab and durvalumab to chemotherapy results in considerably increased toxicity, in particular relating to higher incidence of serious and grade 5 adverse events. Furthermore, the symptomatic burden and safety risks from immune-mediate events whose incidence raise with CTLA-4 blockade –e.g. colitis/diarrhoea, pneumonitis– are a particular concern from added tremelimumab. Special caution must be exerted when considering this regimen for patients ≥75 years.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Imfinzi in combination with tremelimumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include first-line treatment, with Imfinzi in combination with tremelimumab and platinum-based chemotherapy, of adults with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) positive mutations, based on final results from Study D419MC00004 (POSEIDON); This was a Phase III, randomised, multicentre, open-label, comparative global study to determine the efficacy and safety of tremelimumab and durvalumab or durvalumab in combination with platinum based chemotherapy for first-line treatment in patients with metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.2. Version 8.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Imfinzi-II-41’