15 December 2022
EMA/42903/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tremelimumab AstraZeneca

International non-proprietary name: tremelimumab

Procedure No. EMEA/H/C/004650/0000

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line
ADA	Anti-drug antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion Exchange Chromatography
ALB	Serum albumin
ALK	Anaplastic lymphoma kinase
AUC	Analytical Ultracentrifugation
BICR	Blinded Independent Central Review
BIP	Boehringer Ingelheim Pharma Gmbh & Co. KG
BLA	Biologics License Application
BOR	Best objective response
BSA	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalopathy
bTMB	Blood tumor mutational burden
CCI	Container Closure Integrity
CD	Cluster of differentiation
CD	Circular Dichroism
CDC	Complement-Dependent Cytotoxicity
CDR	Complementarity Determining Region
CEP	Certificate Of Suitability
CEX	Cation Exchange Chromatography
CFU	Colony-Forming Unit
CGE	Capillary Gel Electrophoresis
CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CL	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
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
DF	Diafiltration
dFBS	Dialyzed Fetal Bovine Serum
DNA	Deoxyribonucleic Acid
DoR	Duration of response
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDQM	European Directorate For The Quality Of Medicines & Healthcare
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ES-SCLC	Extensive-stage small cell lung cancer
EU	Endotoxin Unit
EVA	Ethyl Vinyl Alcohol
FAS	Full Analysis Set
FBS	Fetal Bovine Serum
Fc region	Fragment Crystallizable Region
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices

Abbreviation	Definition
HA	Health authority
HC	Heavy Chain
HCP	Host Cell Protein
HPLC	High Performance Liquid Chromatography
HPSEC	High Pressure Size Exclusion Chromatography
HR	Hazard ratio
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
ICI	Immune checkpoint inhibitor
IEC	Ion Exchange Chromatography
IgG	Immunoglobulin G
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IPC	In-Process Control
IPT	In-Process Test
ITT	Intent-to-treat
IV	Intravenous
JP	Japanese Pharmacopoeia
KM	Kaplan-Meier
KPP	Key Process Parameter
LC	Light Chain
LDH	Lactate dehydrogenase
LIVCA	Limit Of In Vitro Cell Age
LRV	Log Reduction Value
MAA	Marketing Authorization Application
mAb	Monoclonal antibody
MCB	Master Cell Bank
MTP	Multiple testing procedure
Mut/Mb	Mutations per megabase
MVM	Minute Virus Of Mice
nAb	Neutralizing antibody
NCPP	Non-Critical Process Parameter
NF	National Formulary (United States)
NK cell	Natural Killer Cell
NKPP	Non-Key Process Parameter
NLR	Neutrophil-to-lymphocyte ratio
NOR	Normal Operating Range
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PACMP	Post-Approval Change Management Protocol
PAR	Proven Acceptable Range
PD-1	Programmed cell death-1
PDE	Permitted Daily Exposure
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO	Polyolefin
PopPK	Population pharmacokinetics
PP	Process Parameter
PPQ	Process Performance Qualification
PR	Partial response
PRO	Patient-reported outcome
PRS	Primary Reference Standard
PRV	Pseudorabies Virus
PT	Preferred term
PV	Process Validation
PVC	Polyvinyl Chloride
QoL	Quality of life
QxW	Every x week

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
Reo-3	Reovirus Type 3 Reovirus Type 3
RLP	Retrovirus-Like Particle
RT-qPCR	Reverse Transcription Quantitative Real-Time Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics License Application
SoC	Standard-of-care
SOC	System organ class
sPD-L1	Soluble programmed cell death ligand-1
SPR	Surface Plasmon Resonance
TC	Tumor cell
TEM	Transmission Electron Microscopy
TMB	Tumor mutation burden
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold Of Toxicological Concern
TTD	Time to deterioration
UC	Urothelial carcinoma
UF	Ultrafiltration
UPB	Unprocessed Bulk
USP	United States Pharmacopoeia
UV	Ultraviolet
V_1	Central volume of distribution
WCB	Working Cell Bank
WRS	Working Reference Standard
XMuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 24 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Tremelimumab AstraZeneca, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016.

The applicant applied for the following indication: "Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0107/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0107/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.4.2. New active substance status

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. 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

The application was received by the EMA on	24 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 March 2022
The CHMP Co-Rapporteur'critique Report was circulated to all CHMP and PRAC members on	04 April 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 July 2022
The following routine GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 3 sites in Germany, USA and Canada between 21 February 2022 and 25 March 2022. The outcome of the inspection carried out was issued on	05 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding	2 December 2022

Issues to all CHMP and PRAC members on	
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positiveopinion for granting a marketing authorisation to Tremelimumab AstraZeneca on	15 December 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	15 December 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applied indication is: *Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.*

2.1.2. 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 will be diagnosed with lung cancer in 2021, accounting for approximately 25% of all cancer diagnoses, and an estimated 267,700 lung cancer associated deaths will 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 will 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).

2.1.3. 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).

2.1.4. 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).

2.1.5. 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 have been authorised in the EU. Conversely, regardless of PD-L1 expression, a series of combinations of immunotherapy with histology-selected platinum-based chemotherapy have also shown survival benefits and were authorised in the EU:

- 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

The addition of chemotherapy to nivolumab + ipilimumab, a combination of PD-1/CTLA-4 inhibitors, 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 (EMEA/H/C/WS1783).

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.

2.2. About the product

Tremelimumab is a selective, fully human IgG2 monoclonal antibody (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, resulting in increased T-cell diversity and enhanced anti-tumour activity.

Tremelimumab AstraZeneca is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. This application seeks to register one pharmaceutical form (concentrate for solution for infusion), one strength (20 mg/mL) and two presentations (25 mg single-dose vial presentation and a 300 mg single-dose vial presentation).

Tremelimumab AstraZeneca contains as excipients (for each presentation) histidine/histidine-HCl monohydrate, trehalose dihydrate, disodium edetate dihydrate and Polysorbate 80.

The CHMP adopted a positive opinion for the following indication: Tremelimumab AstraZeneca 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.

Treatment with Tremelimumab AstraZeneca must be initiated and supervised by a physician experienced in the treatment of cancer.

Posology

The recommended dose of Tremelimumab AstraZeneca is presented in Table 1.

Table 1: Recommended dose of Tremelimumab AstraZeneca

Indication	Recommended Tremelimumab AstraZeneca dose	Duration of therapy
Metastatic NSCLC	<u>During platinum chemotherapy:</u> 75 mg[a] in combination with durvalumab 1 500 mg[b] and platinum-based chemotherapy[c] every 3 weeks (21 days) for 4 cycles (12 weeks) <u>Post-platinum chemotherapy:</u> Durvalumab 1 500 mg[c] every 4 weeks and histology-based pemetrexed maintenance [c,d] therapy every 4 weeks A fifth dose of Tremelimumab AstraZeneca 75 mg[e,f] should be given at week 16 alongside durvalumab dose 6	Up to a maximum of 5 doses Patients may receive less than five doses of Tremelimumab AstraZeneca in combination with durvalumab 1 500 mg and platinum-based chemotherapy if there is disease progression or unacceptable toxicity

[a] For Tremelimumab AstraZeneca, metastatic NSCLC patients with a body weight of 34 kg or less must receive weight-based dosing, equivalent to 1 mg/kg of Tremelimumab AstraZeneca until the weight improves to greater than 34 kg. For durvalumab, patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until the weight improves to greater than 30 kg.

[b] When Tremelimumab AstraZeneca is administered in combination with durvalumab and platinum-based chemotherapy, refer to the summary of product characteristics (SmPC) for durvalumab for dosing information.

[c] When Tremelimumab AstraZeneca is administered in combination with durvalumab and platinum-based chemotherapy, refer to the SmPC for nab-paclitaxel, gemcitabine, pemetrexed and carboplatin or cisplatin for dosing information.

[d] Consider maintenance administration of pemetrexed for patients with non-squamous tumours who received treatment with pemetrexed and carboplatin/cisplatin during the platinum-based chemotherapy stage.

[e] In the case of dose delay(s), a fifth dose of Tremelimumab AstraZeneca can be given after Week 16, alongside durvalumab.

[f] If patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of Tremelimumab AstraZeneca (up to a total of 5) should be given during the post-platinum chemotherapy phase.

Dose escalation or reduction is not recommended for Tremelimumab AstraZeneca in combination with durvalumab. Dose withholding or discontinuation may be required based on individual safety and tolerability.

Method of administration

Tremelimumab AstraZeneca is for intravenous use, it is administered as an intravenous infusion after dilution, over 1 hour.

When Tremelimumab AstraZeneca is given in combination with durvalumab and platinum-based chemotherapy, Tremelimumab AstraZeneca is given first, followed by durvalumab and then platinum-based chemotherapy on the day of dosing.

When Tremelimumab AstraZeneca is given as a fifth dose in combination with durvalumab and pemetrexed maintenance therapy at week 16, Tremelimumab AstraZeneca is given first, followed by durvalumab and then pemetrexed maintenance therapy on the day of dosing.

Tremelimumab AstraZeneca, durvalumab, and platinum-based chemotherapy are administered as separate intravenous infusions. Tremelimumab AstraZeneca and durvalumab are each given over 1 hour. For platinum-based chemotherapy, refer to the SmPC for administration information. For pemetrexed maintenance therapy, refer to the SmPC for administration information. Separate infusion bags and filters for each infusion should be used.

During cycle 1, Tremelimumab AstraZeneca is to be followed by durvalumab starting approximately 1 hour (maximum 2 hours) after the end of the Tremelimumab AstraZeneca infusion. Platinum-based chemotherapy infusion should start approximately 1 hour (maximum 2 hours) after the end of the durvalumab infusion. If there are no clinically significant concerns during cycle 1, then at the physician's discretion, subsequent cycles of durvalumab can be given immediately after Tremelimumab AstraZeneca and the time period between the end of the durvalumab infusion and the start of chemotherapy can be reduced to 30 minutes.

2.3. General comments on compliance with 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 Tremelimumab Astra Zeneca 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.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 20 mg/mL of tremelimumab as active substance.

Other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate, polysorbate 80 and water for injections.

The product is available in a 2 mL type I glass vial with an elastomeric stopper and a violet flip-off aluminum seal for the 25 mg presentation and in a 20 mL type I glass vial with an elastomeric stopper and a dark blue flip-off aluminum seal vial for the 300 mg presentation.

2.4.2. Active substance

2.4.2.1. General information

Tremelimumab (INN) active substance is a human monoclonal antibody from the immunoglobulin (Ig) G2a subclass comprising of 2 heavy chains (HC) and 2 light chains (LC) covalently linked with 6 inter-chain disulfide bonds. There is one N-linked glycosylation site at Asn-301 on each HC (Fc region). The molecular weight of tremelimumab is 149,145 Da. The theoretical and experimentally confirmed extinction coefficient is 1.43 $(mg/mL)^{-1}cm^{-1}$ and the pI is in the range of 8.5–9.0.

The mechanism of action is blocking of the interaction between CTLA-4, a cell surface receptor expressed on activated T cells, and the natural B7 ligands (CD80 and CD86) on antigen-presenting cells resulting in enhanced T cell-mediated immune response such as T cell activation, proliferation, and lymphocyte infiltration into tumors leading to tumor cell death.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturing and testing of the active substance is performed by Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach an der Riss 88397, Germany. The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described and is considered acceptable. It comprises of upstream process (cell culture steps) and downstream process (purification steps).

The upstream process comprises of vial thaw, inoculum expansion, seed bioreactors, production bioreactor and harvest. Cell culture process is initiated with the thaw of cells from one working cell bank (WCB) vial. One production bioreactor results in one batch of active substance (parent batch), for which a unique batch number is assigned. Subsequently, this parent batch may be subject to splitting/pooling (sub-lotting) and stored under refrigerated or frozen conditions. The applicant defined the material inputs, critical process parameters (CPPs) and non-critical process parameters (NCPPs), and process outputs (in-process controls, microbial controls, and performance attributes) for each manufacturing step and are considered acceptable. The harvest is initiated by lowering the bioreactor temperature and followed by continuous centrifugation and filtrations (depth filtration and membrane filtration). The pre-harvest samples are taken from the production bioreactor on the harvest day to perform unprocessed bulk (UPB) testing. Harvest product is tested for bioburden and endotoxins.

The protein is then purified using a series of packed bed chromatographic and membrane filtration techniques. All purification steps were sufficiently described. The used buffers and solutions, chromatography media, filters and other product contact disposables were presented. CPPs, NCPPs, in-process controls (IPCs), microbial controls and performance attributes with the proposed limits (proven

acceptable range - PARs, acceptance criteria or action limits) were adequately defined for each purification step.

The purification process is followed by a formulation step, which consists of product concentration, diafiltration and dilution to formulate the bulk active substance at a concentration of 20 g/L. The formulated bulk is then filtered into a stainless-steel mobile vessel. The filtered bulk is then 0.2 µm filtered into the active substance containers (Ethyl Vinyl Acetate – EVA - bags) for long-term storage at 2-8°C. Shipment to the finished product manufacturing site is carried out using EVA bags.

There is one optional step "controlled freeze, frozen storage and controlled thaw of the active substance" during the manufacturing process, to facilitate frozen storage of the active substance. The formulated bulk active substance is transferred through a filter into cryovessels and subjected to controlled freezing. The frozen bulk can be stored in stainless-steel cryovessels for up 48 months at -40±10°C. The frozen active substance can be thawed and filtered into a stainless-steel mobile vessel. After the indicated hold times in mobile stainless-steel vessels at specified temperatures, the thawed active substance is again filtered into the EVA bags which are then shipped to the finished product manufacturing site to initiate the manufacturing process of the finished product. The applicant justified its strategy to include this optional manufacturing step as it is required for commercial supply and inventory management. The applicant clarified that the release testing of the active substance is performed on the bulk active substance under GMP part II (i.e. freezing, thawing, filtrations, storage and transfer between storage containers). This approach is considered unusual, however, all manufacturing steps between the bulk active substance and the active substance filled in EVA bags were appropriately validated and it was shown that after these additional processing steps, all quality attributes comply with the active substance specification. Further, bioburden and endotoxin testing are routinely performed at each filtration step to ensure the microbial quality of the active substance. Stability data under frozen and refrigerated storage conditions were provided and indicated that no significant change in product quality attributes was observed over the proposed storage hold times in the individual containers (stainless steels and EVA bags). In conclusion, the proposed strategy is not considered in conflict with GMP principles. Nonetheless, it is recommended that the proposed active substance manufacturing process and control strategy should be under intensive surveillance of the GMP supervisory authority during future inspections.

Reprocessing steps have been adequately described by the applicant.

The primary packaging component for the liquid active substance stored at 2-8°C is a disposable, single-use EVA bag, constructed from a multilayer film, with the product contact layer composed of ethylene vinyl acetate (EVA) copolymer and a gas barrier film composed of ethyl vinyl alcohol. The materials of construction of the individual components were provided and a representative certificate of release from the supplier was provided. Acceptance of the EVA bags for use is based on confirmation from the supplier's CoA that all acceptance criteria were met. The bags are pre-sterilised by the vendor using validated gamma irradiation (25 kGy minimum) and a representative certificate of irradiation from the approved sub-contractor was also provided in the dossier. Compatibility of the active substance with EVA bags was demonstrated through stability studies. Extractables and leachables assessment for EVA bags was performed and the EVA bags were found to be of low risk for leachables upon review of data from the process qualification study.

The mobile vessel and the cryovessel are both made of 316L stainless-steel (manufactured from non-corroding chromium-nickel-molybdenum), cleaned-in-place (CIP), steamed-in-place (SIP) and integrity-tested via a pressure hold test prior to use. Both are equipped with a 0.2 µm liquid filter, so the active substance is filtered prior to entry into these containers. Compatibility of the active substance with stainless-steel cryovessels and mobile vessels was demonstrated through stability studies. The stainless-steel tanks are considered low risk for extractables and leachables. A risk

assessment for the presence of elemental impurities has been performed by the applicant, in line with ICH Q3D, and the conclusion that no specific control of elemental impurities at the active substance level is endorsed.

Control of materials

Sufficient information regarding the raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

The preparation of cell culture media and nutrient feed was adequately described in the dossier. Storage temperature and storage duration were provided for both cell culture media and nutrient feed. Information related to the origin of the cell culture medium and specifications for the material were provided. No animal sourced ingredients or animal derived reagents are used in their manufacture.

Materials of animal origin were used during cell line development and also in the banking of the master cell bank (MCB) and adequate information regarding these materials was included in the dossier.

The tremelimumab antibody was initially generated in a hybridoma cell line. The genes encoding tremelimumab were isolated from hybridoma cells and were used for generation of the expression plasmid.

The host cell line (NS0 mouse myeloma cell line) was used for the preparation of the production cell line by electroporation of NS0 cells with the expression plasmid. These cells were subsequently used to prepare a pre-MCB stock, which was tested for sterility and mycoplasma.

A two-tiered cell banking system is used for tremelimumab manufacturing. Preparation of the MCB and WCB is adequately presented in the dossier. In line with ICH Q5D, 2 independent WCB storage sites are used to ensure continuous, uninterrupted production of pharmaceuticals in case of catastrophic events. The cell banks were tested for identity, purity, cell substrate stability including sterility, mycoplasma, adventitious viruses and genetic stability. MCB and limit of in vitro cell age (LIVCA) bank were also tested for infectious retroviruses. The range of used tests is considered sufficient in accordance with ICH Q5A requirements and all tests met the acceptance criteria. The results confirmed the identity, cell banks viability and that the cell banks are free of bacteria, fungi, mycoplasma and adventitious viruses. Phenotypic stability was demonstrated by assessing growth, productivity, and product quality for a certain number of days from the WCB thaw. The genetic stability of the expression plasmid and integrated genes for tremelimumab was characterised based on testing of the MCB, WCB, and the LIVCA bank. Based on cell line stability data and viral safety data from LIVCA, the limit of in vitro cell age is considered adequately justified.

The applicant has provided a stability protocol for MCB and WCB, indicating the stability tests and the acceptance criteria. The stability programme with respect to growth and viability (recoverability) of the MCB and WCB was introduced with 5 years measure intervals.

In conclusion, sufficient information is provided regarding testing of MCB and WCB and release of future WCBs.

Control of critical steps and intermediates

A comprehensive overview of the critical IPCs and critical in-process tests (IPTs) applied throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regards to critical, as well as non-critical operational parameters and IPTs. Actions taken if limits are exceeded are specified.

Process validation

A three-stage strategy is followed to define and validate the active substance manufacturing process throughout the process lifecycle. Stage 1 (process design) included the process characterization and determination of CPPs. Stage 2 (process qualification stage) included the evaluation of the process design to determine if the process is capable of reproducible commercial manufacturing. Stage 3 (continued process verification) is considered as ongoing assurance gained during routine production that the process remains in a state of control.

The overall approach is in line with ICH Q7 Guideline and it is considered acceptable. Process validation was completed using consecutive active substance lots at the proposed commercial manufacturing scale at the proposed manufacturer (Boehringer Ingelheim Pharma GmbH & Co. KG - BIP). Continued process verification identified 2 new critical quality attributes (CQAs) which resulted in the re-classification of some process parameters and hold times. Additional concurrent validation data demonstrated that results for the process parameters and process outputs for the recently produced lots are consistent with the outcomes of the prospective validation study.

All manufacturing steps were covered during the process validation studies and the process parameters selected included all the CPPs and selected NCPPs, the latter being further classified as Key Process Parameters (KPPs) and Non-Key Process Parameters (NKPPs), based on their potential impact on process performance. Regarding the process outputs, results for IPCs, microbial controls (MCs) and performance attributes (PAs) were monitored in the process validation study. The validation acceptance criteria for monitored process parameters were established within the PARs which were determined based on process characterisation study. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the IPTs are fulfilled, demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. Deviations observed in the process validation study were investigated and it was concluded that no impact on the process validation study could be expected.

Process intermediates and active substance hold times were validated through a small-scale study evaluating biochemical hold stability and are supported by equipment qualification hold time studies, demonstrating effective microbial control. Resin lifetime and carryover studies were also conducted at small-scale to establish the maximum number of product-contacting cycles for each chromatography resin used in the purification process and to demonstrate that the cleaning procedures for the chromatography resins are sufficient to reduce carryover of protein and host cell DNA to acceptable levels. Overall, the validation lifetime and carryover studies met the acceptance criteria and therefore the proposed maximum number of product-contacting cycles for the affinity resin and maximum cycles for both ion exchange resins are considered acceptable.

Filtration membrane studies were conducted at commercial scale to validate membrane carryover cleaning, reuse and storage for the filtration steps in the purification process. The target maximum number of membranes uses is adequately defined by the applicant. Validation of reprocessing steps was performed using small-scale studies. In line with the Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014), the verification protocols to be applied in case of the need for reprocessing at large scale were provided and are considered adequate. The applicant demonstrated the suitability of all components that come into contact with the active substance formulation during the manufacture. Materials evaluated for leachables and details regarding the risk assessment were provided.

In conclusion, the active substance manufacturing process has been adequately validated.

Manufacturing process development

Different manufacturing processes have been described. Process A to E batches were used in non-clinical and clinical studies. All clinical studies in this application were conducted by AstraZeneca utilizing Process E (the intended commercial process) active substance lots. During the development, several formulations and manufacturing sites were used. The applicant adequately described changes that were made throughout the development of the manufacturing process, as well as the comparability assessments that were conducted.

The applicant provided detailed results of analytical testing for the active substance lots manufactured from processes C, D and E. Furthermore, batch analysis data for process B and C and a summary of min-max ranges for early development Process A batches (used for early toxicology studies and non-clinical PK study) were provided. Overall, the lots met the specifications in place at the time of release. Side-by-side testing of the characterization tests for each comparability assessment was summarized in tabular format. The results demonstrate that the active substance lots manufactured using Process C, D and E are highly comparable in terms of product quality, physicochemical and biological properties.

Characterisation

A comprehensive physicochemical and biological characterisation of the tremelimumab molecule was presented. The characterisation of tremelimumab involved primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties.

In conclusion, the active substance has been sufficiently characterised, revealing that tremelimumab has the expected structure of a human IgG2a subclass antibody. The analytical results are consistent with the proposed structure.

Product-related impurities have been well characterised and studied. These attributes are considered CQA and the impact of these attributes on biological activity was adequately discussed. Adequate characterisation of product-related impurities has been presented, and therefore, the controls strategy for such impurities can be endorsed.

Process-related impurities comprise of impurities which arise from the cell substrates, cell culture and purification processing. Clearance and control of process-related impurities have been sufficiently discussed.

In summary, the characterisation is considered appropriate for this type of molecule.

2.4.2.3. Specification

Tremelimumab active substance specification has been defined in accordance with ICH Q6B and includes: general tests (clarity, colour, pH), oligosaccharide analysis, total protein content, identity, product-related impurities, process-related impurities), potency and safety attributes tests (bioburden, endotoxin).

Results from the statistical analysis of both release and stability data were used to support the justification of the proposed specifications. Justification for the omission of certain tests has been adequately presented by the applicant. During the assessment, acceptance criteria for several quality attributes (i.e. purity, product-related impurities and potency) were tightened upon request. In conclusion, the proposed tests panel is considered appropriate and acceptance criteria clinically justified.

The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for certain tests conducted only at release. The stability acceptance criteria are set wider than the release acceptance criteria for several parameters, which is in principle acceptable. As the number of available batches for setting the acceptance criteria was limited, the applicant should further revise the active substance stability specification acceptance criteria for these parameters, when data from additional batches are available **(REC)**.

Analytical methods

Analytical procedures performed in accordance with Ph. Eur. are appearance (color, clarity), pH, bioburden and endotoxin. Non-compendial methods are generally described with a sufficient level of detail (including equipment, reagents, system suitability and sample acceptance criteria) and are appropriately validated in accordance with ICH guidelines. The biological activity (potency) of the active substance is determined using a cell-based potency assay.

Batch analysis

The applicant provided detailed results of analytical testing for the active substance lots manufactured from processes C, D and E. The results are within the specifications in place at the time of release and confirm consistency of the manufacturing process.

In addition, batch analyses data for Process B and Process C active substance lots were provided and min-max ranges for Process A lots were summarised.

Reference materials

The history of the used reference materials was provided. Several reference standards were used during development, however only the current primary reference standard (PRS) was used to test clinical material for this application. A two-tiered system of reference standards (PRS and working reference standard - WRS) is established and a portion of PRS was used as the first lot of WRS. Both PRS and WRS are representative of the production process and clinical performance and meet the release specifications. The preparation, storage and qualification of future standards was described in the dossier and is considered acceptable.

2.4.2.4. Stability

The applicant proposed that the active substance shelf-life is up to 48 months storage at -50°C to -30°C in stainless-steel vessels, followed by up to 24 months storage in EVA bags at 2°C to 8°C. The total storage duration should not exceed 72 months.

The applicant provided stability data to support storage of frozen bulk active substance in stainless-steel containers at -50°C to -30°C (long-term storage conditions), and 2-8°C and 23-27°C/55-65% RH (accelerated storage conditions).

Stability studies for the frozen bulk active substance were performed using reduced-scale stainless-steel containers (considered representative of the full-scale vessels) and lots manufactured at the commercial site (BIP) using the commercial manufacturing process (Process E). Long-term stability studies (48 months) are completed for 4 representative lots and for one lot data for 36 out of 48 months have been provided. No meaningful change was observed under frozen storage conditions. The results demonstrate stability of the frozen bulk active substance at -50°C to -30°C in stainless-steel vessels for up to 48 months.

Additionally, 12 months stability data have been provided for 5 bulk active substance lots stored at accelerated storage conditions (2-8°C and 23-27°C/55-65% RH). All stability lots met the acceptance criteria, however some trends in the studied parameters were observed which were more significant under storage at 23-27°C/55-65% RH. The applicant sufficiently discussed all these trends. Based on these results, the short-term storage of liquid active substance in stainless-steel containers is considered justified.

The stability of the active substance when stored in EVA bags has been demonstrated for 36 months at 5±3°C. Stability studies were performed using reduced-scale EVA bags and lots manufactured at the commercial site (BIP) using the commercial manufacturing process (Process E).

Data from long-term (2-8°C, for 36 months) and accelerated (23-27°C/55-65% RH, for 6 months) stability studies were provided. Long-term studies are completed for 3 representative lots and for one lot data for 6 out of 36 months have been provided.

Additionally, the applicant provided a summary of active substance photostability studies, conducted in accordance with ICH Q1B guideline. Based on the conclusions of these studies, the active substance should be protected from light during storage.

A sequential stability study supporting the proposed cumulative shelf-life (48 months storage at -50°C to -30°C in stainless-steel vessels followed by up to 24 months storage in EVA bags at 2°C to 8°C) has not been performed. However, 3 active substance stability batches which were included in the stability study for the active substance filled in EVA bags for 36 months at 2°C to 8°C followed the 12 months storage in stainless steel tanks at -50°C to -30°C. Therefore, based on the overall presented stability data, the proposed cumulative shelf-life for the active substance is considered acceptable. The applicant committed to perform a sequential stability study utilizing at least one active substance batch stored in accordance with the above-mentioned conditions **(REC)**.

A post-approval stability protocol and stability commitment have been given. For ongoing studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Tremelimumab finished product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. The finished product is provided in 2 single-dose presentations: a 25 mg/1.25 mL vial presentation and a 300 mg/15 mL vial presentation.

Both presentations contain 20 mg/mL tremelimumab in 20 mM histidine/histidine-HCl monohydrate, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate and 0.02% (w/v) polysorbate 80.

The finished product is filled with a volume in excess of the label-claim volume to meet the USP/Ph. Eur./JP test requirements. The proposed overfill volumes are 0.26 mL and 1 mL for 25 mg and 300 mg presentations respectively, resulting in target fill volumes of 1.51 mL and 16 mL. The proposed overfill was adequately justified based on development data. The finished product does not contain any overages.

The primary packaging components consist of a type I borosilicate glass vial (2R or 20R) and grey butyl elastomer stopper (13 mm or 20 mm) capped with an aluminium seal. The vials comply with Ph. Eur. 3.2.1 for Type I borosilicate glass. The butyl elastomer stopper complies with Ph. Eur. 3.2.9. Stoppers are silicone coated and the compliance with Ph. Eur. Monograph 3.1.8 was confirmed. Extractables and leachables from primary container components were evaluated based on a 3-stage risk-based strategy. All results were either below the Threshold of Toxicological Concern (TTC), not detected over time or found below the established and toxicologically justified Permitted Daily Exposure (PDE) level. The choice of the container closure system has been validated by finished product stability data and is adequate for the intended use of the product.

The active substance is delivered ready-to-fill and no formulation or dilution steps are performed during the finished product manufacturing process. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients or no excipients of human or animal origin are used in the finished product formulation. Compatibility of tremelimumab with these excipients was demonstrated in long-term stability studies.

Pharmaceutical development

The formulation composition was developed based on experience with the solubility, structural integrity and stability of the product. A summary of the formulation development studies was provided and the rationale for introduced changes to develop the intended commercial formulation was thoroughly discussed. A characterisation study was executed to evaluate the robustness of the intended commercial formulation, to identify any critical formulation parameters and to understand the impact of those critical parameters on the finished product CQAs. In conclusion, the suitability of the intended formulation has been demonstrated based on development studies.

The applicant presented 4 versions of the manufacturing process used throughout the clinical development. Process 4 for the commercial 25 mg and 300 mg finished product vials uses Process E active substance. Overall, the finished product manufacturing process development was clearly described. The rationale of the performed changes throughout the development was discussed accordingly and did not raise concerns.

Three studies were presented to demonstrate the comparability between lots produced in different stages of development. The performed comparability studies are considered well designed and in accordance with ICH Q5E guideline. The provided results demonstrate the comparability of the lots produced by different finished product manufacturing processes and sites.

Process characterisation studies were performed. Individual unit operations were evaluated regarding impact on CQAs and process performance parameters. Based on the results from the process characterisation studies, parameters that impact CQAs are classified as CPPs, while process parameters that do not impact any CQA are classified as NCPPs. Based on the tested ranges for process parameters, their respective PARs were defined. It was demonstrated that in the defined PARs there is no impact on the quality attributes of the product. As part of the characterisation study, the impact of manufacturing environment was evaluated. Leachables from in-process product contact materials were evaluated based on risk assessment. Potential leachables were found at concentrations well below the TTC limit. Therefore, the provided conclusion that the risk to patient safety is low is considered acceptable.

In-use compatibility

The finished product must be diluted into 0.9% (w/v) saline or 5% (w/v) dextrose solutions prior to dose administration. Compatibility of the finished product was assessed in 250 mL polyolefin (PO) and polyvinyl chloride (PVC) intravenous (IV) bags. Compatibility with PVC administration sets and 0.2 µm polyethersulfone in-line filters was also tested.

In summary, the physical-chemical and microbiological in-use stability of the diluted product in IV bags has been demonstrated for up to 28 days at 2°C to 8°C and for up to 48 hours at room temperature (up to 30°C) from the time of preparation. The provided results support the proposed instructions for use and handling of the finished product stated in the SmPC (i.e., if not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be normally longer than 24 hours at 2°C to 8°C or 12 hours at room temperature (up to 25°C), unless dilution has taken place in controlled and validated aseptic conditions).

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP at qualified vendors. The finished product is released in the EEA by AstraZeneca AB, Gärtunavägen, SE-151 85 Södertälje, Sweden. A process flow diagram for the manufacture of the finished product is provided in the dossier. Detailed descriptions of the manufacturing steps are presented. Batch formula has been provided for the intended commercial batch size ranges: for the 25 mg finished product (1.51 mL target fill volume) and for the 300 mg finished product (16 mL target fill volume).

The finished product manufacturing process consists of pre-filtration and pooling, mixing, and sterile filtration of the active substance, followed by aseptic vial filling and stoppering with sterile container closure components. There are no reprocessing steps in the finished product manufacturing process.

Process control strategy is sufficiently detailed and considered acceptable. In line with the process characterisation study, CPPs and NCPPs are defined in the manufacturing process and controlled with appropriate limits. Elements of microbial control strategy were described in detail. Process parameters are monitored and maintained within established PARs. Overall, the manufacturing process and the equipment used are considered adequately described.

The manufacturing process validation study was performed following a traditional approach. The manufacturing process was validated with consecutive lots for each vial presentation at the proposed commercial manufacturing site. Production scale process validation data were presented. All process parameters (CPPs, KPPs and NKPPS) were maintained within the specified operating ranges, based on PARs established in the characterisation study. To confirm process consistency, additional IPTs (process outputs) were monitored in the process validation study and all results fell within the predefined acceptance criteria.

The pre-filtration and pooling process is designed to enable pooling of multiple active substance bags. The provided results demonstrate that homogeneity of the bulk active substance prior to filling is achieved and therefore, pooling and mixing of active substance is considered validated.

The microbial control strategy includes process design and controls, material controls, facility controls, and testing. In the process validation study, all process steps were performed as expected and the results demonstrate adequate microbial control and sterility assurance.

Sterilisation of primary container components is performed at the manufacturing site under GMP surveillance. The performed validation studies are in line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) and the provided data demonstrated the suitability of the selected sterilisation processes.

Aseptic filling process is validated using media fill runs. The matrix approach alternates the smallest and largest vial format for media fill simulations. It is therefore ensured that the commercial batches are filled within the qualified aseptic filing time.

Shipping qualification studies for the bulk vials and shipping validation for finished product packaging were performed. Details regarding the validation protocols and analytical testing results were provided in dossier and are considered acceptable.

In conclusion, the validation study demonstrated consistency and robustness of the manufacturing process for both product presentations.

2.4.3.3. Product specification, analytical procedures, batch analysis

The proposed release specifications for the finished product were defined in accordance with ICH Q6B.

The finished product specification for both 25 mg and 300 mg presentation is generally based on the active substance release specification and includes general testing (appearance, osmolarity, pH, sub-visible particles, extractable volume), quantity testing, identity testing, purity testing, charge heterogeneity testing, potency testing and safety attributes testing (sterility and endotoxin). Most of the quality attributes are also tested during stability with wider acceptance criteria.

Overall, the selection of tests is endorsed and the proposed acceptance criteria are generally acceptable. Acceptance criteria for product-related impurities and variants were revised during the procedure to better reflect the clinically qualified ranges. However, as number of available batches for setting the acceptance criteria was limited, the applicant should revise the finished product release and stability specification acceptance criteria when data from an additional 30 batches are available (REC).

No additional impurities are introduced in the finished product manufacturing process. Product-related impurities are tested as part of release specification and monitored in stability studies. Process-related impurities are controlled in finished product release and stability specifications.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Detailed assessment of elemental impurities in accordance with ICH Q3D guideline was provided. It is concluded that the overall risk of a potential release of elemental impurities into the finished product is low and no specific control is considered necessary. This conclusion is agreed.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Most of the analytical methods used for the finished product testing are identical to the ones used for testing of the active substance. Transfer of analytical methods between testing sites has been successfully completed.

Batch analysis

Summary of individual batch release results for Process 3 (clinical, stability) and Process 4 (validation, commercial, clinical, stability) lots was included in the dossier. Results for finished product lots manufactured by Process 3 and finished product 25 mg lots and 300 mg lots manufactured by Process 4 were provided. Only a summary of historic ranges of quality attributes were provided for Process 1 and Process 2 finished product lots, which is acceptable. The results are within the specifications set in place at the time of release and confirm consistency of the finished product manufacturing process.

Reference materials

See active substance section on Reference materials.

2.4.3.4. Stability of the product

The finished product stability studies were performed at long-term storage conditions (2-8°C), accelerated conditions (23-27°C/55-65% RH) and stressed conditions (38-42°C/70-80% RH), in accordance with ICH guidelines. In addition, photostability studies were conducted in accordance with ICH Q1B guideline. The stability studies are performed using the proposed commercial primary container and closure systems.

Tremelimumab 25 mg and 300 mg commercial presentations (Process 4) and 400 mg presentation (Process 3, used during finished product development) were included in stability studies. Concerning the 25 mg finished product presentation, stability data are provided, with three process validation (PV) lots designated the primary stability lots. Stability testing is ongoing for additional lots manufactured post-PV. For the 400 mg strength, stability data are provided for multiple production scale lots (PV and post-PV lots). These data are included as primary data for the 300 mg finished product presentation and supporting data for the 25 mg presentation. For the 300 mg finished product presentation, stability data are provided for 3 PV lots. Results for elemental impurities from leachable studies for up to 48 months are available for the 25 mg presentation and only initial values were provided for the 300 mg presentation. The elemental impurities stability testing and the formal stability study for the 300 mg vial presentation are still ongoing and the applicant committed to submit the results for Agency review when available **(REC)**.

The claimed finished product shelf-life of 48 months at 2-8°C for both 25 mg and 300 mg presentations was established based on real-time data (up to 48 months) for the 25 mg presentation at long-term storage conditions. Data for 300 mg presentation are currently very limited (up to 6 months), however, up to 48 months of stability data were provided for the 400 mg presentation used during finished product development. The applicant proposes that a combination of stability data from the 400 mg vial presentation and 25 mg vial presentation could be considered in the assignment of shelf-life for the 300 mg vial presentation. Suitability of this approach was thoroughly discussed. An identical primary container is used for both 400 mg and 300 mg presentations. All finished product

presentations have the same formulation, are produced using active substance from the commercial process and the comparability between finished product Process 3 and Process 4 materials was demonstrated. Taken together, all these considerations and the comparison of stress stability study data demonstrating the highly comparable degradation profiles between the 25 mg and the 300 mg presentations, it is agreed that the data for 25 mg and 400 mg finished product presentations may be extrapolated to support the proposed shelf-life claim for the 300 mg finished product presentation.

The provided stability data at accelerated stability conditions support the proposed finished product total time out of refrigerator of 30 days, as detectable changes are observed only after 2-6 months at 23-27°C/55-65% RH, with no significant degradation trend.

Thermal stress stability studies (38-42°C/70-80% RH) were performed to reveal the finished product degradation profile. Up to 6 months of stability data for the 400 mg and 25 mg presentations and 3 months for the 300 mg presentation are available. Clear degradation trends were observed for purity, methionine oxidation and charge heterogeneity. Slight decrease in potency was observed. It was demonstrated that changes in quality profile under stress conditions are detectable by suitable analytical methods and attributes like purity, charge heterogeneity and potency are considered stability indicating.

Finished product lots exposed to light showed an increase in acidic variants, higher methionine oxidation rate, and a slight decrease in purity. No significant differences were observed for other quality attributes, including potency. It is therefore agreed that the finished product should be stored protected from light.

In conclusion, based on the provided stability data, the proposed shelf-life for the finished product of 48 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light*) are acceptable. Reconstitution and in-use instructions in the SmPC are consistent with the reported stability findings of the in-use studies, as previously discussed.

A post-approval stability protocol and stability commitment have been given. For ongoing studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. The ongoing stability programme will be followed up by the annual incorporation of at least one additional commercial-scale batch as stated in a stability commitment.

2.4.3.5. Adventitious agents

Materials of animal origin were used only during cell line development as well as during preparation of specified cell banks and used also during cryopreservation of the specified cell banks. Certificates of analysis including information regarding the origin and certificates of suitability (CEPs) issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) were provided for all these materials. A TSE/BSE (Transmissible/Bovine Spongiform Encephalopathy) risk assessment for all these materials was performed with the conclusion that the risk of transmission of TSE/BSE from these materials is extremely low, which is endorsed. The applicant also provided the certificate of origin for the cell culture medium. This material is considered sufficiently documented, with negligible TSE/BSE risk of transmission.

A comprehensive programme, in accordance with ICH Q5A, is employed to test, evaluate and eliminate the potential risks of adventitious and endogenous viral agents. The programme includes control of raw materials used in the manufacturing, viral testing and characterisation of the cell banks (MCB, WCB, LIVCA) used in the GMP process, virus testing of UPB and viral clearance and inactivation assessment of the purification process.

Viral clearance capability of the active substance purification process was evaluated in scale-down experiments using 4 model viruses. The viral clearance experiments were performed matching pre-defined acceptance ranges for process parameters and performance outputs. The level of purification of the scaled-down version was shown to be representative of the production procedure.

All viral clearance experiments were performed in duplicate. The lower $\log_{10}$ reduction value (LRV) from the duplicate experiments was used to calculate cumulative LRV. The viral clearance experiments demonstrated that the purification process provides a cumulative LRV of ≥21.16, ≥18.28, ≥17.05, and ≥16.49, respectively, for the 4 model viruses. For the chromatography steps, the used chromatography resin provided LRVs either comparable to (within 0.5 $\log_{10}$) or better than the new chromatography resin, demonstrating that resin reuse has no negative impact on the viral clearance capacity of the chromatography steps. The resin sanitisation and storage studies demonstrated that the solutions used for the sanitisation and storage of the resins meet acceptable levels of antimicrobial efficacy and that the risk of cross contamination is minimal.

Endogenous retrovirus-like particles (RLPs) may be present in the cell line used to produce the tremelimumab active substance. These particles are measured by TEM analysis of the UPB. A safety factor for the removal of RLPs was calculated, resulting in a factor of greater than 9.0 $\log_{10}$ for the removal of endogenous virus, which is equivalent to less than 1 retrovirus-like particle for every 1.0×10^9 doses of tremelimumab. The results are considered adequate.

2.4.3.6. GMO

Not applicable.

2.4.3.7. Post-approval change management protocol(s)

The applicant introduced a Post-Approval Change Management Protocol (PACMP) to support the use of alternative single-use disposable filters across a number of steps in the active substance manufacturing process. Details regarding the planned technical assessment, assessment of extractables and leachables, small-scale studies and at-scale verification studies for the purpose of demonstration of comparability were provided. The upcoming changes will not have an impact on the composition, active substance and finished product specifications, active substance manufacturing process, critical steps, in-process controls or hold times and at-scale active substance batches will be placed on stability. Overall, the proposed PACMP is considered acceptable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to lack of data for cumulative active substance stability study, revision and potentially tightening of the active substance stability specification and finished product release/shelf-life specification acceptance criteria for product-related impurities and variants when additional data become available and submission of elemental impurity stability testing and formal stability study results for the 300 mg finished product presentation. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should review and, if found appropriate, revise the active substance stability specification and finished product release/shelf-life specification acceptance criteria when data from an additional 30 batches are available.

2. The applicant should perform a sequential stability study according to the post-approval sequential stability protocol and provide the results supporting a shelf-life for the active substance of 48 months storage at -40°C ± 10°C in stainless-steel vessels, followed by up to 24 months storage in EVA bags at 5°C ± 3°C (for a total of up to 72 months).

3. The elemental impurities stability testing and the formal stability study for the 300 mg finished product presentation are still ongoing. The results should be submitted for Agency's review when available.

2.5. Non-clinical aspects

2.5.1. Introduction

A comprehensive package of in vitro and in vivo studies was designed to characterize the pharmacological properties of tremelimumab with respect to mechanism of action and antitumor activity, pharmacokinetics (PK), pharmacodynamics (PD), and toxicological profile.

Based on the selective binding to human and cynomolgus monkey CTLA-4, the cynomolgus monkey was considered to be the only pharmacologically relevant species for assessment of nonclinical safety of tremelimumab. Tremelimumab binds to recombinant cynoCTLA-4 (rcynoCTLA-4) with binding affinity comparable to that for the binding to recombinant human CTLA-4

The nonclinical safety testing strategy for tremelimumab appears to meet the requirements as outlined in relevant ICH guidance, including ICH S6(R1), 'Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals', and ICH S9, 'Nonclinical Evaluation for Anticancer Pharmaceuticals'. All pivotal nonclinical safety studies were conducted in an Organization for Economic Co-operation and Development (OECD) member country in accordance with OECD GLP guidance. The IV route of administration was used for nonclinical toxicity studies as this is the intended clinical route of administration. No safety or general toxicity studies were presented for the combination of tremelimumab and durvalumab.

2.5.2. Pharmacology

Tremelimumab is a fully human immunoglobulin gamma-2 (IgG2) monoclonal antibody (mAb) engineered to bind to cytotoxic T lymphocyte-associated antigen-4 (CTLA-4; CD152), a cell surface

receptor expressed on activated T cells. Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are CD80 [B7.1] and CD86 [B7.2], which are present on antigen-presenting cells (APCs). Binding of CTLA-4 to CD80/CD86 functions to limit T-cell activation, primarily by competing with CD28 for access to CD80/CD86 (Walker and Sansom 2015).

In vitro, tremelimumab enhances T-cell function, measured by increased release of interleukin 2 (IL-2), interferon gamma (IFN-γ), and other cytokines (Tarhini and Kirkwood 2008).

In animal models of cancer, blockade of CTLA-4 function using anti-mouse CTLA-4 antibodies results in enhanced T cell function and antitumor activity that is enhanced by concomitant PD-L1 blockade (Wu et al 2012).

2.5.2.1. Primary pharmacodynamic studies

In vitro Pharmacology

Selectivity of tremelimumab was demonstrated by comparing binding to rhCTLA-4-Ig and 3 related proteins (hCD28-Ig, hB7.2, and hIgG1) at 1 (n=5), 10 (n=5), 100 (n=2) and 300 (n=2) µg/mL using ELISA to quantify the binding. Selectivity was >500 in most instances except one at 1 µg/mL in which the selectivity was only 14 towards B7.2.

In a more functional assay of binding, activated T cells was used to demonstrate that tremelimumab (CP-675,206 at 10 µg/mL) only bind to human and monkey CTLA-4. No binding to activated T cells from rat, mouse, hamster, or rabbit could be detected (Report 15-CP-675,206). For the mouse a positive control was included. It was stated in the report that tremelimumab in excess generally displayed ~ 3-fold higher total binding (surface plus intracellular) to stimulated human CD3+ cells than to rhesus or cynomolgus CD3+ cells as judged by median fluorescence intensities. The affinity of tremelimumab to rhCTL-4 and rcynoCTLA-4 was quantified using the BIAcore 2000 technology showing a slight difference in KD values for binding of tremelimumab to rhCTLA-4 and rcynoCTLA-4. KD values were 0.28 and 0.98 nM, respectively (Report 14-CP-675,206).

It was demonstrated that tremelimumab inhibited CD80 and CD86 binding in a competitive ELISA assay with sub-nanomolar EC50s (0.78 and 0.46 nM respectively, Report 03-CP-675,206).

In a functional assay of activated primary human T cells cocultured with Raji cells expressing CD80 and CD 86 an increase in secretion of IL2 (510%) and INF-γ (54%) was observed when treated with tremelimumab at 30 µg/mL as compared to the negative isotype control anti-KLH (Report 02-CP-675,206). This concentration corresponds to Cmax after the fifth dose at the lower end of patient body weight quartiles (POP PK report) and therefore can be considered clinically relevant.

The involvement of CD80 and CD86 was further demonstrated in a superantigen assay (Report 08-CP-675,206) according to which, the following was concluded: Effects of B7 blockade on IL-2 production and enhancement of IL-2 by tremelimumab at 30 µg/mL were tested in staphylococcal enterotoxin A (SEA)-stimulated human PBMC and blood cultures from 3 healthy donors. Anti-B7.1 and anti-B7.2 antibodies (CD80 and CD86) and CTLA4-Ig (all at 30 µg/mL) were used to block B7 signalling. In PBMC cultures, blockade of B7.2 or B7.1 plus B7.2 reduced IL-2 baseline levels and also enhancement of IL-2 produced by tremelimumab by 89% to 100%. Blockade of B7.1 (CD80) was less effective, inhibiting both baseline IL-2 and IL-2 enhancement by tremelimumab by ~ 50%. In general, blockade of B7 in human blood cultures produced similar results to PBMC cultures with slightly less reduction of baseline IL-2 or enhancement of IL-2 induced by tremelimumab. These studies clearly demonstrate that SEA superantigen stimulation is highly B7 dependent (08-CP-675,206).

In study 01-CP-675,206 PBMC and blood from further 15 healthy donors was used in the SEA assay to demonstrate that tremelimumab enhanced the production of IL-2 as compared to anti-KLH isotype control.

The final study using the SAE assay on human biomaterial included PBMC and blood from further 15 healthy donors and from >80 cancer patients as well (Report 13-CP-675-206). Tumour types included prostate (minimal and advanced disease), renal, rectal, colon, ovarian, melanoma, non- Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma, but not NSCLC. Although the numerical IL-2 response was variable and PBMCs and blood from a few patients did not respond to tremelimumab, the increase in IL-2 response at 30 µg/mL tremelimumab can be considered consistent as observed across the range of tumour types in this study. Moreover, the response was also demonstrated to be concentration dependent with enhancement of IL-2 production from 10 µg/mL and to increase further at 30 and 100 µg/mL.

Similarly, cultures of whole blood from 5 cynomolgus monkeys confirmed that tremelimub enhanced IL-2 production in the SEA assay at 30 µg/mL (Report 04-CP-675,206). Hence, the cynomolgus monkey is considered pharmacologically relevant.

As stated by Ohue, 2019, regulatory T cells (T-regs) suppress the activation of other T-cell populations and that Tegs are recruited into the microenvironment inside cancer tumours to enhance tumour immunity.

Study 11-cp-675-206 was aimed at determining if blockade of CTLA4 by tremelimumab affects the ability of peripheral blood human Treg cells (CD4+CD25+) to inhibit IFN-γ production or ^{3}H-thymidine incorporation of anti-CD3/anti-CD28 activated T responder cells (CD4+CD25-) in an in vitro co-culture system. Treg cells were isolated from peripheral blood mononuclear cells. FACS analyses indicated that 84% ± 5% of the isolated CD4+ Tregs were CD25+ and Foxp3+.

Under the assay conditions, a 2:1 ratio of peripheral blood Treg cells cultured with T responder cells markedly inhibited IFN-γ production and ^{3}H-thymidine incorporation compared to cultures without Treg cells. Moreover, these studies indicated that tremelimumab does not reverse the ability of human peripheral Tregs to suppress IFN-γ production or thymidine incorporation of stimulated human peripheral T responder cells at 30 or 100 µg/mL.

Studies in mice suggested that anti-CTLA-4 mAbs may also selectively deplete intratumoral FOXP3+ regulatory T cells via an Fc-dependent mechanism. In a key publication by Sharma et al, 2019, it is shown that ipilimumab and tremelimumab are not depleting intratumoral FOXP3+Tregs in human cancers and that this represents an opportunity for future improvement of these types of cancer treatments. Hence, for tremelimumab, increased activation of effector T-cells is the more likely mechanism of action.

In vivo Pharmacology

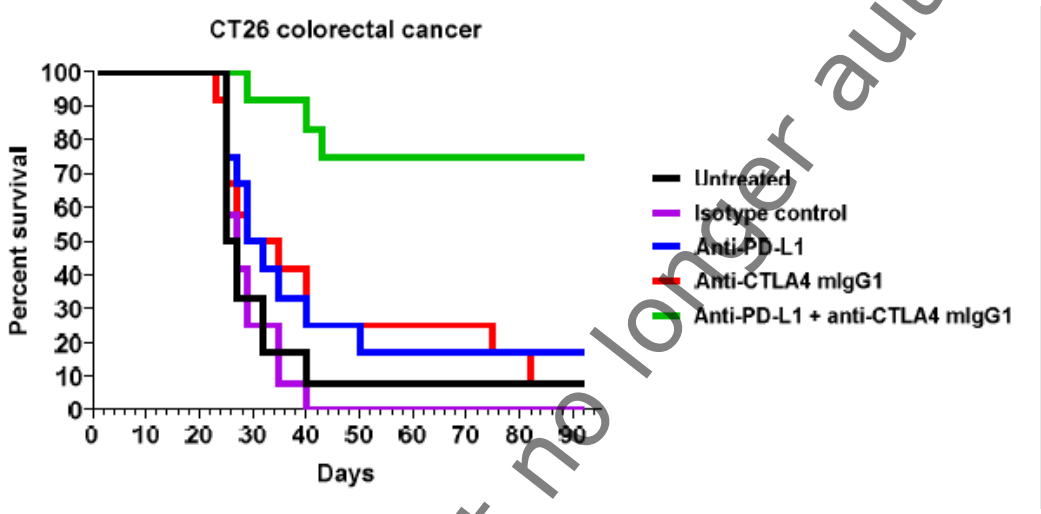
A mouse surrogate antibody (hamster anti-mouse CTLA-4 mAb named 9H10) of tremelimumab showed relevant efficacy in a mouse tumour model (12-cp-675-206). Syngeneic SA1N fibrosarcoma cells were injected subcutaneously into A/J mice (5/group). Treatment with 9H10 at 200 µg on day 0, 3 and 6 resulted in a 90% reduction in average tumour size on Day 28 compared to treatment with an isotype-control Ab. Plasma-concentrations of 9H10 24 hours after administration was 102 µg/mL and decreased to 34 µg/mL 3 days later, hence were somewhat higher than clinically relevant. Further studies showed a dose dependent tumour reduction at 200, 100 and 50 µg, although with no effect at 25 µg. Hence, a mouse surrogate of tremelimumab demonstrated efficacy as monotherapy in a mouse tumour model, when treatment was initiated at the same day as the inoculation.

All previous studies were conducted at Pfizer Groton. A new proof of concept study was sponsored by AstraZeneca (experimental work in 2017 and 2018, report signed 2021) demonstrating pharmacological activity of murine surrogates for tremelimumab and durvalumab in mouse syngeneic tumour models (ONC1123-0001).

In this study, treatment was initiated when the tumours reached 100 to 150 mm^3 and can therefore be considered more clinically relevant than study 12-CP-675,206 in which treatment was initiated at the time of inoculation.

The anti-mouse CTLA-4 mIgG1 tremelimumab surrogate mAb demonstrated modest antitumor activity as monotherapy, but good effect in combination with anti-PD-L1 in the EMT6 breast and CT26 colon syngeneic mouse tumour models (tumour growth and survival).

Figure 1: Survival curves for CT26 antitumor efficacy study - Experiment 1



Likewise, the tremelimumab surrogate showed combination activity with anti-PD-L1 therapy in the MCA205 fibrosarcoma model, but no relevant effect as monotherapy. However, the effects were not fully comparable, while the addition of tremelimumab to durvalumab monotherapy increase the efficacy in colon model, in breast model, the combination effect is mainly due to durvalumab, thus in this case, addition of tremelimumab do not provide an increase in efficacy compared to durvalumab monotherapy. Likewise, the tremelimumab surrogate showed combination activity with anti-PD-L1 therapy in the MCA205 fibrosarcoma model, but no relevant effect as monotherapy. Monotherapy and combination with anti-PD-L1 also induced in-tumour CD4+ or CD8+ T cell proliferation in these 3 mouse tumour models, demonstrating the pharmacodynamic activity of the tremelimumab surrogate with respect to T-cell activation. As shown previously in vitro for tremelimumab, that peripheral Tregs was not depleted (11-CP-675,206), the tremelimumab surrogate did not deplete peripheral Tregs in vivo, establishing the mAb as a relevant surrogate to explore the pharmacodynamic and antitumor activity in these mouse syngeneic tumour models.

A study entitled "Profiling of Biomarkers Relevant to Immunotherapies in Paediatric Solid Tumours" was included in the submission. Immunohistochemistry data for PD-L1 and CD8 were generated for 76 and 77 paediatric tumours, respectively. Only one sample was positive for PD-L1 staining, defined as ≥ 1% of TC expression of PD-L1. The level of CD8 T-cell infiltration within the paediatric tumours was relatively low as compared to adult tumours. Overall, these IHC data suggest a limited immune response against these pediatric tumours.

It was further concluded that these data were illustrative of a group of samples with relatively low levels of mutation and with a limited degree of immunogenicity and immune activation. These characteristics suggest that checkpoint blockade, using molecules such as durvalumab and

tremelimumab, would be unlikely to result in significant activity in paediatric tumours, and is in keeping with the relatively low levels of activity observed to date for similar molecules in this setting.

2.5.2.2. Secondary pharmacodynamic studies

Study 07-CP-675,206 showed that plate-bound tremelimumab did not inhibit T cell activation in the SEA assay (0.01-100 µg/mL) as the IL-2 response was not changing in any direction at any plating-concentration. This is presented as a surrogate measure of non-specific surface bound or aggregated tremelimumab in vivo in which then tremelimumab is not expected to have any effect.

In study 05-CP-675,206 tremelimumab was added to unstimulated human whole blood from healthy volunteers at concentrations of 10 or 100 µg/mL and did not induce levels of TNF-α, IL-6, or IL-1β in vitro that would be predictive of cytokine release syndrome in vivo. The positive control anti-CD3 induced cytokine release as expected in this assay. Hence, tremelimumab is not expected to induce spontaneous cytokine release in vivo, which is confirmed in clinical trials.

Study 10-CP-675,206 evaluated whole blood incubated with tremelimumab and a positive control antibody CP-642,570. Only the positive control reduced platelet number in the incubations. Tremelimumab and the negative control antibody anti-KLH did not reduce platelet numbers over the 24 -hour period the experiment lasted. It is agreed that data do not indicate that tremelimumab could elicit any effect in platelet counts at concentrations up to 30 µg/ml. This is similar to the concentrations reached in human plasma after the 75 mg dose (C_{max} 26.8 µg/ml), thus no safety margin has been established. Nevertheless, thrombocytopenia is a very common side-effect of tremelimumab, when administered in combination with durvalumab and platinum-based chemotherapy. It appears to be due to the platinum-based chemotherapy, since durvalumab monotherapy is not inducing thrombocytopenia (Imfinzi SPC).

A human IgG1 antibody has much higher affinity for most human Fcγ receptors compared to a human IgG2 antibody such as tremelimumab. A study (16-CP-675,206) of competitive binding between a low concentration of 125I-labeled antibody compared to when added 500-fold excess of unlabeled antibody to blood leucocytes, showed that an average of 53%, 43%, and 62% of the binding of hIgG1 antibody was inhibited by addition of excess unlabeled IgG1 antibody to human healthy donor, human prostate cancer patient, or cynomolgus monkey peripheral blood leukocytes. An average of 0%, 15%, and 2% of the binding of tremelimumab was inhibited by addition of excess unlabeled tremelimumab to human healthy donor, human prostate cancer patient, or cynomolgus monkey peripheral blood leukocytes. These results indicate that tremelimumab shows minimal specific binding to Fc receptor-bearing leukocytes, whether originating from humans or cynomolgus monkeys or cancer patients. Hence, Fc binding is not anticipated to be part of the mechanism of action of tremelimumab. Moreover, the tremelimumab binding to FcγRI, FcγRIIa, FcγRIIb and FcγRIII was evaluated using SPR assays and the K_D obtained are not expected to be reached in the clinical setting.

In a study of antibody-dependent cell-mediated cytotoxicity (ADCC) against naïve and activated human T cells using a FACS-based assay (09-cp-675-206), it was demonstrated that tremelimumab (100 µg/mL) added to naïve or anti-CD3/CD28 activated human T cells ± IL-2- activated NK cells (up to an effector-to-target ratio of 25:1) produced no increases in ADCC compared to the no-treatment controls. The positive control anti-CD3 (Mu-IgG2a) did induce T-cell toxicity in both naïve and activated T cells in this assay. Hence, ADCC is not anticipated to be part of the mechanism of action of tremelimumab. CDC risk was evaluated using doses below clinical concentration (5 µg/ml). CDC activity was not seen in cells incubated with tremelimumab under this condition. However, given the lack of effects on T cell depletion in the non-clinical in vivo studies and clinical studies, it is likely that the occurrence of CDC in vivo does not occur at biological relevant levels.

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were conducted for tremelimumab. This is acceptable and according to guideline, especially when non-human primate is the only relevant species.

ECG, heart rate, blood pressure and vital signs (respiration rate and body temperature) was evaluated twice pre-dose and 5 min post dose in the GLP single dose study (tmax) and on several occasions during the dosing and recovery phase in the two repeat-dose studies. No dose-related changes from normal were observed in any study or on any occasion.

No dedicated CNS safety study was conducted. Instead, daily observations of the behaviour of the animals during the studies served this purpose. This is also acceptable as it is not expected that tremelimumab will cross the blood brain barrier. Any CNS effects is expected to be secondary to the pharmacological effect of increased systemic inflammation. Histopathology revealed mononuclear cell infiltration of choroid plexus of the brain and pituitary in the 6 months repeat-dose study. Dose-related mononuclear cell inflammation was present in kidney. Clinical signs of diarrhoea in the 50 mg/kg/week group generally correlated with inflammation in the cecum and colon.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies of tremelimumab were submitted.

2.5.3. Pharmacokinetics

Bioanalysis

An ELISA bioanalytical method was developed and revised over the time providing versions each of which was validated according to GLP and used for the three pivotal studies in monkeys. For the 6-month toxicity and the EFD study an ELISA method validated as described in report DM2004-675206-014 was used. These studies were conducted in 2005 and 2007, prior to issuing of the current bioanalytical guidelines. Hence, incurred sample reproducibility was not demonstrated. Nevertheless, the bioanalytical method appears to have been in good control and to be validated in GLP compliance according to common practice at the time of conduct including e.g. dilutional integrity up to 2000-fold, hook effect and specificity.

In the assay, the ELISA plate was coated with a capture antigen (human CD152/CTLA-4). The samples were aliquoted in duplicate and allowed to incubate. The drug-antigen complex was then detected using a biotin-mouse anti-human IgG2 conjugate and a streptavidin HRP conjugate. A colorimetric signal is produced using a commercial TMB substrate solution. The intensity of color generated is directly proportional to the concentration of tremelimumab in the sample. Sample concentrations were determined by interpolation from a standard curve which was fit using a four-parameter curve fit. The minimum required dilution (MRD) for all samples was 1:20 and the required sample volume was 0.050 mL in duplicate. The quantitation range was 156 to 3000 ng/mL. Samples were stored at a nominal temperature of -80° C prior to analysis. Using this method, stability at -80° was demonstrated in monkey plasma for 174 days.

ADA analysis

GLP compliant ADA analysis was used in the 1 month and 6 months toxicity studies (validation report DM2007-675206-022 from 2001). Samples were collected in the EFD study, but not analysed, since pharmacokinetics implied that this was not necessary. This is accepted.

The ADA method was a qualitative sandwich ELISA assay in which the plate was coated with F(ab')2 fragments prepared from tremelimumab. Anti-tremelimumab antibodies in plasma was then captured by the immobilised tremelimumab F(ab')2- fragment, washed and then detected and visualized by Protein G conjugated to horseradish peroxidase (HRP) and tetramethylbenzidine (TMB). A normal cynomolgus sodium heparin plasma pool and a reference standard plasma (diluted 1:500, 1:1500, and 1:4500) were included on each plate as negative and positive controls, respectively. Results were reported as the net signal at the 1:500 dilution if not ≥3.0, then the 1:1500 was reported.

The reference standard plasma was pooled plasma from eighteen monkeys that received a single dose of tremelimumab. The plasma was collected following clearance of tremelimumab as measured by ELISA. This reference standard served as a quality control sample in all subsequent assays.

This is not the state of the art, however it appears to be a feasible way of determining ADA.

Reference range, dilution effects, stability, lot to lot variation of the negative control and intra/inter assay variability (robustness) was included in the validation. Long term stability was not presented. In this assay ADA could not be detected in the presence of tremelimumab above LLOQ of the bioanalytical method. A new method was developed for clinical samples with good assay drug tolerance.

NAb assay

Positive samples identified in the ADA assay were subjected to a nAb assay, which was also validated (validation report DM2007-675206-023).

A non-functional qualitative sandwich enzyme immunoassay technique was utilized to determine anti-tremelimumab neutralizing antibodies to tremelimumab F(ab')2 in cynomolgus sodium heparin plasma. with specificity and sufficient affinity to disrupt the binding of tremelimumab to its ligand (CTLA4) in cynomolgus sodium heparin plasma.

Samples were diluted with CTLA4/Ig and incubated with F(ab')2 fragments prepared from tremelimumab which had been immobilized on an ELISA plate. After incubation, unbound material was washed away and CTLA4/Ig was detected using goat anti-mouse Ig-HRP and visualized with TMB. A normal cynomolgus sodium heparin plasma pool and a reference standard plasma (diluted 1:10, 1:50, and 1:100) were included on each plate as negative and positive controls. The presence of nAb is indicated by a reduction in signal intensity as compared to normal cynomolgus monkey plasma (naive to tremelimumab). Study samples were run at 1:10 and 1:50 dilution, and the results were reported as the percentage of normal plasma signal generated by a dilution of test plasma in a given concentration of CTLA4IIg (10 ng/mL). This is considered an acceptable strategy for a nAb assay. It should be mentioned that the nAb assay was not functional in the presence of tremelimumab above LLOQ of the bioanalytical assay.

Absorption

Absorption was evaluated for the subcutaneous route at 5 mg/kg. Bioavalability was 54% when comparing clearance/F for SC administration with mean clearance from two studies of 0.75 mg/kg IV. It should be noted that tremelimumab is for intravenous administration together with durvalumab in a hospital setting. Hence this study is of minor clinical relevance. Pharmacokinetics after intravenous administration is discussed in section Other pharmacokinetic studies below.

Distribution

As expected for a monoclonal antibody, volume of distribution is mostly confined to the vascular space as the volume of distribution in monkey demonstrate (Vss = 54 mL/kg).

Metabolism

There is no evidence of nonlinearity of the pharmacokinetics of tremelimumbab over the dose range of 0.75 to 100 mg/kg single dose. Therefore, it can be assumed that tremelimumab is not cleared via target mediated disposition but only through proteolytic degradation and catabolism.

Excretion

Excretion was not studied for tremelimumab. This is acceptable due to nature of the molecule and that it is expected to be cleared as small peptides or amino-acids or incorporated in the endogenous aminoacid pool.

Pharmacokinetic drug interactions

Pharmakokinetic drug interactions were not studied. This is acceptable as PK drug interactions are not expected.

Other pharmacokinetic studies

Single dose IV pharmacokinetics

Pharmacokinetics of clonally and non-clonally derived tremelimumab was evaluated after IV administration of 0.75 mg/kg to cynomolgus monkey. This is a very low dose compared to the highest doses used in the toxicity studies (50 and 30 mg/kg/week). Minor differences in Vss (0.0705 and 0.0538 L/kg), clearance (0.00339 and 0.00300 mL/min/kg) and resulting half-life (11 and 9.1 days), for clonally and non-clonally derived tremelimumab were observed.

A single dose toxicity study was performed in cynomolgus monkeys at dose levels of 10, 30 and 100 mg/kg. The toxicokinetic report was very brief providing only C_{max}, T_{max} and AUC and no pharmacokinetic profiles. A trend towards lower increments in systemic levels at lower dose ranges in all pharmacokinetic and toxicokinetic studies were observed. For example, when comparing $AUC_{0\text{-tlast}}$ for 0.75 and 10 mg/kg, the increase in dose of 13.3-fold (from 0.75 to 10 mg/kg) only increased AUC by 7.8 and 6.8, the increase in dose of 3-fold (from 10 to 30 mg/kg) increased AUC by 2.3 and the increase in dose of 3.3-fold (from 30 to 100 mg/kg) increased AUC by 3.1. In addition, in the 1-mont and 6-month toxicity studies, accumulation on Day 29 was more pronounced at the lowest dose ($AUC_{0\text{-}24h}$ D29/ $AUC_{0\text{-}24h}$ D1 were 1.8 and 1.6 at 5 mg/kg, 1.1 at 15 mg/kg and 1.4 at 50 mg/kg).

New submitted PK data support that the higher accumulation observed at the lowest dose might be due to lower CL, although the high variability in exposure hinders understanding the PK profile of tremelimumab in animals. Despite the observed variability in exposure might be due to the impact of ADA on clearance of tremelimumab, it should be noted that the ADA analysis was limited to samples that showed pre-dose exposure below LLOQ (8/30 and 7/28 animals in the 1-month and 6 months toxicity studies, respectively) and thus, are limited to conclude the impact of ADA in exposure variability.

It should be noted that the dose of 0.75 mg/kg is the most clinically relevant. The dose in patients is a flat dose of 75 mg every 3 weeks providing C_{max} in the range of 22 to 30 µg/mL at the fifth dose. This is closely comparable to C_{max} in the monkeys administered a single dose of 0.75 mg/kg of 25-30 µg/mL.

Repeat-dose toxicokinetics

Repeat-dose toxicokinetics was evaluated in the 1-month toxicology study in which tremelimumab was administered IV once weekly at 5, 15 and 50 mg/kg (DM2001-675206-006). A few animals showed concentrations of tremelimumab above LLOQ at Day 1. However, so low as this is not anticipated to impact the conclusions of the study.

No gender-related differences in exposure was observed, why data was pooled across gender. AUC increased according to increase in dose on day 1, however slightly more than dose-proportional on Day 29.

Slight accumulation was observed as a result of pre-dose plasma concentration being 30-50% of C_{max} over the following doses. The accumulation was most pronounced at the lowest dose. This could be due to neutralising antidrug antibodies at the lower dose levels, see below$AUC_{0\text{-}30days}$ was 69500 µg/mL*h at 5 mg/kg (NOAEL). This could roughly be compared to AUC_{3weeks} after fifth dose in patients of 6360 µg/mL*hours. Hence, in this study the NOAEL provide a safety margin of ~8 ((=69500/30)/(6360/21)).

Antidrug antibodies were detected in 8/12 monkey in the recovery phase. As expected, variability in plasma concentrations tended to increase from Day 22 and onwards. On Day 29 at the mid dose of 15 mg/kg, 5/8 animals showed lower plasma concentrations indicating antibody mediated increased clearance in selected animals. At the low dose only 2/8 and at the high dose only 1/8 showed lower plasma concentrations demonstrating that the animals were, in general, exposed as intended.

Repeat-dose toxicokinetics was evaluated in the 6-month toxicology study in which tremelimumab was administered IV once weekly at 5 and 15 mg/kg/week, n=4 (DM2001-675206-006) for 26 weeks. The high dose group of 50 mg/kg/week was terminated on Day 78 due to excess toxicity (last dose on day 43). Two male and two females continued in to a 100 days recovery phase (Study day 177). There were no recovery animals allocated for the low and the mid dose. Pre-dose samples were below LLOQ (0.156 µg/mL) on Day 1 and so were all samples collected from control animals. The observed slight gender differences in exposure were ascribed to variability due to neutralising antibodies and resulting waning exposure later in the study in some animals. Hence, the pharmacokinetic data were pooled across gender.

As expected, slight accumulation was observed between day 1 and 29. A slight decrease was evident on Day 176 probably due to increased clearance in some animals. Only one animal (34F, 15 mg/kg dose) developed antidrug antibodies already on day 22 were the predose sample was below LLOQ. From day 43, 3 more animals (28F, 12M and 14M) showed up with exposure at or below LLOQ and from Day 141 one more (12F). When pre-dose samples showed exposure below LLOQ, these were subjected to ADA assays. Anti-tremelimumab antibodies were detected in animal 12M, 14M and 34F in predose samples from Day 44, 44 and 23, respectively correlating with waning exposure in predose samples.

The systemic exposure to tremelimuab appeared to increase with increase in dose in a linear manner on Day 1. On day 29, the increase was slightly lower than the increase in dose. This was even more obvious on Day 176 due to the increase in neutralising antidrug antibodies and waning exposure in some animals. However, on Day 176, a 3-fold increase in dose still increased the exposure 2-fold. All monkeys at 5 and 15 mg/kg dose groups had measurable plasma concentrations of tremelimumab throughout the 6-month treatment period following each dose except one, which reached LLOQ on Day 141. Hence, the animals were subjected to adequate dose-related exposure during the dosing phase and the validity of the study.

Since exposure was relatively stable during the study, the $AUC_{day1\text{-}30}$ can be acceptable as a rough estimate of for calculating exposure margins. No NOAEL could be established in this 6-months study as the monkeys also at the low dose experienced diarrhoea requiring supportive care and skin rash. The low dose provided exposure from Day 1 to 30 of 94700 µg/mL*h ((=94700/30)/(6360/21)) = 23675/2120 ~ 10 times higher than clinical exposure.

Exposure was also followed in the EFD study. Pregnant female monkeys (n=12 or 14) per group were dosed 5, 15 or 30 mg/kg/week IV from GD20 to GD49 (5 doses). Systemic exposure (C_{max} and

$AUC_{GD20-49}$) appeared to increase with increase in dose in a linear manner. Slight increase in exposure was observed between GD20 and GD 49 as expected for a product with a half-life longer than the dosing interval. ADA samples were obtained in the study, but since only very few animals showed increased clearance during the study as evident from low plasma concentrations in pre-dose samples on day 48 (12884 in the low dose group, 12702 and 13004 in the mid dose group and animal 12836 in the high dose group), these samples were not subjected to ADA analysis.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Two single dose toxicity studies were presented for tremelimumab. The first one was with only a 10 mg/kg dose in one female and one male monkey and 12 weeks treatment-free observation period (Study 00-1985-06, non-GLP). This dose was well tolerated with no clinical signs, only a slight increase in lymphocyte counts was considered related to the pharmacological effect of tremelimumab. Exposure (AUC0-tlast) was documented to be similar to the same dose level in next study (Study 99-1985-01) and the female monkey was found positive for ADA.

The second study was GLP compliant and included 3 monkeys of each sex in each group (control, 10, 30 and 100 mg/kg) and a 15 weeks treatment free observation period (Study 99-1985-01).

This study included core end points such as mortality, clinical signs (daily), body weight, food consumption, physical examinations, haematology, clinical chemistry, inspection of administration site, gross pathology, microscopic pathology. Only the control and high dose group was subjected to necropsy on Day 106. The others were returned to colony. Moreover, this study included evaluation of some safety pharmacology parameters (ECG, heart rate, respiration rate and blood pressure 5 min post dosing).

$AUC_{0-tlast}$ was proportional to the increase in dose and all 9 animals were found positive for ADA.

All animals survived until the end of the study. The most prominent clinical sign was diarrhoea/loose stool which was dose related in incidence and severity. However, this did not result in change in food intake or body weight.

Haematology revealed a general drug-related increase in lymphocyte counts, which occurred in both males and females at ≥30 mg/kg. Moreover, a general drug-related increase in eosinophil counts was observed in females at all dose levels and males at 100 mg/kg. These effects are considered a result of the pharmacological effect of tremelimumab. The increase in circulating lymphocytes was not associated with corresponding microscopic changes in the organs examined. Other changes in haematology were consistent with stress leucogram profile as they were also observed in the control group or were characteristic for an inflammatory response against a foreign protein (human CTLA4 antibody, tremelimumab).

All microscopic findings were comparable between drug-treated and control animals and consistent with those commonly or sporadically found in non-human primates.

Safety pharmacology evaluation was included in this study by assessing vital signs (heart rate, respiration rate and body temperature) and ECG/blood pressure twice pre-study and 5 minutes (T_{max}) after dosing. Hence, only acute effects were monitored. No acute drug-related changes were observed. This is endorsed.

2.5.4.2. Repeat dose toxicity

1-month i.v toxicity study with 2 months post-dose observation in cynomolgus monkey (Study 00-1985-04, GLP)

The 1 month repeat-dose toxicity study was performed in compliance with GLP as a multi-site study with Pfizer, Groton, CT, USA as the primary site. Only the immunophenotyping and serology was not performed to GLP.

Animals (5/sex/group) were administered tremelimumab at 5, 15 or 50 mg/kg via once-weekly IV bolus injection on Day 1, 8, 15, 22 and 29. Control animals (5/sex) received vehicle according to the same dosing schedule. Scheduled necropsies were conducted on Day 30 (3/sex/group), and following a 2-month treatment-free period (Day 105; 2/sex/group). I.e. there were recovery animals in all four groups.

Weekly IV bolus administration of tremelimumab over a period of 1 month was associated with intermittent diarrhoea or loose stool in individual animals across all treated groups during the dosing phase. In the 2-month treatment-free period, this effect was only observed in the high dose group. Reversible increases in the absolute number and/or percent of peripheral blood lymphocytes that correlated with increases in circulating T cells and/or B cells at 15 and 50 mg/kg/week was observed. Histopathology revealed periportal mononuclear cell infiltrates in the liver at 15 and 50 mg/kg/week, which reversed in females but not in males after a 2-month treatment-free period. Additional histopathology findings included lymphoid hyperplasia in the spleen and mesenteric lymph node, which was observed at all dose levels. Based on the above findings, the 5 mg/kg/week dose was considered to be the NOAEL and the 50 mg/kg/week dose was considered to be the highest non-severely toxic dose (HNSTD) for tremelimumab in this study. This is endorsed.

$AUC_{0\text{-}21days}$ in patients was 6360 µg/mL*h. The NOAEL of 5 mg/kg/week showed exposure: $AUC_{0\text{-}7days}$ of 13200 µg/mL*h, providing a safety margin of 13200/(6360/3) ~ 6 at one month treatment duration.

6-month i.v toxicity study in cynomolgus monkey (Study 2004-0150, GLP)

The 6 month repeat-dose toxicity study was performed in compliance with GLP as a multi-site study with Pfizer, Kalamazoo, MI, USA as the primary site. Test formulation and analysis was performed at Pfizer, Chesterfield, MO. Plasma analysis at Pfizer, Richmond, VA, ADA analysis and TK, immune-phenotyping were performed at Pfizer Groton, CT and finally the ECG analysis by an associate professor at Michigan University, East Lansing, MI, USA. The quality assurance statement includes dates of audits/inspections which cover from draft protocol across in-life phases to ECG, necropsy and study reporting. Individual quality assurance statement was provided for bioanalysis, toxicokinetics, immunophenotyping and ADA reports. No quality assurance statement was associated with the report of analysis of the dosing solutions.

The plasma concentration of tremelimumab collected from the control group animals at 0.5-hour post-dose on treatment Days 1, 29 and 176 and recovery Day 99 were less than the LLOQ (0.156 µg/mL).

Cynomolgus monkeys were administered a solution of tremelimumab in vehicle intravenously at doses of 5, 15, and 50 mg/kg/week for 6 months (the same dose levels as in the 1-month study).

Six monkeys/sex were assigned to the 0 (control) and 50 mg/kg/week groups (with 4 monkeys/sex designated as main study monkeys and 2 monkeys/sex designated as recovery-phase monkeys). Four monkeys/sex were assigned to the 5 and 15 mg/kg/week groups (no recovery-phase monkeys).

Dosing had to be suspended in the high dose group already after 6 or 7 weeks due to persistent diarrhoea and what seems to be rather severe adverse skin conditions. Several of the animals failed to improve after suspension of dosing and had to be euthanized despite supportive treatment of fluids,

snacks, benadryl and prednisolone. On Day 79, the remaining 50 mg/kg/week monkeys (2/sex) and the control monkeys originally designated as recovery monkeys (2/sex) were placed in a newly designated 99-day recovery phase. Mortality was observed in the low dose group, which were not associated with treatment (broken forearm and peracute diarrhoea due to acute infection).

As expected from the pharmacodynamic effects of tremelimumab, changes were observed in hematological, immunophenotyping and clinical chemistry endpoints, such as increased numbers of white blood cells and lymphocytes and slightly decreased A/G ratio.

A decrease in thyroid hormones (T3 and T4) in combination with increased TSH was observed in one male and 1 female in each of the mid and high dose. These changes correlated with moderate to marked thyroid atrophy as observed microscopically at day 170 at the mid dose and at Day 42 at the high dose.

Tremelimumab-related histologic findings were generally consistent with the intended pharmacology of increased immune reactivity. All treated groups had a dose-related increase in the incidence of mononuclear cell infiltration and mononuclear cell inflammation in numerous organs apart from skin and intestinal system in which adverse effects were obvious by clinical signs.

Dose-related mononuclear cell infiltration was present in the cecum, colon, skin, brain (choroid plexus), esophagus, eye (conjunctiva), heart, liver (periportal area), kidney, skeletal muscle, pancreas (acinar), parathyroid, pituitary, prostate, salivary gland, thyroid, tongue and uterus of the 5, 15, and 50 mg/kg/week groups.

Histological evaluation of the recovery animals showed minimal inflammation of salivary gland (1/4 animals) and skin (3/4 animals).

(NOAEL) was not determined based on clinical observations that required supportive care (prednisolone, benadryl, IV or gavage fluids, snacks) in the 5 mg/kg/week and 50 mg/kg/week groups and mononuclear cell inflammation in the kidney, skin and salivary gland of all tremelimumab-treated groups. Exposure to tremelimumab, assessed by mean C_{max} and AUC values, was largely maintained throughout the dosing phase despite antidrug antibodies in individual animals and there were no consistent gender differences in mean exposure. The maximum tolerated dose was considered to be 15 mg/kg/week. At 15 mg/kg/week on Day 176 the combined-sex C_{max} and $AUC_{0\text{-}24h}$ means were 444 µg/mL and 7820 µg•h/mL, respectively. This is much higher than C_{max} of 30 µg/ml and $AUC_{0\text{-}21days}$ of 6360 µg/mL*h in patients. Exposure at 5 mg/kg/week was also 11 times higher than in patients indicating that the dose setting in this study was too high. Mean $AUC_{1\text{-}30days}$ was 94700 µg/mL*h in the monkey. $AUC_{0\text{-}21days}$ in patients were modelled to be 6360 µg/mL*h. Hence, exposure margin to the lowest dose was (94700/30)/(6360/21) ~ 10. Nevertheless, the majority of the findings appeared to be clinically relevant, even the palliative treatment of corticosteroids in the most affected animals.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with tremelimumab.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted with tremelimumab.

2.5.4.5. Reproductive and developmental toxicity

Tremelimumab potential for influencing fertility and early embryonic development was not evaluated.

In the 6 months toxicity study (Study 2004-0150; GLP), mammary gland, uterus, vagina, oviduct, cervix, ovary, epididymides, prostate, seminal vesicle and testes were included in the list of organs subjected to histopathology on Day 177, where the low and mid dose animals had been dosed weekly up until sacrifice and the high dose animals had been off dosing for 99 days.

As for the male reproductive organs, mononuclear cell inflammation/infiltration was observed as minimal or mild in seminal vesicle (1/4 in High dose), testes (1/4 in Low dose and Mid dose with 1/4 with mild inflammation in the high dose), epididymides (1/4 in control, 1/4 in Low dose, 1/4 in Mid dose and 2/4 in High dose). Prostate was more affected in incidence and severity compared to the other male reproductive organs, as one of the four high dose animals also showed moderate mononuclear cell inflammation.

As for the female reproductive organs, mononuclear cell inflammation/infiltration was observed as minimal or mild in uterus (0/4 in control, 3/4 in low dose, 1/4 in mid dose and 3/4 in high dose). In vagina, this finding was dose related in incidence and severity was found to be moderate in 1/4 in mid dose and 2/4 in the high dose. In mammary gland, mononuclear infiltration was mild in 1/4 in low and mid dose and mononuclear inflammation was present in the 3/4 of the high dose animals with one classified as moderate. Other findings were only present in one animal and is considered incidental.

The embryofetal development study of tremelimumab was a multisite study performed with Covance, Münster, Germany as the primary site with a comprehensive audit program covering most phases of the study (2501-001). Analysis of a stock solution took place at Covance using UV absorbance. Bioanalysis (GLP) was conducted at Nerviano Medical Sciences, Italy and toxicokinetics (GLP) at Pfizer, Groton, CT. ADA analysis was decided not to be performed, since the pharmacokinetics appeared to be minimally affected by possible neutralising antibodies towards tremelimumab. Moreover, exposure was dose-related and similar to the repeat-dose toxicity studies.

In this study, the animals were dosed once weekly with tremelimumab from day 20 to 50 of gestation (e.g. on days 20, 27, 34, 41, and 48 of gestation) at dose levels of 0, 5, 15 or 30 mg/kg/week.

Toxicokinetic samples were collected: days 20 and 48 of gestation: predose, and at approximately 0.5, 8, and 24 hours post-dose and days 27, 34, and 41, of gestation: predose and at approximately 0.5 hours post-dose, hence exposure was well-covered throughout the study.

All animals were observed once daily for behaviour and appearance. A second examination was performed on all animals later in the day as a cage side observation, including another faeces evaluation. Additionally, a detailed fur examination was performed at weekly intervals for each individual animal.

The only clinical signs assigned to treatment was slight dose-related increase in the incidence of days with diarrhoea.

Foetuses were delivered via caesarean section and euthanized on day 100 ± 1 of gestation, followed by examination for weight, external, visceral, and skeletal abnormalities, and weights of selected organs. Placentae were examined for weight and gross appearance.

There was no effect of treatment on the incidence of prenatal loss. There were no treatment-related changes in fetal body or organ weights, fetal body measurements, or placental weights among the live fetuses. External and visceral examination revealed several minor findings in fetuses of all groups including the control group. Type, frequency and pattern of those findings did not show any dose-relationship.

Hence, there were no signs of tremelimumab having adverse effects on the outcome of pregnancy and embryofoetal development at doses up to 30 mg/kg/week during pregnancy (GD20 to GD48) in the monkey providing sufficient margin of exposure.

A pre- and postnatal development study (PPND) was not performed.

Studies in juvenile animals were not performed.

2.5.4.6. Toxicokinetic data

Table 4.2.2. Key Findings in Toxicity Studies with Tremelimumab in Cynomolgus Monkeys

Dose (mg/kg)	Key Findings	C_{max}[a] (µg/mL)	AUC[a] (µg·hr/mL)
Single-dose with 3-month observation period after dosing (3 animals/sex)			
10	↑ eosinophil counts; ADA detected	251	29000
30	↑ eosinophil counts loose stools;↑ lymphocyte counts; ADA detected	688	66900
100	↑ eosinophil counts loose stools;↑ lymphocyte counts; ADA detected No gross or microscopic findings after 3-month observation period	2970	209000
1-month repeat-dose with 2-month observation period after dosing (5 animals/sex)[b]			
5 (NOAEL)	Loose stools; lymphoid hyperplasia in the spleen and mesenteric lymph nodes; ADA detected	107 164	69500 88600
15	Loose stools; lymphoid hyperplasia in the spleen; ↑ peripheral blood CD3+CD4+ T cells; periportal infiltration of mononuclear cells ADA detected	357 433	186000 210000
50 (HNSTD)	Loose stools with supportive care; lymphoid hyperplasia in the spleen;↑ peripheral blood lymphocytes; ↑ peripheral blood CD3+CD4+ T cells, CD3+ T cells, and/or CD20+ B cells; ↓ RBC, hemoglobin, and hematocrit	1,090 1,480	590000 775000
6-month repeat-dose (4 or 6 animals/sex)[c]			
5	Diarrhoea requiring supportive care; skin rash; lymphoid hyperplasia; ↑incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ADA detected	145 234 192	94700
15 (HNSTD)	Diarrhoea; skin rash (requiring supportive care in 1 male); lymphoid hyperplasia; ↑ incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ↑ CD3+CD4+ peripheral blood lymphocytes; inflammation of cecum and colon; thyroid atrophy; ADA detected	418 505 444	212000
50	Diarrhoea; skin rash; lymphoid hyperplasia; ↑ incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ↑ CD3+CD4+ peripheral blood lymphocytes; inflammation of duodenum, cecum, and colon; acinar pancreatic and thyroid atrophy; ADA detected; early euthanasia due to progressive skin condition, diarrhea, and ↓ body weight	1400 2030 NC	776000
Embryo-Fetal Development (16 females/group)[d]			
5	Slight increase in diarrhoea	154 187	76800
15		498 707	208000
30 (NOAEL)		954 1230	454000

↑ = increased; ↓ = decreased; ADA = antidrug antibody; AUC = area under the plasma concentration-timecurve; $AUC_{0\text{-}Tlast}$ = area under the plasma concentration-time curve from time 0 to last measurable concentration; $AUC_{Days1\text{-}30}$ = area under the plasma concentration-time curve from Day 1 to Day 30; $AUC_{Day\ 20\text{-}49}$ = area under the concentration-time curve from GD 20 to GD 49; C_{max} = maximum observed concentration; GD = gestation day; NC = not calculated; NOAEL = no-observed-adverse-effect level; HNSTD = highest non-severely toxic dose; RBC = redblood cell.

[a] In the single-dose study, AUC is $AUC_{0\text{-}Tlast}$ from Day 1 through Day 105. In the 1-month repeat-dose study, C_{max} values are on Day 1 and Day 29 and AUC values are $AUC_{Days1\text{-}30}$ and $AUC_{0\text{-}Tlast}$, where T_{last} is from Day 1 through the end of the observation period (Day 105). In the 6 month repeat-dose study, C_{max} values are from Days 1, 29 and 176 and AUC values are $AUC_{Days1\text{-}30}$. In the EFD study, C_{max} values are from GD 20 and 48 and AUC values are $AUC_{GD20\text{-}49}$

[b] Tremelimumab was administered on Days 1, 8, 15, 22, and 29.

[c] Tremelimumab at dose levels of 5 and 15 mg/kg was administered once weekly for 26 consecutive weeks, and at dose level of 50 mg/kg once weekly for 7 consecutive weeks.

[d] Tremelimumab was administered on GD 20, 27, 34, 41, and 48.

Interspecies comparison

The repeat-dose toxicity studies were conducted with exposure of tremelimumab well in excess of patient exposure even at the lowest dose level. This is unfortunate as no NOAEL could be determined from the 6-month study. It should be noted that AUC in monkey is for 1 week and AUC for human is for 3 weeks in the table below.

Group Mean Total Tremelimumab AUC (µg·hr/ml) Following Repeated IV Administration in Cynomolgus Monkey and Human:

Dose (mg/kg/week)	AUC (µg·hr/ml) [SD]	
	Monkey[a] 6-Month Repeat-Dose	Human[c, d]
1[b]		6360 [1202]
5	13200 [2500]	
15 HNSTD	33900 [3000]	
50	121000 [18000]	

AUC = area under the concentration-time; HNSTD = highest non-severely toxic dose; SD = standard deviation

[a] AUC from 0 to 168 hours

[b] Human dose of 75 mg is equivalent to 1 mg/kg assuming a 75 kg subject.

[c] The tremelimumab population PK analysis was based on a pooled dataset including 6 clinical trials: D4190C00002 (Phase 1), D4190C00006 (Phase 1b), D4190C00010 (Phase 1), D4880C00003 (DETERMINE, Phase 2b), D4884C00001 (BASKET, Phase 2), and D419MC00004 (POSEIDON, Phase 3). The studied dose range was 1-10 mg/kg, or 75 to 750 mg Q4W or every 12 weeks (Q12W).

[d] Derived AUC from the fifth dosing interval (Cycle 5, 0-21 days); converted from µg·day/ml.

2.5.4.7. Local Tolerance

Local tolerance was assessed in both single and repeat-dose toxicity studies. When changes were observed, these were considered procedurally related and similar in incidence and severity between control and tremelimumab dosed animals.

2.5.4.8. Other toxicity studies

Tissue cross reactivity

Tissue cross reactivity studies of tissue binding of a fluorosceinated version of tremelimumab to cynomolgus monkey and human tissues was presented in reports IM645 and IM676. The studies were conducted according to GLP at Pathology Associates, a Charles River Company, Maryland, USA. The range of tissue was sufficiently broad and covered tissues of vital organs such organs of reproduction, heart and lung apart from expected target organs of gastrointestinal system, thymus, pancreas and lymph system. Human lymphocytes and human cerebellum tissue were used as positive and negative control, respectively.

The tissue binding profile of the two species was remarkably similar. The tissues binding tremelimimab were tonsils, lymphocytes in stomach, colon, spleen, lymph nodes and thymus in monkey. In human tissues it was tonsils, lymph nodes, thymus, lymphocytes in spleen, colon and small intestine with low binding in 1 out of three donors of thyroid. Tissue binding correlates with expected pharmacological effect and adverse findings in the monkey and adverse effects in patients.

Antigenicity

Tremelimumab did give rise to antidrug antibodies in the monkeys, however with limited impact on exposure. Only few animals showed decreasing exposure over time due to neutralising antidrug antibodies. This seems to be the case in patients as well, where 10.7% tested positive for ADAs and 8.9% for neutralising ADAs. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety.

Immunotoxicity

Tremelimumab is a product, which enhance the reactivity of the immune system by inhibiting one of the down-regulating functions (CTLA4). This gives rise to general inflammation (in essence autoimmune reactions) in a range of organs - most severely in the intestinal system and skin as observed from clinical signs. The increase in general inflammation seems to be well documented in the studies in cynomolgus monkeys also on the cellular level but may be less obvious in the patient population in which leucopenia and neutropenia are very common adverse effects.

2.5.5. Ecotoxicity/environmental risk assessment

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

2.5.6. Discussion on non-clinical aspects

Pharmacology

It is acknowledged that tremelimumab inhibits CTLA4 and thereby activate T cells. A range of both in vitro, in vivo pharmacology and repeat-dose toxicity studies documents this effect, which in vivo translates into severe systemic inflammation and mortality after repeat-dosing. However, the lack of effects on Tregs ability to dampen IFN-γ production by activated T cells is a concern. According to e.g. Ohue, 2019, Tregs may be part of cancer tumours microenvironment to enhance tumour immunity providing a possibility for evading the activated T cells.

To further explain the fact that tremelimumab does not target the intratumoral Tregs limiting its efficacy in cancer treatment, a scientific discussion was provided. Depletion of Tregs is dependent on ADCC of which tremelimumab is not capable mainly due to lack of FcR affinity. Selby et al. demonstrated that in mouse tumor models surrogate antibodies with higher affinity for FcR showed both the ability of depleting Tregs and enhanced antitumor activity.

There is a difference in affinity of IgG isotypes for FcR between mouse and human. IgG2a is a mouse isotype, with relatively potent Fc binding properties and is broadly equivalent to human IgG1. Additionally, human IgG2 (such as tremelimumab) has very minimal Fc binding properties and is broadly equivalent to mouse IgG1 (as used in the in vivo studies described below) (Stewart et al 2014).

This discrepancy between nonclinical and clinical findings could be summarized as translational challenges associated with: 1) differences between IgG isotypes across species; 2) type of effector cells infiltrated in tumour and expression of different FcγRs on the surface between mouse and human; 3) varying CTLA-4 expression level on Tregs.

To conclude, tremelimumab is not capable of performing ADCC and therefore does not reduce Tregs number. In the context of immune related adverse events, that property is desirable, but intratumoral

Tregs might be potential target for more efficient therapy because reducing Tregs inside tumors is associated with superior antitumor activity. Tremelimumab achieves its effect by targeting CTLA-4 on activated effector T cells and should be administered in combination with anti-PD-L1 antibody. Results from nonclinical studies showed that combination is superior to monotherapy with tremelimumab in cancer treatment, but similar to anti-PD-L1 monotherapy. Totality of data suggest that not affecting Tregs might be the reason for weaker efficacy of tremelimumab.

Key in vitro and in vivo studies highlight applicant´s statement that tremelimumab is not capable of affecting Tregs, however, the absence might be associated with weaker clinical outcomes and questionable contribution of tremelimumab in antitumor efficacy.

This deficiency might also explain the modest effect in the in vivo mouse cancer models. In addition, the clinical combination ratio, tremelimumab 75mg Q3W with durvalumab 1500 mg Q3W has not been justified from a non-clinical point of view, only a ratio 1:1 has been tested in *in vivo* and studies of combination with platinum-based chemotherapy have not been provided, although at this time of the clinical development it is considered acceptable to address these issues with clinical data and additional non-clinical studies are not warranted.

Pharmacokinetics

As expected for a monoclonal antibody, volume of distribution is mostly confined to the vascular space as the volume of distribution in monkey demonstrate (Vss = 54 mL/kg). The major elimination pathway of tremelimumab is expected to be through protein catabolism. Pharmacokinetic drug-drug interactions of tremelimumab with other therapeutics are not anticipated.

The pharmacokinetics of tremelimumab showed a trend towards lower increments in systemic levels at lower dose ranges in all pharmacokinetic and toxicokinetic studies. This may imply no signs of target mediated clearance, but rather target mediated protection at the low doses or this could be due to biological variation.

Antidrug antibodies (ADAs) were observed in several animals during the repeat-dose toxicology studies and in some cases appeared to increase clearance. However, the overall exposure was deemed sufficient securing the validity of the studies.

Toxicology

Repeat-dose toxicity studies were conducted in monkeys of 1- or 6- months duration. In the 1-month study findings were consistent with tremelimumab pharmacology by inducing inflammation but not severe.

In the chronic 6-month study in cynomolgus monkeys, treatment with tremelimumab was associated with dose-related incidence in persistent diarrhoea and skin rash, scabs and open sores, which were dose-limiting. These clinical signs were also associated with decreased appetite and body weight and swollen peripheral lymph nodes. Histopathological findings correlating with the observed clinical signs included reversible chronic inflammation in the cecum and colon, and mononuclear cell infiltration in the skin and hyperplasia in lymphoid tissues. A dose-dependent increase in the incidence and severity of mononuclear cell infiltration with or without mononuclear cell inflammation was observed in the salivary gland, pancreas (acinar), thyroid, parathyroid, adrenal, heart, esophagus, tongue, periportal liver area, skeletal muscle, prostate, uterus, pituitary, eye (conjunctiva, extra ocular muscles), and choroid plexus of the brain. No NOAEL was found in this study with animals treated with the lowest dose of 5 mg/kg/week requiring supportive care. This dose provided an exposure-based safety margin of 3 to clinical relevant exposure (taking species difference in potency into account).

Mononuclear cell infiltration in prostate and uterus was observed in repeat dose toxicity studies. Since animal fertility studies have not been conducted with tremelimumab, the clinical relevance of these

findings for fertility is unknown. In reproduction studies, administration of tremelimumab to pregnant Cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or effects pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs. Human IgG2 is known to cross the placental barrier.

Tremelimumab potential for influencing fertility and early embryonic development was not evaluated or discussed by the applicant. According to ICH S9, effects on reproductive organs from the repeat-dose toxicity studies can make the basis for this evaluation.

Pre- and postnatal development studies were not performed, and this is acceptable and in line with ICH S9.

No studies in juvenile animals were performed, and this is acceptable since the sought indication is only including adult patents.

Tremelimumab was not evaluated for genotoxic potential, and this is acceptable for a monoclonal antibody. Carcinogenic potential of tremelimumab was not evaluated, and this is acceptable given the indication sought in the treatment of advanced NSCLC.

RMP

The findings observed in the pivotal repeat-dose general toxicity studies of inflammation in cecum, colon and skin were also observed in patients. Moreover, clinical chemistry findings in patients and monkeys related to liver toxicity correlated to histological changes. As for toxicity to reproduction, it is acknowledged that the EFD study in monkeys did not give rise to concerns. However, inflammatory markers were present in organs of reproduction of both male and female animals even after 99 days of recovery.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data submitted support the marketing authorisation of tremelimumab.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 2: 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				

Table 2: 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
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
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

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Tremelimumab and durvalumab are human monoclonal antibodies (mAb) that act as checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response triggered by chemotherapy.

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

The applicant is currently seeking marketing approval for the use of tremelimumab in combination with durvalumab 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 clinical pharmacology data that support this proposed indication is summarized below.

No dedicated human PK studies have been conducted for tremelimumab. The PK of tremelimumab and/or durvalumab has been investigated in patients enrolled in:

- Three Phase I/Ib studies: D4190C00006 (Study 06), D4190C00010 (Study 10), and D4190C00002 (Japan Study 02).
- One Phase I/II study: D4190C00022 (Study 22).
- Three Phase II/IIb studies: D4193C00003 (CONDOR), D4880C00003 (DETERMINE), and D4884C00001.
- Six Phase III studies: D419MC00004 (POSEIDON), D419QC00001 (CASPIAN), D419AC00001 (MYSTIC), D419AC00003 (NEPTUNE), D4191C00004 (ARCTIC), and D4193C00002 (EAGLE).

The Phase III study POSEIDON is the pivotal study for this application, while the other studies are supportive studies.

The PK of tremelimumab as monotherapy has been determined in 5 supportive studies (Study 22, ARCTIC, CONDOR, DETERMINE, and D4884C00001). In these studies, however, only sparse sampling was performed for the assessment of PK.

Overall, the peak and trough concentrations of tremelimumab were in a similar range across studies at the same dosing regimens.

All studies included male and female patients aged 18 years and older with advanced solid tumors. No PK data has been obtained from healthy volunteers.

Table 3. Key tremelimumab PK results across studies

Study **Primary objectives** **Design**	**Phase**	**Patient type** **N (M/F)** **Age (median [range])**	**Dosing regimen**	**Key pharmacokinetic results and conclusions**
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	Tremelimumab PK concentrations were within the expected exposure range following 75 mg Q3W. T + D + SoC: C_{max1}: 23.17 µg/mL $C_{trough,ss}$: 4.16 µg/mL (Week 3), 7.82 µg/mL (Week 12) Follow-up (last dose + 3 months): 0.86 µg/mL

			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	1 mg/kg Q4W (expansion): C_{max1}: 20.3 µg/mL $C_{max,ss}$: 20.5 µg/mL $C_{trough,ss}$: 5.59 µg/mL
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	1 mg/kg Q4W - biliary tract carcinoma: C_{max1}: 19.5 µg/mL $C_{max,ss}$: 22.5 to 22.8 µg/mL $C_{trough,ss}$: 3.98 to 4.10 µg/mL 1 mg/kg Q4W - esophageal carcinoma: C_{max1}: 17.4 µg/mL $C_{max,ss}$: 21.0 to 21.3 µg/mL $C_{trough,ss}$: 4.02 to 4.50 µg/mL
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	The observed exposure levels of tremelimumab were within the expected ranges based on prior knowledge. 1 mg/kg Q4W: C_{max1}: 22.0 µg/mL $C_{trough,ss}$: 4.89 µg/mL
D4190C00022 (Study 22) Safety and tolerability Open-label, randomized	I/II	Advanced HCC Part 1: 40 (30/10) 60.5 (47-87 y) Parts 2 and 3: 332 (284/48) 64.0 (26-89 y) China Cohort: 14 (13/1) 49.5 (26-66 y) Part 4: 47 (41/6) 64.0 (37-84 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 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	Parts 2 and 3: Similar exposures were observed following the weight-based 1 mg/kg and the equivalent fixed 75 mg dose and following the weight-based 10 mg/kg and the equivalent fixed 750 mg dose. C_{max} values were 3.3-fold (arithmetic mean) or 3.7-fold geometric mean) higher following a 300 mg dose compared to a 75 mg dose. Exposures increased generally dose-roportionally with increasing weight-based doses from 1 to 10 mg/kg and fixed doses from 75 to 750 mg, respectively. No accumulation of tremelimumab exposure (C_{max} or C_{trough}) was observed following repeated dosing in any of the cohorts. 1 mg/kg Q4W: C_{max1}: 22.22 µg/mL, $C_{max,ss}$: 23.43 µg/mL $C_{trough,ss}$: 4.545 µg/mL (Week 13) 10 mg/kg Q4W: C_{max1}: 214.7 µg/mL $C_{max,ss}$: 203.7 µg/mL (Week 13), 202.4 µg/mL (Week 25) $C_{trough,ss}$: 43.90 µg/mL (Week 13), 38.78 µg/mL (Week 25) 75 mg/kg Q4W: C_{max1}: 26.99 µg/mL, $C_{max,ss}$: 27.80 µg/mL $C_{trough,ss}$: 4.178 µg/mL (Week 5), 4.113 µg/mL (Week 13) 300 mg:

				C_{max1}: 99.06 µg/mL $C_{trough,ss}$: 11.67 µg/mL (Week 5) 750 mg/kg Q4W: C_{max1}: 224.8 µg/mL, $C_{max,ss}$: 225.2 µg/mL $C_{trough,ss:}$ 26.69 µg/mL (Week 5), 31.25 µg/mL (Week 13), 35.61 µg/mL (Week 25)
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	Tremelimumab concentrations were consistent with the expected concentrations based on previous studies. 1 mg/kg Q4W: C_{max1}: 20.8 µg/mL $C_{max,ss}$: 21.7 µg/mL $C_{trough,ss}$: 3.8 µg/mL
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	Tremelimumab concentrations were similar to those observed in previous studies. 1 mg/kg Q4W: C_{max1}: 20.3 µg/mL $C_{max,ss}$: 20.8 µg/mL $C_{trough,ss}$: 3.4 µg/mL
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	10 mg/kg Q4W: C_{max1}: 170 µg/mL $C_{max,ss}$: 133 µg/mL $C_{trough,ss:}$ 6.22 to 28.8 µg/mL
		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	1 mg/kg Q4W: C_{max1}: 22.4 µg/mL $C_{trough,ss}$: 4.10 µg/mL
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	The PK concentrations of tremelimumab were within the expected exposure at the dosing regimen. Tremelimumab 75 mg Q3W in combination with D and EP: Week 0 C_{max}: 22.7 µg/mL Week 3 C_{trough}: 4.245 µg/mL Week 12 C_{trough}: 7.576 µg/mL
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	Tremelimumab concentrations were broadly similar to previously reported tremelimumab PK data. 10 mg/kg Q4W: C_{max1}: 158 µg/mL $C_{max,ss}$: 190 to 253 µg/mL $C_{trough,ss}$: 33.5 to 35.1 µg/mL
		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	The observed exposure levels of tremelimumab were within the expected ranges based on prior knowledge. 1 mg/kg Q4W: C_{max1}: 20.5 µg/mL $C_{max,ss}$: 29.2 µg/mL

			Tremelimumab IV 1 mg/kg Q4W for 4 doses	$C_{trough,ss}$: 6.0 µg/mL
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	Tremelimumab concentrations were similar to previously reported PK data. 1 mg/kg Q4W: C_{max1}: 15.2 µg/mL $C_{max,ss}$: 19.3 µg/mL $C_{trough,ss}$: 4.4 µg/mL
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	Tremelimumab concentrations were broadly similar to previously reported tremelimumab PK data from weight-based equivalent dosing. 750 mg Q4W: C_{max1}: 157 µg/mL $C_{max,ss}$: 209 to 290 µg/mL $C_{trough,ss}$: 28.5 to 33.9 µg/mL
			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	Tremelimumab concentrations were broadly similar to previously reported tremelimumab PK data from weight-based equivalent dosing. 75 mg Q4W: C_{max1}: 50.9 µg/mL $C_{max,ss}$: 34.1 µg/mL $C_{trough,ss}$: 3.59 to 12.9 µg/mL
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	Tremelimumab concentrations were similar to previously reported PK data. 10 mg/kg Q4W: C_{max1}: 207 µg/mL $C_{max,ss}$: 233 to 250 µg/mL $C_{trough,ss}$: 35.2 to 37.1 µg/mL

ALK, anaplastic lymphoma kinase; C_{max1}, maximum serum concentration following the first dose; $C_{max,ss}$, maximum serum concentration at steady state; $C_{trough,ss}$, minimum serum concentration at steady state; 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.

Key tremelimumab PK results from POSEIDON (D419MC00004)

Tremelimumab PK data were available for a total of 327 patients in the T + D + SoC arm.

Following tremelimumab 75 mg Q3W in combination with durvalumab and SoC chemotherapy, geometric mean (n, geometric %CV) of peak concentrations are shown in Table 4.

Tremelimumab PK concentrations were within the expected exposure range following 75 mg Q3W.

Table 4 Summary of Tremelimumab Serum Concentrations (µg/mL)

Nominal time	**Concentration (µg/mL)**	**T + D + SoC N = 327**
		Geometric mean (n, geometric %CV)
Week 0	Peak concentration	23.17 (n = 294, 65.62%)
Week 3	Trough concentration	4.16 (n = 285, 80.83%)
Week 12	Trough concentration	7.82 (n = 183, 75.68%)
Follow-up	Last valid dose + 3 months	0.86 (n = 105, 87.65%)

Trough concentrations on Weeks 3 and 12 are the pre-infusion concentrations of Weeks 3 and 12, respectively. Peak concentration on Week 0 is the post-infusion concentration of Week 0. Only PK visits as per protocol are summarized.
CV, coefficient of variation; D, durvalumab; n, number of samples; N, total number of patients with tremelimumab PK data; PK, pharmacokinetic(s); SoC, standard of care chemotherapy; T, tremelimumab.

Dose rationale

In POSEIDON, a dose of 75 mg Q3W IV tremelimumab in combination with 1500 mg Q3W IV durvalumab and SoC for 4 cycles was administered, with one additional dose of tremelimumab 75 mg at Week 16, followed by 1500 mg Q4W IV durvalumab monotherapy to disease progression or unacceptable toxicity for the first-line treatment of patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations.

The chosen dose was based on the results from the dose finding study (Study 06), in which tremelimumab 1 mg/kg was selected, as patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile without dose-limiting toxicities and the dose showed evidence of clinical activity. There was evidence of augmented pharmacodynamic activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab.

A fixed dose of tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W for an average body weight of 75 kg) was predicted to result in similar AUC and only a modest difference in median peak and trough levels at steady state compared to tremelimumab 1 mg/kg Q4W based on simulations in a Population PK model developed for tremelimumab using data from Study 10, Japan Study 02, Study 06, D4884C00001, DETERMINE, and POSEIDON.

Simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with the fixed dose regimen.

In order to further evaluate the suitability of a fixed dosing regimen of tremelimumab versus body weight-based dosing, tremelimumab exposure was compared by body weight quartiles. The exposure difference was small (< 20%) for all metrics (AUC, C_{max}, C_{min}), with a large overlap between body weight brackets (Table 5).

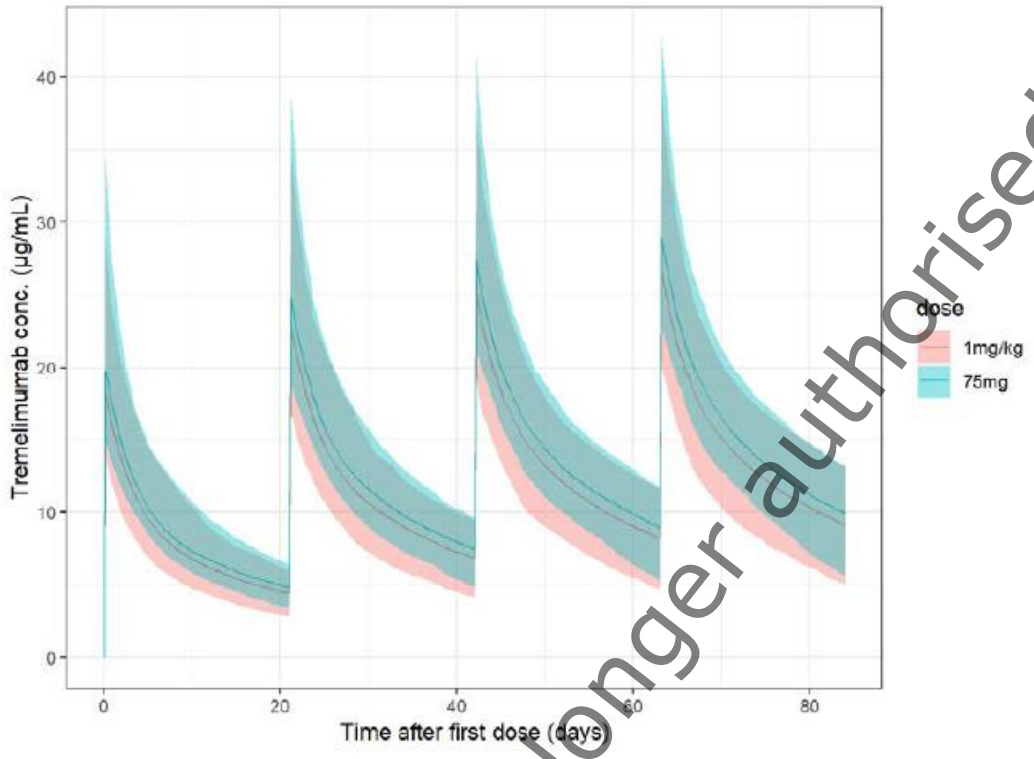
Table 5. Tremelimumab exposure across body weight quartiles

	Q1	Q2	Q3	Q4
Individuals				
N	84	81	80	81
Body weight (kg)				
Geometric mean (%CV)	51.4 (12.3)	63.4 (4.50)	73.1 (3.81)	90.2 (12.5)
Median [min-max]	53.6 [34.0-58.0]	63.7 [58.5-68.2]	73.0 [68.5-78.5]	87.0 [78.6-134]
AUC Fifth dose				
Geometric mean (%CV)	285 (15.9)	266 (15.0)	257 (17.2)	239 (13.4)
Median [min-max]	291 [173-520]	266 [174-362]	256 [188-755]	241 [163-396]
%change	9.12	1.64	-1.61	-8.68
C_{max} Fifth dose				
Geometric mean (%CV)	29.9 (16.0)	27.5 (20.8)	25.0 (20.3)	22.5 (19.1)
Median [min-max]	30.0 [20.9-44.7]	26.2 [20.4-62.6]	24.0 [16.2-49.7]	21.9 [15.6-48.6]
%change	14.6	5.15	-4.35	-13.7
C_{min} Fifth dose				
Geometric mean (%CV)	8.29 (23.8)	7.39 (26.6)	7.44 (26.8)	6.94 (26.4)
Median [min-max]	8.73 [3.93-19.1]	7.61 [2.80-12.0]	7.63 [3.84-32.2]	7.21 [1.68-14.5]
%change	10.5	-1.60	-0.919	-7.53

Note: %change was computed with the geometric mean of the entire population as a reference.
AUC, area under the serum concentration-time curve; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; CV, coefficient of variation; max, maximum; min, minimum; N, number of patients; PK, pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile.

Simulations were conducted to compare the tremelimumab exposure between the 75 mg Q3W dosing regimen and 1 mg/kg Q3W dosing regimen in order to evaluate the suitability of a fixed dosing regimen of tremelimumab versus body weight-based dosing. Tremelimumab serum concentrations were simulated based on the individual Empirical Bayes estimates obtained from the final model for the POSEIDON patients. The concentration profiles were summarized over time (Figure 2). The concentration profiles showed a good overlap between the 2 dosing regimens.

Figure 2. Comparison of tremelimumab 75 mg Q3W and 1 mg/kg Q3W – concentration profiles



Note: The blue and red areas represent the 90% prediction interval of the simulated concentrations; the blue and red line represent the median concentration profiles.
Conc, concentration; PK, pharmacokinetic(s); Q3W, every 3 weeks.

Bioanalytical Methods

Bioanalysis methods for quantitation of tremelimumab drug concentration, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) were developed and validated.

Population PK analyses for tremelimumab and durvalumab

A population PK model was developed for tremelimumab based on a pooled dataset from 6 Studies: Study 02, Study 06, Study 10, DETERMINE, BASKET and POSEIDON, which comprised of 5455 serum concentrations from 1605 patients. The final Pop PK model of tremelimumab was a 2-compartment model with linear CL and an additional time-dependent CL component for patients on combination therapy only. The following covariates were identified as statistically significant and included in the final model: body weight and sex on both CL and V1; albumin, primary indication and combination therapy (chemotherapy vs. no chemotherapy) on CL. The effect of body weight was allometrically scaled with estimated exponents of 0.370 and 0.453 for CL and V1, respectively, indicating that the effect of body weight was less than proportional. The final model was evaluated by means of non-parametric bootstrap analysis (n=1000), RSEs, GOF-plots and pcVPCs.

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. 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 effect of body weight was allometrically scaled with estimated exponents of 0.337 and 0.494 for CL and V1. The final model was evaluated by means of non-parametric bootstrap analysis (n=500), RSEs, GOF-plots and pcVPCs.

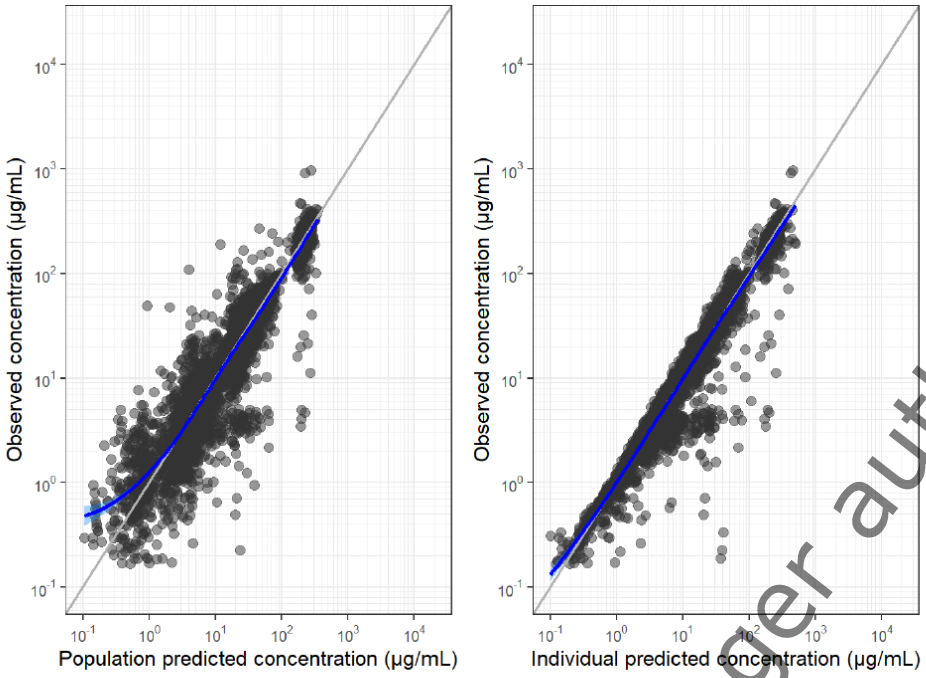
Parameter estimates of the final model for tremelimumab and selected diagnostic plots are shown in Table 6 and Figure 3 and Figure 4.

Table 6. Population PK model parameter estimates (Final model – run079)

Parameter	Estimate	RSE (%)	bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.309	1.56	[0.298 ; 0.342]	--	L/day
V1	3.72	0.869	[3.63 ; 3.78]	--	L
Q	0.454	1.37	[0.378 ; 2.38]	--	L/day
V2	2.61	1.56	[2.38 ; 3.60]	--	L
Tmax change CL	-0.218	15.4	[-0.385 ; -0.127]	--	--
TC50 change CL	81.5	3.18	[35.9 ; 191]	--	days
Covariate					
Bodyweight on V1	0.453	6.31	[0.401 ; 0.520]	--	--
Sex on V1	-0.149	9.27	[-0.181 ; -0.123]	--	--
Bodyweight on CL	0.370	10.6	[0.271 ; 0.477]	--	--
Albumin on CL	-0.809	6.66	[-0.938 ; -0.666]	--	--
Sex on CL	-0.134	14.2	[-0.174 ; -0.0905]	--	--
Comb2 on CL	-0.115	20.7	[-0.162 ; -0.0634]	--	--
Primary indication 6 or 7 on CL	-0.153	19.4	[-0.210 ; -0.0877]	--	--
Interindividual Variability					
ETA CL	0.111	7.94	[0.0908 ; 0.137]	19.2	--
Covariance CL-V1	0.0520	14.2	[0.0361 ; 0.0642]	--	--
ETA V1	0.0402	16.4	[0.0277 ; 0.0531]	25.3	--
Covariance CL-V2	0.0649	24.5	[0.0312 ; 0.133]	--	--
Covariance V1-V2	0.0782	23.9	[0.0393 ; 0.102]	--	--
ETA V2	0.215	18.4	[0.128 ; 0.316]	37.1	--
ETA Tmax	0.754	25.3	[0.283 ; 1.40]	68.8	--
Residual Variability					
Proportional component	0.279	2.47	[0.264 ; 0.293]	15.9	--
Additive component	0.146	15.2	[0.0796 ; 0.198]	15.9	µg/mL

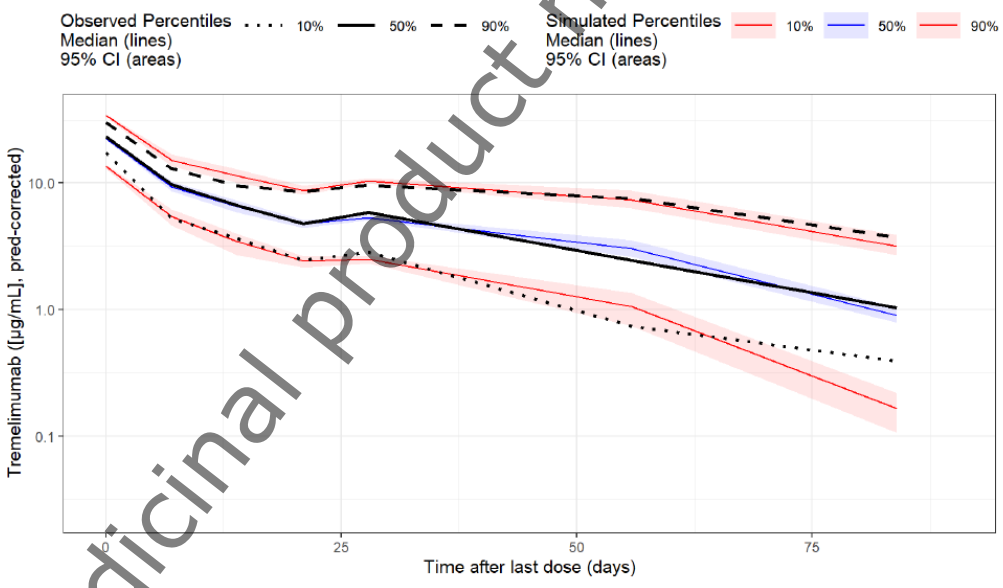
Source: az-durvalumab-pk-model-study-v10.Rmd, Reference: 04e0e5:917e6f
Abbreviations: CI=confidence interval, CL=clearance, Comb2=durvalumab, tremelimumab and chemotherapy (standard of care), as compared to treatment arms without chemotherapy, ETA=random effect, IIV=inter-individual variability, PK=pharmacokinetics, V1=central volume of distribution, primary indication 6=biliary tract carcinoma, primary indication 7=esophagus carcinoma, Q=inter-compartmental clearance, V2=peripheral volume of distribution, RSE=relative standard error, TC50=time to 50% clearance reduction, Tmax=maximum change of CL over time

Figure 3. Final Model GOF Plots for serum tremelimumab concentration: Observations vs Predictions



Source: az-tremelimumab-pk-gof-v10.docx, Reference: 80bb8e:3794d8
Note: Dots are individual data; the grey solid lines are lines of identity. Blue solid lines are smoothed LOESS lines, with confidence areas shown as light blue areas. Predictions below the LLOQ are not shown.
Abbreviation: LLOQ=lower limit of quantification

Figure 4. VPC of the Final Model vs TAD, POSEIDON Study



Source: az-treme-PK-Model-Evaluation_VPC-v6.Rmd
Note: the solid and dashed lines represent the median, 10th, and 90th percentiles of the observations. Red and blue lines are the respective model-predicted percentiles, and the shaded red and blue areas represent the 95% confidence intervals around these predictions. The x-axis is truncated to 90 days, as observed data get too sparse thereafter.
Abbreviations: CI=confidence interval, TAD=time after dose, VPC=visual predictive check

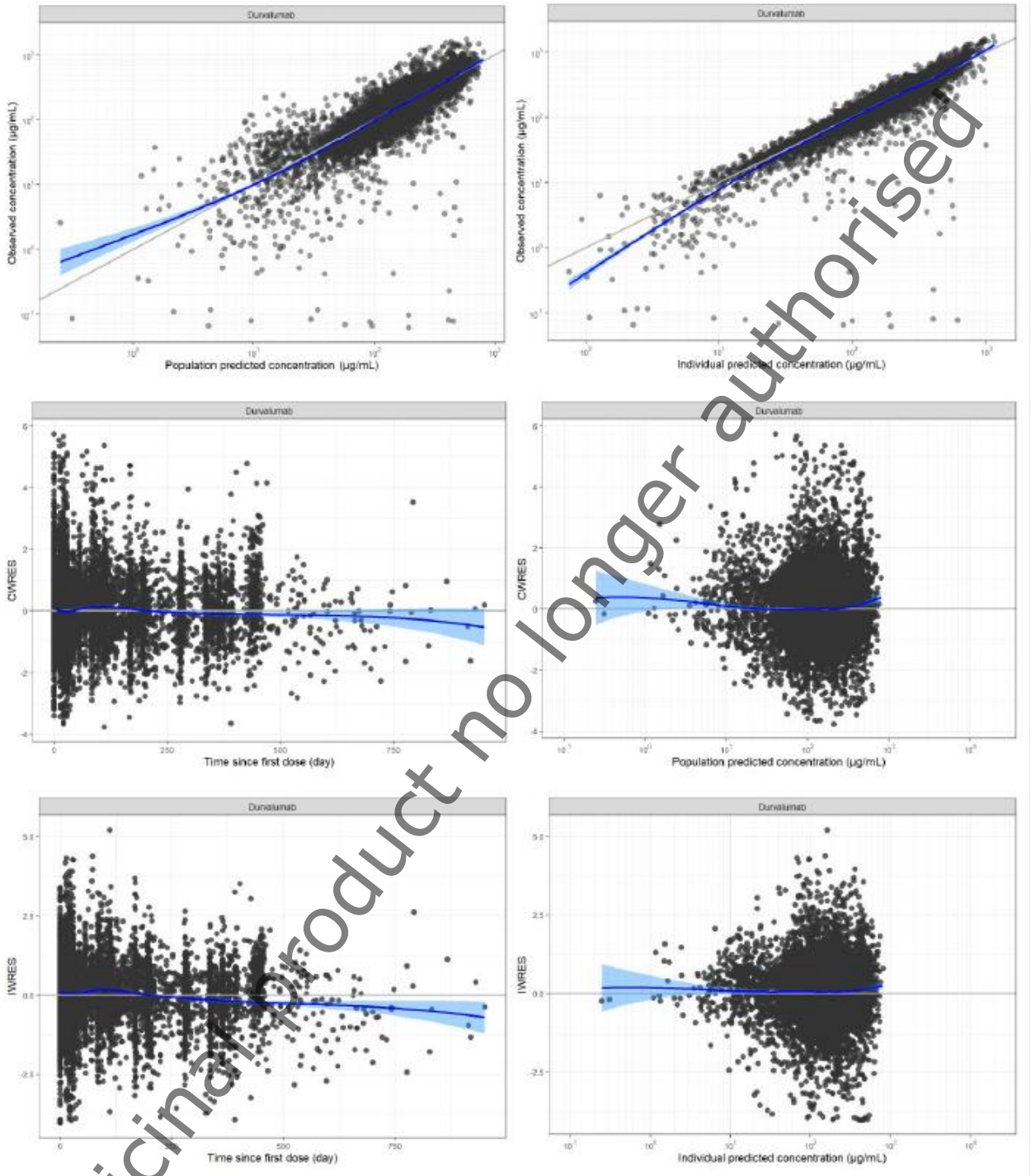
Parameter estimates of the final model for durvalumab and selected diagnostic plots are shown in Table 7, Figure 5 and Figure 6.

Table 7. Population PK Model Parameter Estimates durvalumab (Final Model-run131.mod)

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 ; 0.0780]	--	--
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

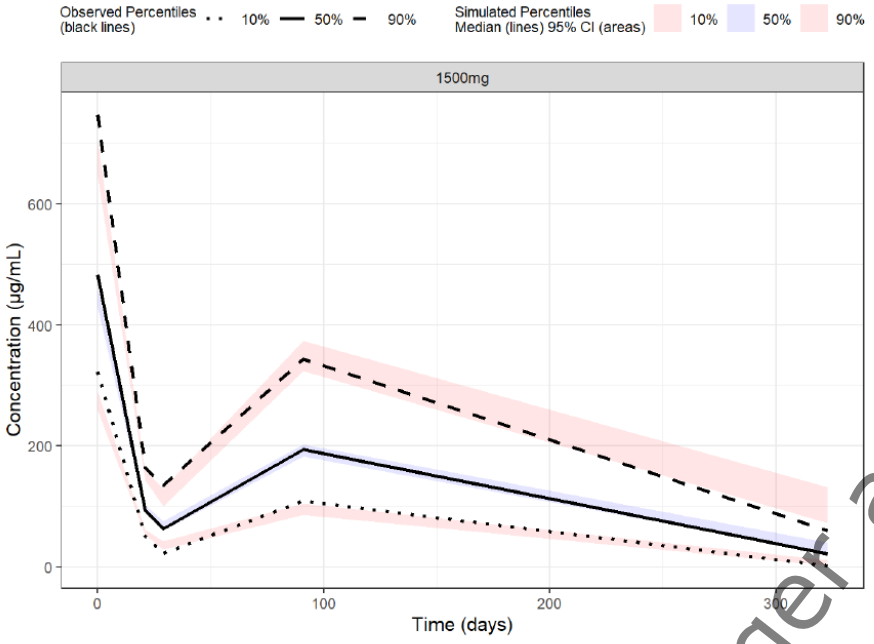
Source: az-durvalumab-pk-model-poseidon-v3.Rmd, Reference: 3781a5:7d4acc
Abbreviations: CI=confidence interval, COMB1=durvalumab+SOC, COMB2=durvalumab+tremelimumab+SOC, Cov=Covariance, ECOG=Eastern Cooperative Oncology Group, ETA=random effect, LAM=Hill factor, LDH=lactate dehydrogenase, RSE=relative 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 5. Final model – basic Goodness of Fit Plots (run131.mod)



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 6. 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

Tremelimumab & durvalumab exposure-response modelling analyses

The final PopPK models of tremelimumab and durvalumab were used to derive individual predicted exposure metrics for the E-R analyses. The tremelimumab/durvalumab E-R relationship for OS, PFS and ORR were analysed using data from POSEIDON, which included 326 patients administered tremelimumab (T) + durvalumab (D) + SoC arm. Both OS and PFS were analysed by Kaplan-Meier plots stratified by model-predicted exposure metrics and CPH models with T + D + SoC. Cmin of tremelimumab following dose 5 and tumour type were statistically significant for OS.

The parameter estimates from the final OS CPH model are presented in Table 8and parameter estimates from the final PFS CPH model are presented in Table 9.

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). Models were evaluated by graphically superimposing model-predictions over the observed data.

Table 8. 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.

Table 9. 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

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 (see Table 10).

Table 10. 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

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.

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 11).

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 12).

Table 11. 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

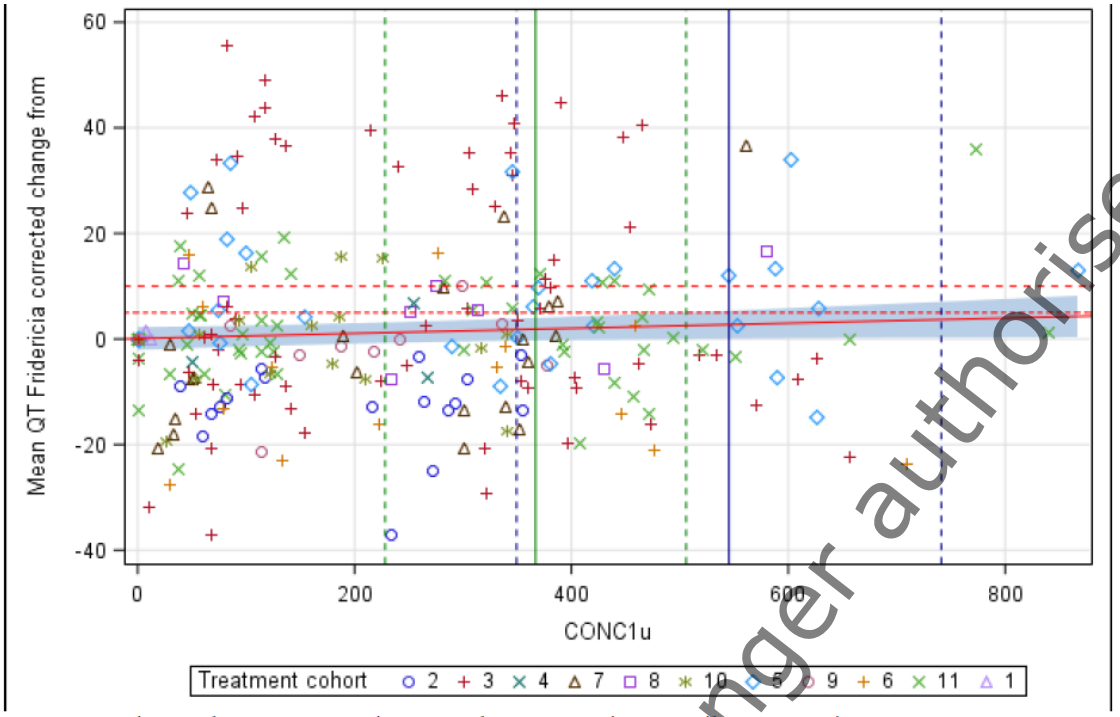
Table 12. Parameter estimates of tremelimumab PF - ΔQTcF relationship

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 7, Figure 8 and Table 13).

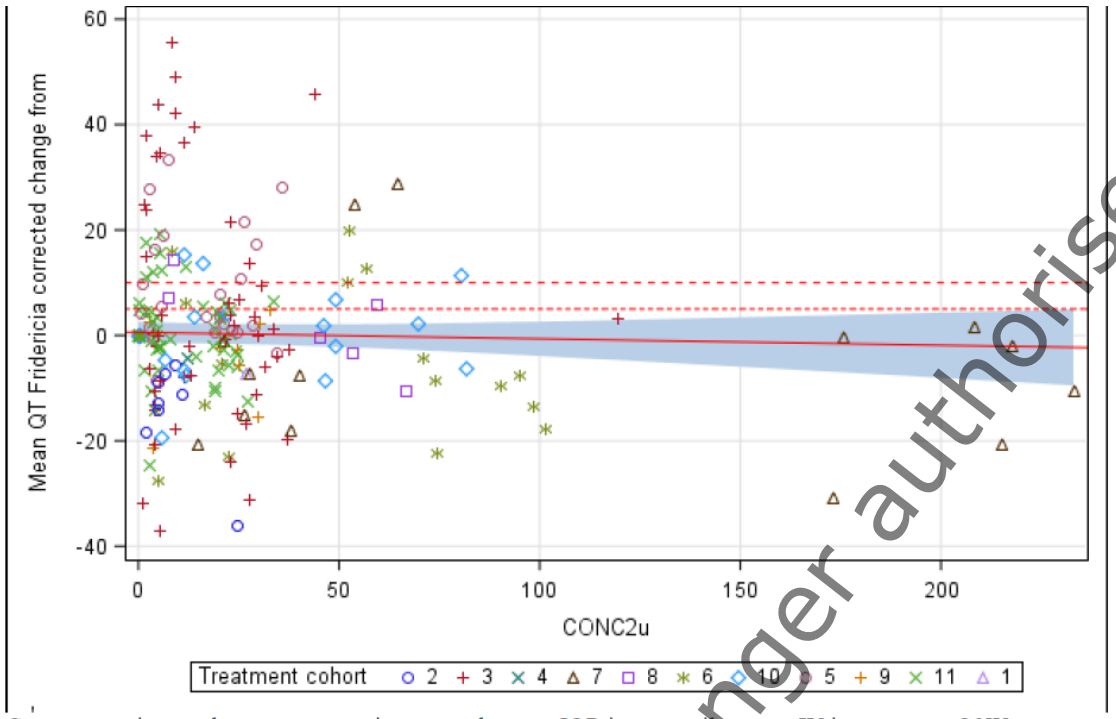
Figure 7. QTcF (change from baseline) versus concentration of durvalumab on intercept full data



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 8. 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 13: 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

The product is intended for intravenous administration. Clinical studies have not been conducted to evaluate the bioavailability or bioequivalence compared to other formulations.

Dose-normalized tremelimumab PK Parameters (C_{max} and AUC_{0-28}) from the dose finding study (Study 06) following administration of tremelimumab in combination with durvalumab are given in Table 14.

Table 14. 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.

Distribution

No distribution studies have been conducted in patients with NSCLC. However, Study 22 evaluated PK parameters in patients with advanced hepatocellular carcinoma, who received a single IV dose of 300 mg on Day 1. In a subset of patients from this study (N=11): for whom intensive PK sampling was done, the estimated volume of distribution was 7.6 L (Table 15).

Based on population PK analysis that included 1605 patients who received tremelimumab monotherapy or in combination with durvalumab with or without chemotherapy in the dose range of ≥ 1 mg/kg, the geometric mean steady-state volume of distribution (V_{ss}) was 6.33 L.

Table 15. Individual values and descriptive statistics of tremelimumab serum PK parameters following single IV dose of 300 mg tremelimumab on Day 1 of Week 1 to patients with advanced hepatocellular carcinoma (PK analysis set) (Study 22)

Allocation number	Tremelimumab PK parameters						
	AUC_{last} (µg/mL*day)	AUC_{inf} (µg/mL*day)	C_{max} (µg/mL)	T_{max} (h)	Apparent terminal $t_{1/2}$ (day)	CL (L/day)	Vz (L)
D4190C00022/20015120016	1814	1903	102.7	1.58	28.2	0.158	6.42
D4190C00022/20015220014	1212	1469	100.9	3.24	67.9	0.204	20.0
D4190C00022/20015240015	1784	1828	73.60	1.18	23.6	0.164	5.59
D4190C00022/20016520005	1009	1022	95.40	1.01	16.0	0.293	6.76
D4190C00022/20018500022	1362	1377	68.50	1.08	25.7	0.218	8.09
D4190C00022/20021190008	1422	1636	117.8	1.25	21.7	0.183	5.73
D4190C00022/20021190009	1267	1310	89.30	1.13	24.3	0.229	8.02
D4190C00022/20021200007	1225	1728	122.1	1.22	18.3	0.174	4.59
D4190C00022/20021200010	1223	1273	84.60	1.27	19.4	0.236	6.58
D4190C00022/20021210007	1303	1597	92.10	1.06	39.4	0.188	10.7
D4190C00022/20021210011	895.5	913.5	80.30	1.13	18.6	0.328	8.83
Number of patients	11	11	11	11	11	11	11
Arithmetic mean	1320	1460	93.39	NR	27.6	0.216	8.30
Standard deviation	279.5	317.4	16.87	NR	14.8	0.0539	4.24
ACV (%)	21.2	21.7	18.1	NR	53.8	25.0	51.1
Median	1267	1469	92.10	1.18	23.6	0.204	6.76
Minimum	895.5	913.5	68.50	1.01	16.0	0.158	4.59
Maximum	1814	1903	122.1	3.24	67.9	0.328	20.0
Geometric mean	1294	1426	92.02	NR	25.1	0.210	7.64
GCV (%)	21.1	23.7	18.2	NR	43.0	23.7	41.3
95% CI	(1124, 1489)	(1219, 1668)	(81.50, 103.9)	NR	(19.1, 33.2)	(0.180, 0.246)	(5.85, 9.97)

ACV, arithmetic coefficient of variation is calculated in the original scale with the equation: 100 × (SD/AM); AUC_{inf}, area under the concentration versus time curve from 0 to infinity; AUC_{last}, area under the concentration versus time curve from 0 to the time of the last quantifiable sample; AUC_{inf}, area under the concentration versus time curve from 0 to infinity after dosing; CI, confidence interval of the geometric mean; CL, clearance; C_{max}, concentration at the end of infusion (TAD < 1 day) in that visit; GCV, geometric coefficient of variation is calculated in the natural log scale with the equation: $100 \times \sqrt{(\exp(\sigma^2) - 1)}$, where σ^2 is the observed variance on the natural log scale; IV, intravenous; NR, not reported; PK, pharmacokinetic; $t_{1/2}$, apparent first-order terminal elimination half-life; TAD, time after dose; T_{max}, time to maximum serum concentration; V_z, volume of distribution during the terminal phase.

Elimination

Tremelimumab, as a typical mAb, is not cleared renally due to its large molecular weight. The primary elimination pathways are protein catabolism via the reticuloendothelial system (RES) or target-mediated disposition.

Based on the findings from the subset of patients from Study 22, for whom intensive PK sampling was done, the clearance was 0.21 L/day and the apparent half-life (apparent terminal t½) was 25.1 days (Table 15).

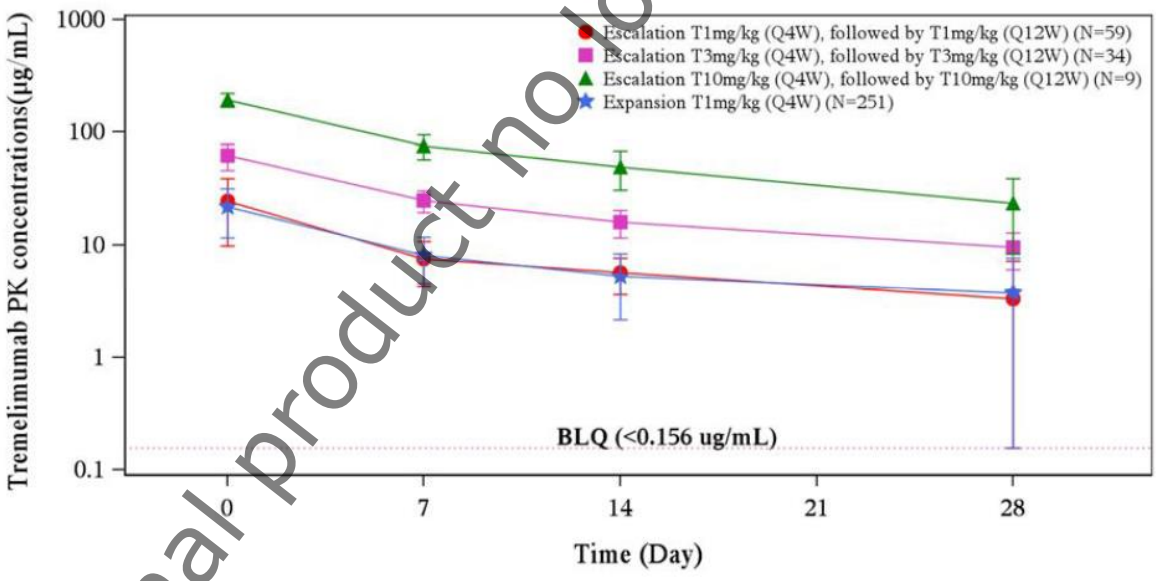
Based on population PK analysis, the geometric mean steady-state clearance (CL_{ss}) was 0.309 L/day and the geometric mean terminal half-life was approximately 14.2 days.

Dose proportionality and time dependencies

In Study 06 an approximately dose-proportional increase in PK exposure (C_{max} and AUC_{0-28}) of tremelimumab was observed over the dose range of 1 to 10 mg/kg tremelimumab Q4W when administered in combination with durvalumab (Table 14). Exposure following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. The PK profile for tremelimumab is shown in Figure 9.

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.

Figure 9. 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.

Intra- and inter-individual variability

For tremelimumab, all fixed and random effects were estimated with good precision (< 25% RSE). The IIV was 33%, 20%, 46% and 87% for CL, V1, V2 and T_{max}, respectively.

For durvalumab, the IIV was limited, amounting to 28%, 24% and 25% on CL, V1 and Tmax, respectively.

Special populations

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

The effect of renal impairment, hepatic impairment, age, race, gender, and body weight on the PK of tremelimumab, however, has been evaluated in the Population PK analysis. In summary, the final Population PK modeling indicated that the baseline patient characteristics of age, race, renal function, and hepatic function had no effect on the PK of tremelimumab.

In contrast, the Population PK analysis identified several covariates that were statistically significant on tremelimumab CL and V1: body weight, ALB, sex, combination therapy and primary indication on CL; and body weight and sex on V1, all identified covariates changed tremelimumab exposure by less than ± 20% and were regarded as of minor clinical relevance.

Impaired renal function

Mild (creatinine clearance (CrCL) 60 to 89 ml/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 ml/min) had no clinically significant effect on the PK of tremelimumab. The effect of severe renal impairment (CrCL 15 to 29 ml/min) on the PK of tremelimumab is unknown.

Impaired hepatic function

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) had no clinically significant effect on the PK of tremelimumab. The effect of moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown.

Gender

Based on the final PopPK model of tremelimumab, gender was identified as a statistically significant covariate on PK of tremelimumab. Based on the final Population PK model using POSEIDON data, the geometric mean CL_{ss} and V1 values were 13.4% and 14.9% lower, respectively, in female patients compared to the respective population mean values.

These differences in CL_{ss} and V1 (< 20%) were not considered clinically meaningful given the lack of exposure-safety and exposure-efficacy relationships in POSEIDON.

Age

Age (range 22 to 97 years) was not identified as a significant covariate in the final PopPK model of tremelimumab

	Durvalumab + Tremelimumab + SoC	Durvalumab + SoC	SoC	All patients in PopPK
N	326	322	333	1605
Age sub-group (yr)				
<65	185 (56.7%)	164 (50.9%)	175 (52.6%)	834 (52.0%)
>=65-75	107 (32.8%)	124 (38.5%)	120 (36.0%)	595 (37.0%)
>=75	34 (10.4%)	34 (10.6%)	38 (11.4%)	176 (11.0%)

Race

Race was not identified as a significant covariate in the final PopPK model of tremelimumab and race did not seem to influence PK of tremelimumab.

Weight

Based on the final PopPK model of tremelimumab, body weight was identified as a statistically significant covariate on PK of tremelimumab. The impact of body weight on CL_{ss} or V1, evaluated based

on the difference in geometric mean parameter values at the 95th or 5th percentile of the weight distribution from that of the overall population, was within -11.8% to +14.7% for CL_{ss} and -14.2% to +18.3% for V1.

Table 16 shows the simulated tremelimumab AUC, C_{max}, and C_{min} at steady state across body weight quartiles. At the highest weight quartile, the simulated geometric mean AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ decreased by 8.68%, 13.7%, and 7.53%, respectively, compared to the geometric mean of the overall population. At the lowest quartile, the simulated AUC_{ss}, $C_{max,ss}$, and Cmin,ss increased by 9.12%, 14.6%, and 10.5%, respectively, compared to the mean of the overall population.

These differences in exposure were not considered clinically meaningful given the lack of exposure-efficacy and exposure-safety relationships in POSEIDON.

Table 16: Tremelimumab exposure across body weight quartiles.

	Q1	Q2	Q3	Q4
Individuals				
N	84	81	80	81
Body weight (kg)				
Geometric mean (%CV)	51.4 (12.3)	63.4 (4.50)	73.4 (3.81)	90.2 (12.5)
Median [min-max]	53.6 [34.0-58.0]	63.7 [58.5-68.2]	73.0 [68.5-78.5]	87.0 [78.6-134]
AUC Fifth dose				
Geometric mean (%CV)	285 (15.9)	266 (15.0)	257 (17.2)	239 (13.4)
Median [min-max]	291 [173-520]	266 [174-362]	256 [188-755]	241 [163-396]
%change	9.12	1.64	-1.61	-8.68
C_{max} Fifth dose				
Geometric mean (%CV)	29.9 (16.0)	27.5 (20.8)	25.0 (20.3)	22.5 (19.1)
Median [min-max]	30.0 [20.9-44.7]	26.2 [20.4-62.6]	24.0 [16.2-49.7]	21.9 [15.6-48.6]
%change	14.6	5.15	-4.35	-13.7
C_{min} Fifth dose				
Geometric mean (%CV)	8.29 (23.8)	7.39 (26.6)	7.44 (26.8)	6.94 (26.4)
Median [min-max]	8.73 [3.93-19.1]	7.61 [2.80-12.0]	7.63 [3.84-32.2]	7.21 [1.68-14.5]
%change	10.5	-1.60	-0.919	-7.53

Note: %change was computed with the geometric mean of the entire population as a reference.
AUC, area under the serum concentration-time curve; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; CV, coefficient of variation; max, maximum; min, minimum; N, number of patients; PK, pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile.

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 C_{max}, 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

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of tremelimumab is based on pooled data in 1337 patients who were treated with tremelimumab 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). One-hundred forty-three patients (10.7%) tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 8.9% (119/1337) of patients.

In the POSEIDON study, of the 278 patients who were treated with tremelimumab 75 mg in combination with durvalumab 1 500 mg every 3 weeks and platinum-based chemotherapy and evaluable for the presence of ADAs, 38 (13.7%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 11.2% (31/278) of patients. Both ADA incidence and prevalence were numerically similar between the T + D + SoC and D + SoC arms, indicating that the presence of tremelimumab did not have an apparent effect on the immunogenicity of durvalumab.

2.6.2.2. Pharmacodynamics

Mechanism of action

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 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 tumour cells and tumour-associated immune cells in the tumuor 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 and durvalumab 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 tumour 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 tumour, 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 tumour cells.

Primary pharmacology

Data from Study 06, Study 10 and Study 22 indicate that a pharmacodynamic effect exists on proliferating CD4+ and CD8+ T cell quantities consistent with the proposed mechanisms of action of both therapeutic agents.

Data from Study 1108, Japan Study 02, Study 06 and Study 10 indicate that durvalumab treatment (with or without tremelimumab) reduces free Soluble Programmed Cell Death Ligand-1 (sPD-L1) in serum.

No PD biomarkers are proposed for monitoring of effect.

Secondary pharmacology

Concentration-QTc Analysis

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.

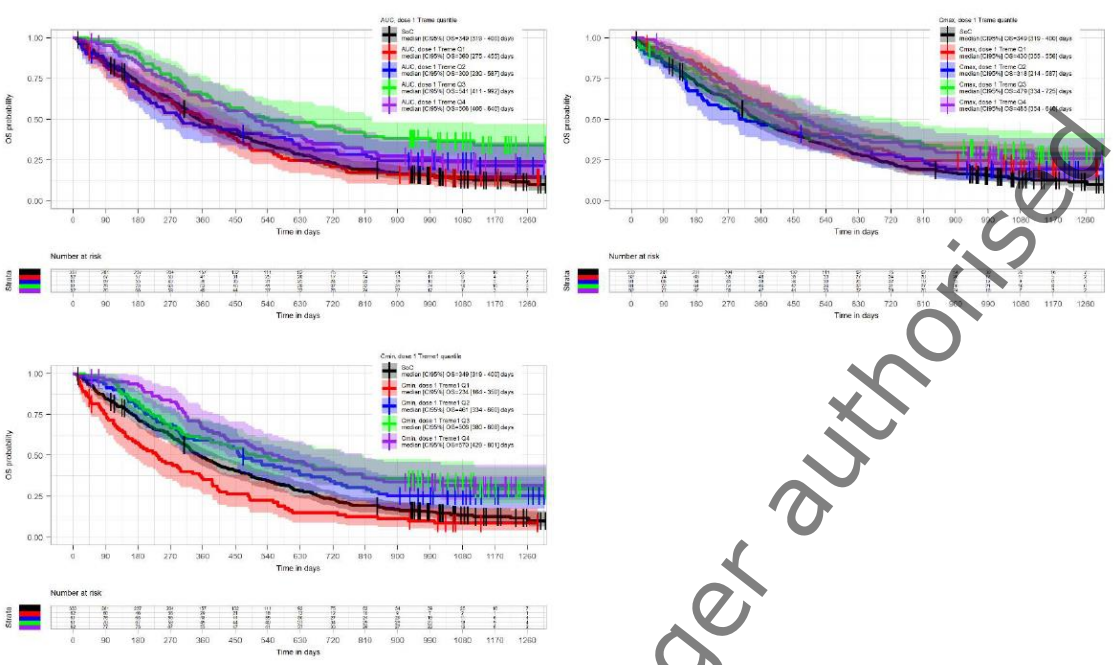
Exposure-response relationships

Assessment of an exposure-efficacy relationship was conducted using overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) as efficacy parameters in patients from POSEIDON, for whom the different exposure metrics could be calculated. The total number of patients included in the analysis of the exposure-efficacy relationship was 326 receiving T + D + SoC, 322 receiving D + SoC, and 333 receiving SoC.

Both OS and PFS were explored by Kaplan-Meier estimates and analyzed by Cox proportional-hazards models based on data from patients in the T + D + SoC arm.

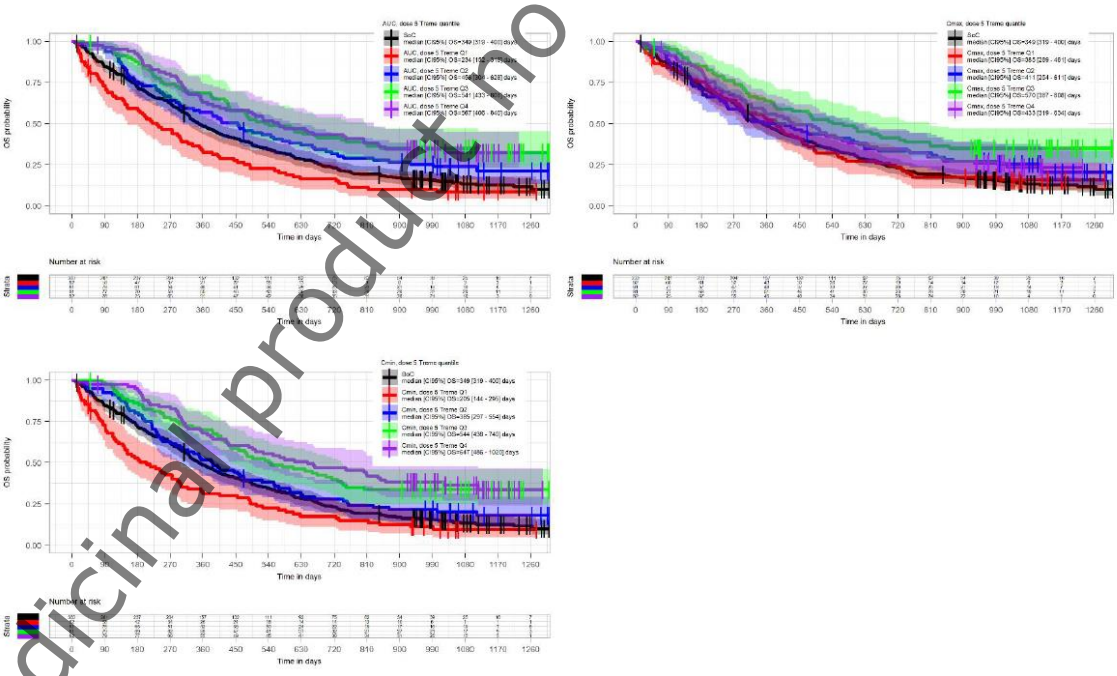
Exposure-efficacy relationship
Overall survival (OS)

Figure 10. OS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at dose 1



Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring.
AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; OS, overall survival; PK pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile; SoC, standard of care chemotherapy; treme, tremelimumab.

Figure 11. OS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at dose 5



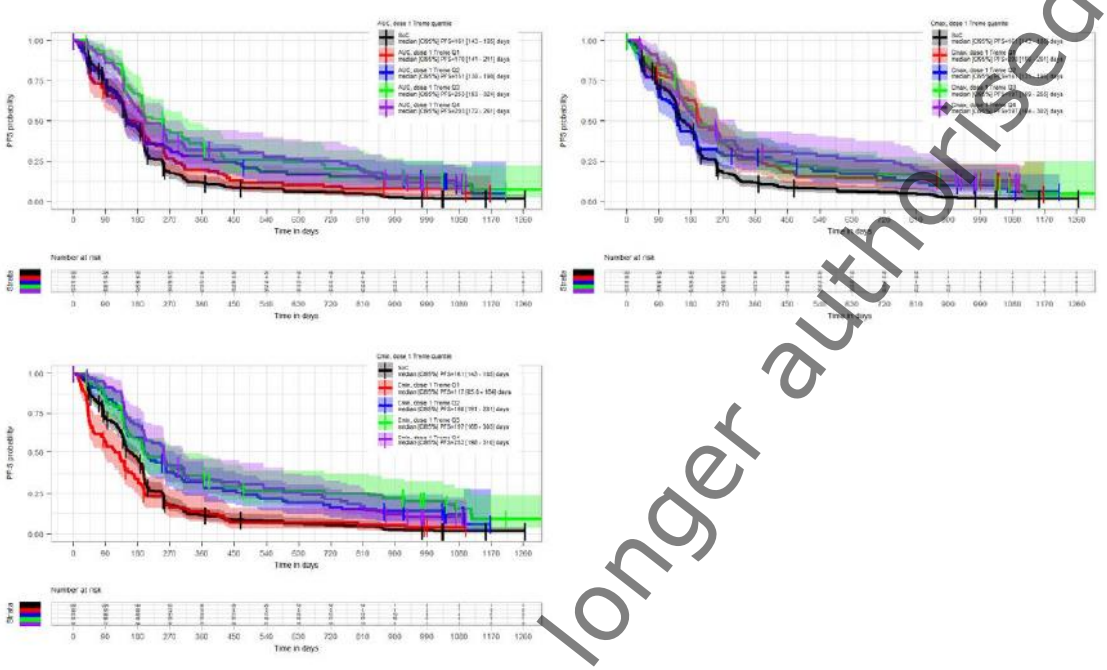
Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring.
AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max} maximum serum concentration; C_{min} minimum serum concentration; OS, overall survival; PK, pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile; SoC, standard of care chemotherapy; treme, tremelimumab.

For $AUC_{Dose\ 5\ Treme}$, $C_{min,\ Dose\ 5\ Treme}$, and $C_{min,\ Dose\ 1\ Treme}$, there was a trend that patients with exposure in the 1st quartile had shorter OS compared to those in the 2nd quartile (Figure 10 and Figure 11). Similarly, patients in the 2nd quartile had also a shorter OS than those in the 3rd quartile. However, no difference was observed between 3rd and 4th quartile. Further, for all quartiles but the 1st, the Kaplan-Meier curves of OS were above that of the SoC arm.

In order to assess whether confounding factors could explain the fact that the 1st quartile had a worse OS than SoC, a case match analysis was performed (see below).

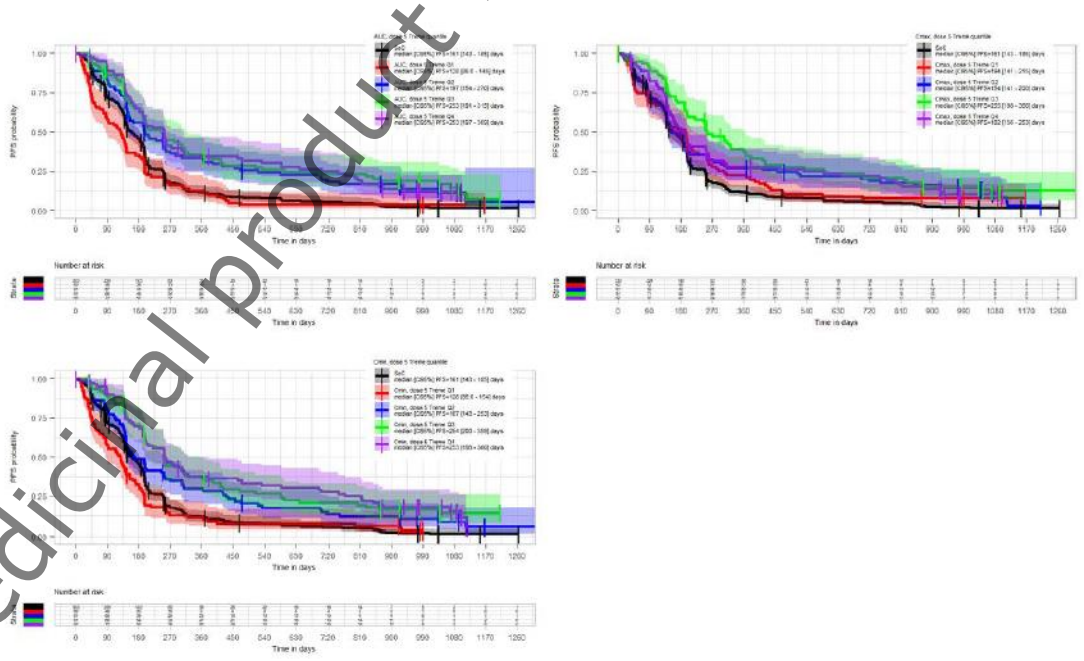
Progression-free survival (PFS)

Figure 12. PFS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at dose 1



Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring.
AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; PFS, progression-free survival; PK, pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile; SoC, standard of care chemotherapy; treme, tremelimumab.

Figure 13. PFS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at dose 5



Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring.
AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; PFS, progression-free survival; PK, pharmacokinetic(s); Q1/2/3/4, 1st, 2nd, 3rd, 4th quartile; SoC, standard of care chemotherapy; treme, tremelimumab.

For $AUC_{Dose\ 5\ Treme}$, $C_{min,\ Dose\ 5\ Treme}$, and $C_{min,\ Dose\ 1\ Treme}$, and similarly to what was observed for OS, for all quartiles but the 1st, the Kaplan-Meier curves of PFS were above that of the SoC arm (Figure 12 and Figure 13).

Exposure-response analyses demonstrated that the C_{min} after tremelimumab dose at Cycle 5 was the most significant exposure metric that influenced OS and PFS in patients enrolled in the POSEIDON study. In addition to tremelimumab exposure, the following covariates also influence OS and PFS: tumour type (both OS and PFS), NLR (PFS), PD-L1 T cells (PFS), and tumor mutational burden (PFS).

Case Match Analysis

The exploratory analysis of OS and PFS by exposure metrics of tremelimumab revealed that the patients in Q1 of $C_{min,\ Dose\ 5\ Treme}$ were associated with a lower survival than those in the SoC arm; however, several confounding covariates could have influenced this observation.

To supplement the CPH models for OS and PFS, patients from the SoC arm were matched with those in Q1 of $C_{min,\ Dose\ 5\ Treme}$ of the T + D + SoC arm. Matching was performed based on the distributions of the following 10 disease-related covariates: baseline tumor size, Eastern Cooperative Oncology Group (ECOG) score at baseline, aspartate aminotransferase (AST), serum albumin (ALB), lactate dehydrogenase (LDH), neutrophil-to-lymphocyte ratio (NLR), tumor burden (> or < 12 mutations per megabase), tumor type (non-squamous vs squamous), 25% of PD-L1 TC, and the chemotherapy used in SoC (abraxane based vs gemcitabine based vs pemetrexed based). All the 82 treated patients in the Q1 subgroup were successfully matched to 82 patients in the SoC arm. All covariates in the selected 82 SoC patients were balanced after matching.

The HR for the comparison of patients in the Q1 subgroup with matched patients from the SoC arm was 1.04 (95% CI: 0.76-1.44) for OS and 0.99 (95% CI: 0.72-1.36) for PFS (Table 7). These results contrast with the HR calculated for the unmatched population. For OS, the HR was 1.42 (95% CI: 1.10-1.84) and was 1.23 (95% CI: 0.95-1.58) for PFS. The 95% CI of PFS HR for both unmatched and matched patients includes 1, suggesting that the apparent difference between groups in the Kaplan-Meier plot is not statistically significant. In conclusion, the case match analysis suggested that the observed relationship with tremelimumab exposure is possibly confounded by disease-related covariates.

Table 17. HR for OS and PFS in patients of Cmin, Dose 5 Treme Q1 subgroup and SoC group

Endpoint	Analysis	Median survival (days)		HR (95% CI)
		SoC	$C_{min,\ Dose\ 5\ Treme}$	
OS	Unmatched	n = 333 349	n = 82 205	1.42 (1.10-1.84)
OS	Matched with disease-related covariates	n = 82 242	n = 82 205	1.04 (0.76-1.44)
PFS	Unmatched	n = 333 161	n = 82 128	1.23 (0.95-1.58)
PFS	Matched with disease-related covariates	n = 82 133	n = 82 128	0.99 (0.72-1.36)

CI, confidence interval; $C_{min,\ Dose\ 5\ Treme}$, minimum serum concentration for tremelimumab following the 5th dosing cycle; HR, hazard ratio, n, number of patients in subgroup; OS, overall survival, PFS, progression-free survival, PK, pharmacokinetic(s); Q1, 1st quantile, SoC, standard of care chemotherapy.

No relationship between durvalumab exposure and OS or PFS was identified in the POSEIDON T + D + SoC arm.

Objective Response Rate (ORR)

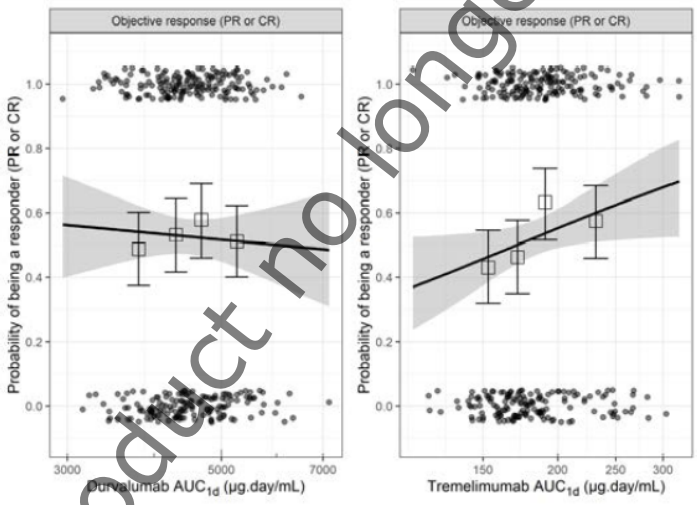
The ORR was dichotomized as partial response (PR) or complete response (CR), vs. stable disease or progression of disease (PD) and analyzed using a logistic regression model relating the probability of

being a responder to durvalumab and tremelimumab exposure metrics. This analysis focused on the combination treatment arm of T + D + SoC in which 330 patients received treatment. The ORR in 8 of the patients was not evaluable and excluded from this analysis. Of the remaining 322 patients, 3 patients did not have durvalumab exposure metrics and 4 patients did not have tremelimumab exposure metrics. Therefore, logistic regression models for assessing effect of durvalumab and tremelimumab were based on 319 and 318 patients, respectively.

In general, there appeared to be no clear trend between durvalumab exposure and the probability of being a responder. For tremelimumab, the plots appear to suggest an increase in the probability of being a responder with increasing exposure (Figure 14). However, the relatively large p-values show that none of the exposure metrics has a statistically significant impact (at the prespecified significance level of α = 0.001) on the probability of being a responder. It should be noted that for tremelimumab, the distribution of AUC after Dose 5, trough concentration after first dose, and after Dose 5 is somewhat narrow and there are a few potentially outlying patients.

In general, there was no clear trend between the covariates and the probability of being a responder.

Figure 14. 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.

Exposure-safety relationship

The safety endpoints of interest were Grade 3 and above treatment-related adverse events (AEs), Grade 3 and above adverse events of special interest (AESIs), AEs leading to durvalumab treatment discontinuation and AEs leading to tremelimumab treatment discontinuation, focusing on the durvalumab + tremelimumab + SoC arm only.

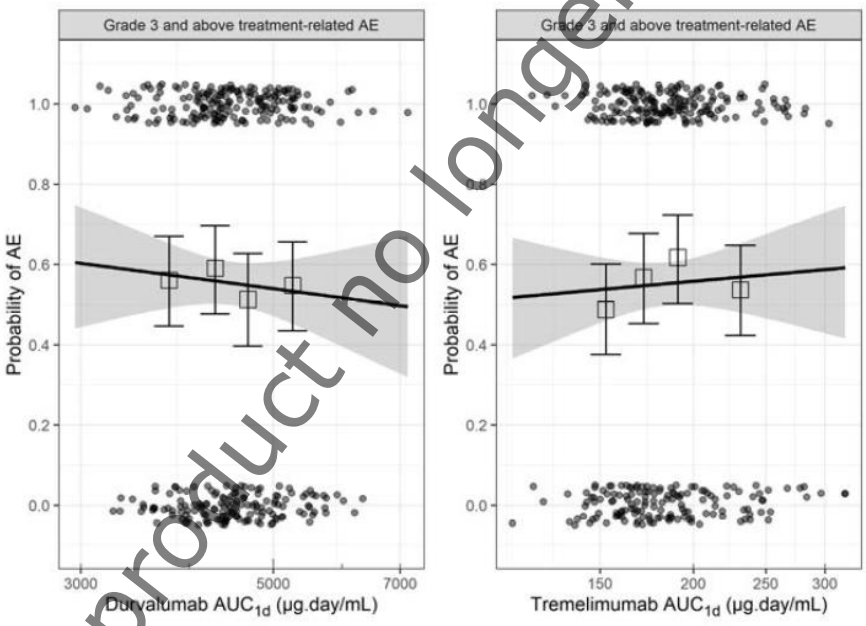
Of the 330 patients in this arm, 3 did not have durvalumab exposure metrics while 4 did not have tremelimumab exposure metrics hence 327 and 326 patients were analyzed in the logistic regression models for durvalumab and tremelimumab respectively.

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 15. 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 16.

In general, there appears to be no clear trend between increasing exposure and the probability of AEs. The p-values associated with exposure effects were relatively large (in comparison to the prespecified significance level of α = 0.001) indicating that the relationship was not statistically significant.

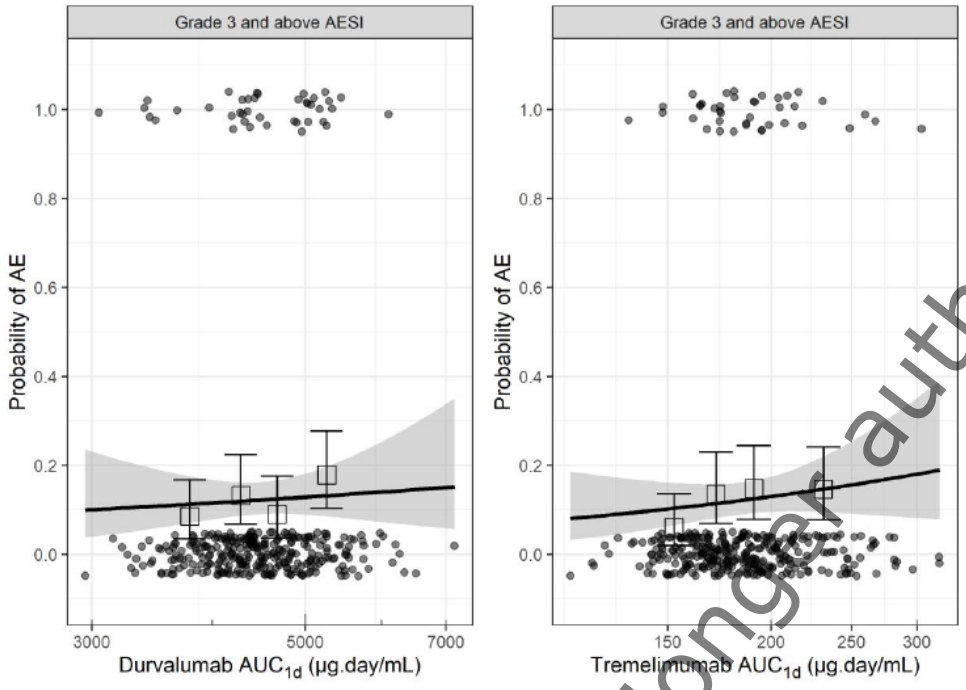
Although not statistically significant, it was notable that the coefficients for the effect of durvalumab on probability of Grade 3 and above treatment-related AEs were negative, suggesting a counterintuitive decrease in the probability of AEs with increasing exposure. However, these effects were small 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 15. 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 16. 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.

2.6.3. Discussion on clinical pharmacology

The PK of tremelimumab alone or in combination with durvalumab have been investigated in patients enrolled in 3 Phase I/Ib studies, 1 Phase I/II study, 3 Phase II/IIb studies and 6 Phase III studies.

The pharmacokinetics (PK) of tremelimumab was assessed as monotherapy and in combination with durvalumab and platinum-based chemotherapy.

The pharmacokinetics of tremelimumab was studied in patients with doses ranging from 75 mg to 750 mg (or 10 mg/kg) administered intravenously once every 4 or 12 weeks as monotherapy. PK exposure increased dose proportionally (linear PK) at doses ≥ 75 mg. Steady-state was achieved at approximately 12 weeks. Based on population PK analysis that included 1605 patients who received tremelimumab monotherapy or in combination with durvalumab with or without chemotherapy in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the geometric mean steady-state volume of distribution (Vss) was 6. 33 L. Tremelimumab clearance (CL) decreased over time in combination with durvalumab and chemotherapy resulting in a geometric mean steady-state clearance (CLss) of 0.309 L/day; the decrease in CLss was not considered clinically relevant. The geometric mean terminal half life was approximately 14.2 days. The primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target mediated disposition.

In the POSEIDON study, overall PK profiles of durvalumab were similar between T + D + SoC and D + SoC arms, suggesting tremelimumab or SoC do not have an impact on PK of durvalumab when administered as combination therapy.

Overall, PK results of gemcitabine and Abraxane were similar between T + D + SoC, D + SoC, and SoC alone arms, suggesting durvalumab or tremelimumab do not have an impact on PK of SoC chemotherapy (gemcitabine or Abraxane) when administered as combination therapy.

In spite of these differences in study design, the assessed PK data (C_{max} and C_{trough}) for tremelimumab appear to be broadly comparable across studies.

A population PK model was developed for tremelimumab based on a pooled dataset from 6 Studies: Study 02, Study 06, Study 10, DETERMINE, BASKET and POSEIDON, which comprised of 5455 serum concentrations from 1605 patients. The final Pop PK model of tremelimumab was a 2-compartment model with linear CL and an additional time-dependent CL component for patients on combination therapy only. The following covariates were identified as statistically significant and included in the final model: body weight and sex on both CL and V1; albumin, primary indication and combination therapy (chemotherapy vs. no chemotherapy) on CL. The effect of body weight was allometrically scaled with estimated exponents of 0.370 and 0.453 for CL and V1, respectively, indicating that the effect of body weight was less than proportional. Residual unexplained variability is low (28%) and low-to-moderate inter-individual random effects were identified on CL (39%), V1 (21%) and V2 (49%). In addition, an omega was included on Tmax to account for a random variation on the time-dependency effect on CL. No trends were observed on the ETA distribution of Tmax across the different covariates evaluated, suggesting that the large IIV on Tmax is caused by a large and random distribution of inter-individual differences that are not linked to any covariate tested. The final model was evaluated by means of non-parametric bootstrap analysis (n=1000), RSEs, GOF-plots and pcVPCs. The evaluation of the GOF confirmed the adequacy of the structural population PK model proposed, but some bias have been observed in the DV vs IPRED plot, where large deviation (>10-fold) were observed between IPRED and DV. Slight model over-prediction was observed in these 22 observations out of 5238 observations. Most of the observations (12/22) were around the Cmax, suggesting that the model slightly over-predicts Cmax concentrations in those individuals. Based on the small proportion of observations that were over-predicted (0.42%), the model misspecification is considered of minor relevance. A large number of bootstrap runs failed to converge (474/1000) due to rounding errors which may indicate an unstable model. However, it seems termination status was not an important indicator of the quality of bootstrap parameter estimates and all median estimates and 95% CI of each parameter were close to the final model parameter estimates. The overall model performance was observed based on the pcVPC, suggesting no significant trends across the different percentiles. No relevant trends were observed across the different pcVPC stratified by the significant covariates, suggesting the overall adequacy of the model to capture the different sub-groups of populations.

Age (22 – 97 years), body weight (34 - 149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, tumour type, race or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

The effect of mild hepatic impairment and mild or moderate renal impairment was evaluated in pop PK analyses showing no impact on the exposure of tremelimumab. Accordingly, no dose adjustment is required in these special populations. There are insufficient data in patients with severe renal impairment for dosing recommendations However, as IgG monoclonal antibodies are not primarily cleared via renal pathways, a change in renal function is not expected to influence tremelimumab exposure. Data from patients with moderate and severe hepatic impairment are limited. However, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function

is not expected to influence tremelimumab exposure and as a consequence, no dose adjustment of Tremelimumab AstraZeneca is recommended for patients with hepatic impairment. No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.2). Data on patients aged 75 years of age or older are limited.

The presence of tremelimumab ADA did not impact tremelimumab PK, as it was not identified as a significant covariate in the tremelimumab PopPK analysis. There was no clear evidence that the presence of tremelimumab ADA had any potential impact on the safety in POSEIDON study.

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. The final model was evaluated by means of non-parametric bootstrap analysis (n=500), RSEs, GOF-plots and pcVPCs. 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.

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. 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.

A weight-based dosing regimen of 1 mg/kg 3W of tremelimumab was proposed for patients weighting 30 kg or less, to align the dosing recommendation with that of durvalumab for which a 30 kg cut-off was set based on a FDA-requested change to the endotoxin acceptance criteria during review of the initial durvalumab Investigational New Drug submission (June 2015). The predicted tremelimumab dose 5 (AUCdose5, Cmin,dose5) exposures for 30 kg or 20 kg body weights were generally lower compared to those observed in POSEIDON across the body weight quartiles. The lack of safety concern with this proposal was acknowledged. In addition, the MAH argued that since no clinically meaningful relationship between exposure and efficacy (OS and PFS) was observed for tremelimumab, and the efficacy results were similar across BW quartiles, the efficacy for patients with body weights less than or equal to 30 kg is expected to be similar to those weighing over 30 kg and receiving equivalent fixed doses in POSEIDON. The fixed dosing regimen of 75 mg Q3W was evaluated through a model-based analysis in patients between 30-34 kg (not enrolled in POSEIDON), and a >30% higher AUCss was predicted compared to patients between 34-58 kg. This increase in exposure gave raise to concerns regarding safety because (1) the predicted AUCss range with the fixed dosing regimen was higher (250-600 micrograms·h/mL) compared to the evaluated AUCss range in the exposure-safety analysis (<300 micrograms·h/mL), and (2) the slight positive exposure-safety relationship observed. A body weight regimen would provide more similar exposure to that observed in patients with higher body weight (>34 kg). Even in case of (slightly) lower exposure, lack of efficacy is not considered a concern,

as discussed above. Considering all this, the cut-off below which tremelimumab is to be administered according to body weight was finally fixed at 34kg and reflected in section 4.2 of the SmPC.

The use of systemic corticosteroids or immunosuppressants before starting tremelimumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of tremelimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting tremelimumab to treat immune-related adverse reactions.

No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab. Since the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected. PK drug-drug interactions between tremelimumab in combination with durvalumab and platinum-based chemotherapy were assessed in the POSEIDON study and showed no clinically meaningful PK interactions between tremelimumab, durvalumab, nab-paclitaxel, gemcitabine, pemetrexed, carboplatin or cisplatin in the concomitant treatment.

Assessment of an exposure-efficacy relationship was conducted using OS, PFS, and ORR as efficacy parameters in patients from POSEIDON.

OS and PFS were explored by Kaplan-Meier estimates and analyzed by Cox proportional-hazards models based on data from patients in the T + D + SoC arm.

ORR was dichotomized as partial response (PR) or complete response (CR), vs. stable disease or progression of disease (PD) and analyzed using a logistic regression model relating the probability of being a responder to durvalumab and tremelimumab exposure metrics.

For some of the tremelimumab PK parameters ($AUC_{Dose\ 5}$, $C_{min,\ Dose\ 5}$, and $C_{min,\ Dose\ 1}$), there was a trend that patients with exposure in the 1st quartile had shorter OS compared to those in the 2nd quartile. Similarly, patients in the 2nd quartile had also a shorter OS than those in the 3rd quartile. However, no difference was observed between 3rd and 4th quartile. Further, for all quartiles but the 1st, the Kaplan-Meier curves of OS were above that of the SoC arm.

Similar to what was observed for OS, the Kaplan-Meier curves of PFS were for all quartiles, but the 1st, above that of the SoC arm for the same tremelimumab PK parameters ($AUC_{Dose\ 5}$, $C_{min,\ Dose\ 5}$, and $C_{min,\ Dose\ 1}$).

In order to assess whether confounding factors could explain the fact that the 1st quartile had a worse OS and PFS than SoC, a case match analysis was performed, and this analysis suggested that the observed relationship with tremelimumab exposure was possibly confounded by disease-related covariates.

In terms of ORR, the plots appeared to suggest an increase in the probability of being a responder with increasing exposure to tremelimumab.

There appeared to be no clear trend between durvalumab exposure and the probability of being a responder.

Since the exposure-efficacy relationships was only evaluated through Kaplan-Meier plots with OS and PFS between tremelimumab vs SoC arms, the evaluation was in the first place considered insufficient. Additional statistical analyses (K-M and cox-regression analyses) conducted between T+D+chemo vs D+chemo arms were requested

As a result, the exposure-response CPH model for OS was updated based on durvalumab and tremelimumab treated patients from T + D + SoC versus D + SoC arms. OS KM plots for tremelimumab exposure metrics by quartiles at dose 1 and at dose 5, respectively, were provided.

The KM curve of D + SoC arm was above that of the SoC arm, and in the middle of those of different tremelimumab exposure quartiles. The impact of a number of identified covariates was assessed via the computation of the Hazard Ratio.

According to the applicant, the exposure-response CPH model for PFS was also updated based on durvalumab and tremelimumab treated patients from T + D + SoC versus D + SoC arms. The impact of a number of identified covariates was assessed via the computation of the Hazard Ratio.

For assessment of an exposure-safety relationship, the evaluated safety endpoints were Grade 3 and above treatment-related AEs from POSEIDON, Grade 3 and above AESIs, AEs leading to durvalumab treatment discontinuation and AEs leading to tremelimumab treatment discontinuation, focusing on the durvalumab + tremelimumab + SoC arm only. None of the tremelimumab or durvalumab exposure metrics were identified to have an influence on safety events in a logistic regression analysis.

In addition, a body weight-AE analysis found no clear sign of a higher frequency of AEs in subjects with low body weight.

The findings related to immunogenicity indicate a low immunogenicity risk of tremelimumab.

With respect to the concentration-QTc-analysis, modeling results did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF.

2.6.4. Conclusions on clinical pharmacology

Considering the nature of the product, the pharmacology package is considered adequate and the dosing of tremelimumab is considered appropriate with the proposed modification to use weight-based dosing for patients below 34kg, as discussed above.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

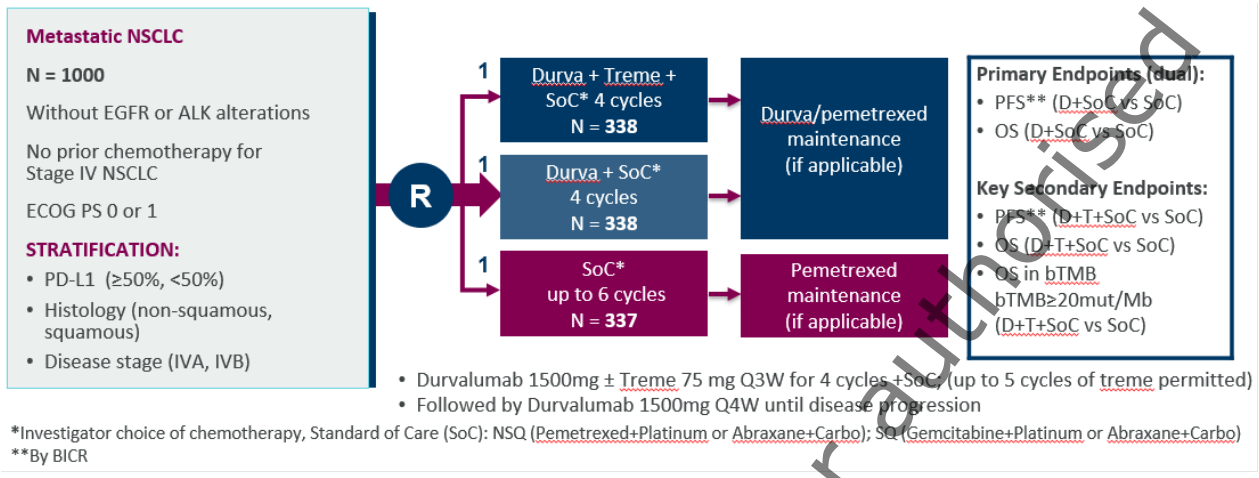
See section 2.6.2.1

2.6.5.2. Main study

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 17. Study design - POSEIDON



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-PFS and OS comparisons were done between arms 1 and 3 (T+D+SoC vs. SoC), also in the ITT.

Tumour scans and response assessment 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 althoughtthe study was open-label, the study team was 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 AstraZeneca or durvalumab.
- Pregnant or breastfeeding women.

- **Treatments**

The full dosing scheme of POSEIDON is presented in Table 18.

Table 18. 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 19.

Table 19. 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 20.

Table 20. 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.
AFP12 [a]	The Kaplan-Meier estimate of PFS at 12 months.

Endpoint	Definition
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 and Blinding (masking)**

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

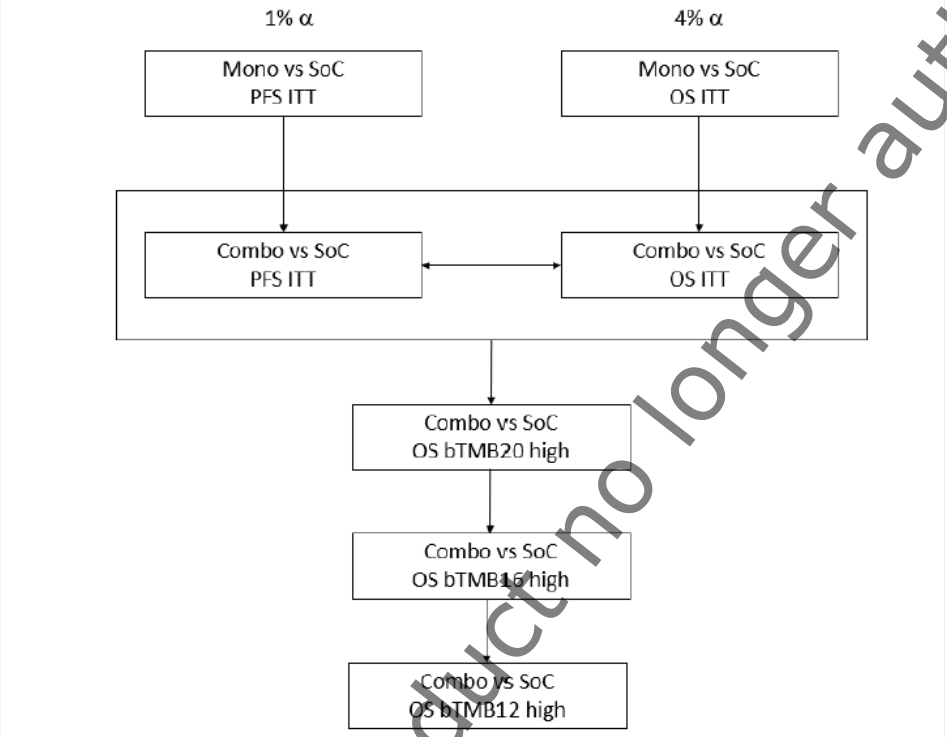
In order to strongly control the type I error at 5% (2-sided), a multiple testing procedure (MTP) with gatekeeping strategy will be used across the dual primary endpoints and the secondary endpoints included in MTP.

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 18. 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.

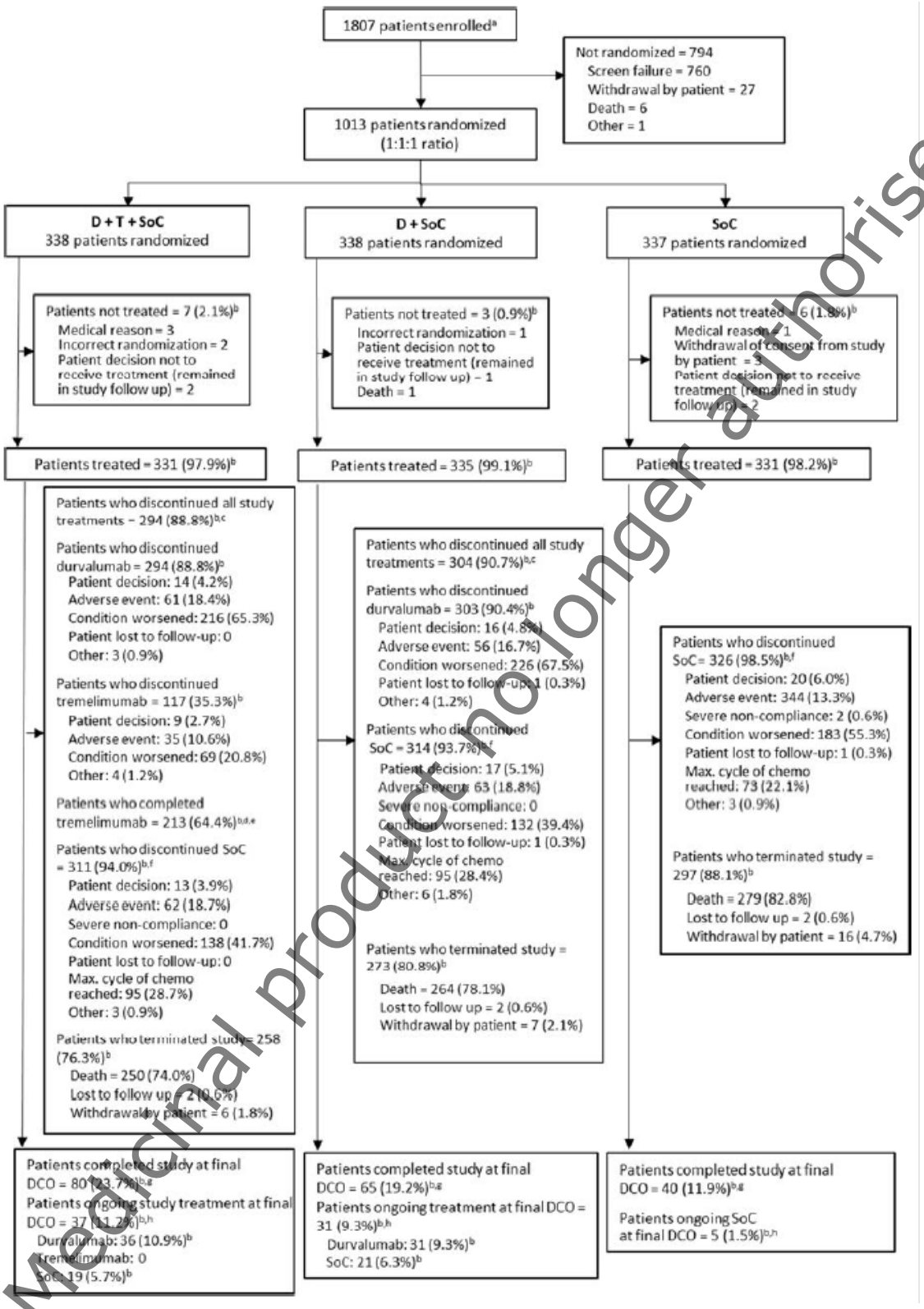
Symptom improvement rate was analysed using logistic regression, using Proc Logistic instead of Proc Genmod.

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 19. 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 21. 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 22. 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 23. 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 3 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 3.2).

- **Baseline data**

Table 24. 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 25. 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 26. 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[c]	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 27. 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	113	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 28. Prior anticancer therapy, ITT - POSEIDON

Previous treatment modalities	Number (%) of patients			
	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 29. 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 30. 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).

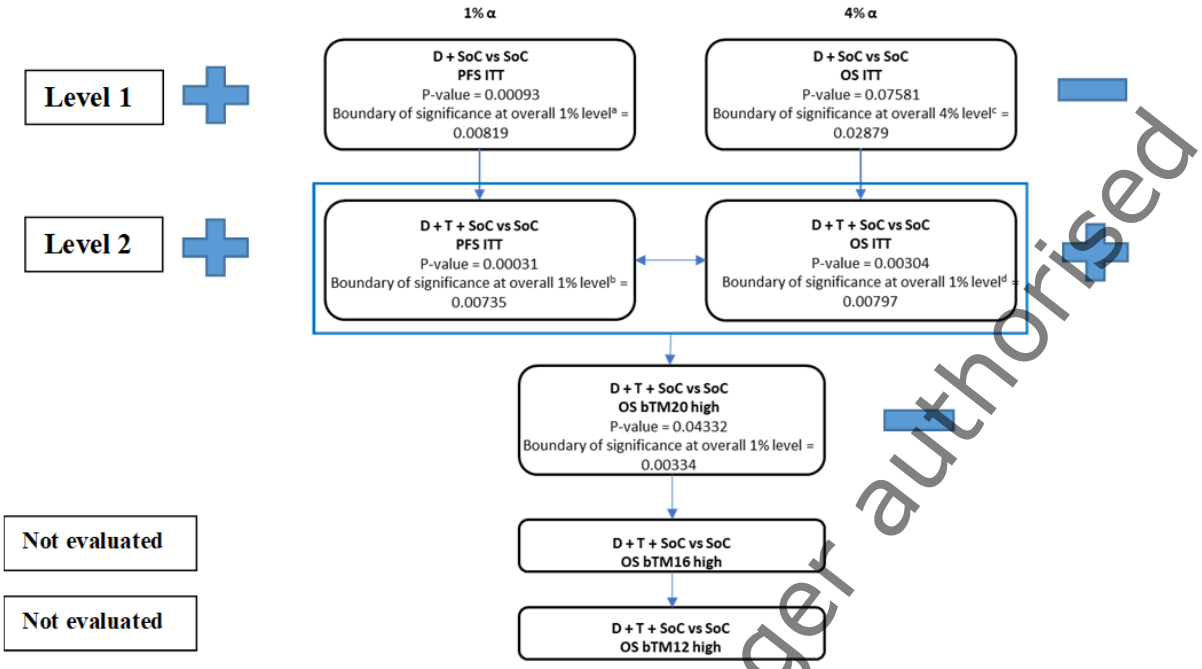
At the time of the PFS analysis DCO date (24-JUL-2019), the PFS data had reached 75.7% maturity (511 PFS events from 675 patients in the D + SoC and SoC alone arms).

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 31. 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 32. 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.

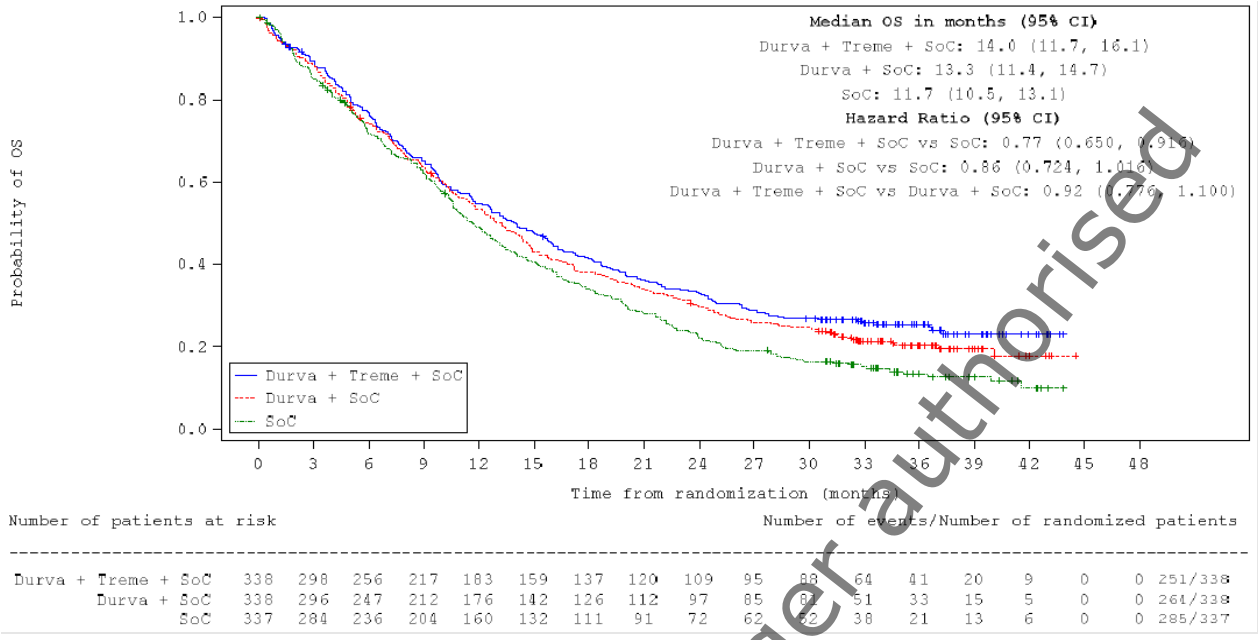
[e] Includes patients with unknown survival status or patients who were lost to follow-up.

[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 20. Overall survival in the ITT, Kaplan-Meier curve, DCO 12-MAR-2021



Key secondary endpoint: Progression free survival by BICR

Table 33. 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.

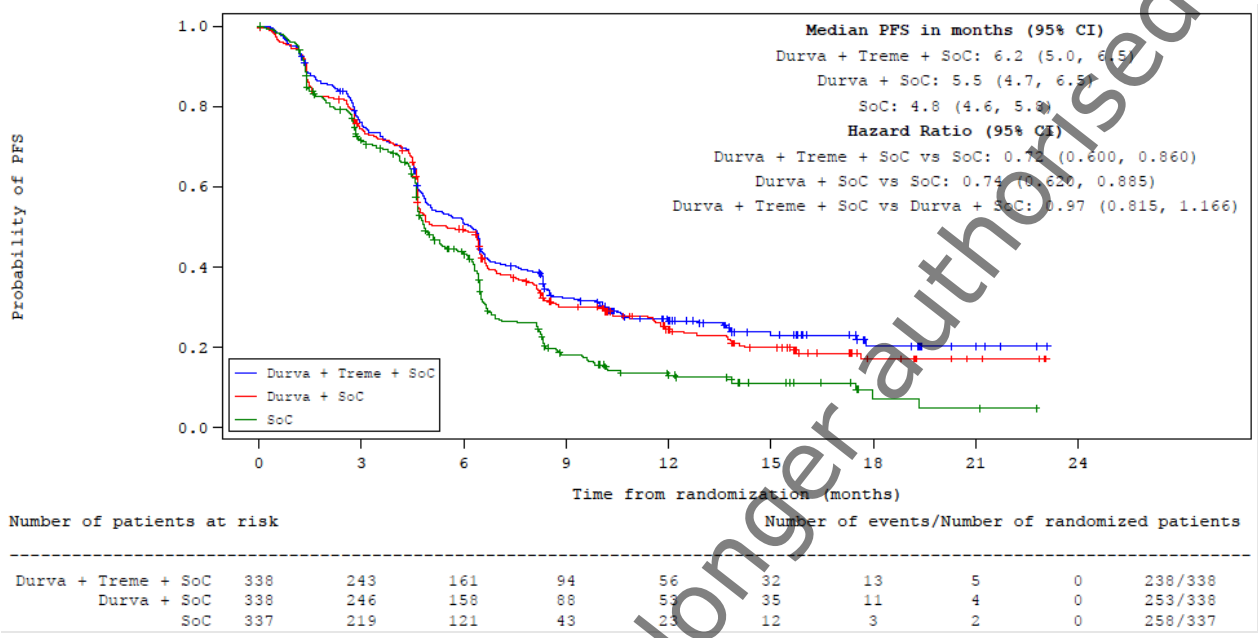
[m] Calculated using the Kaplan-Meier technique.

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



Number of patients at risk

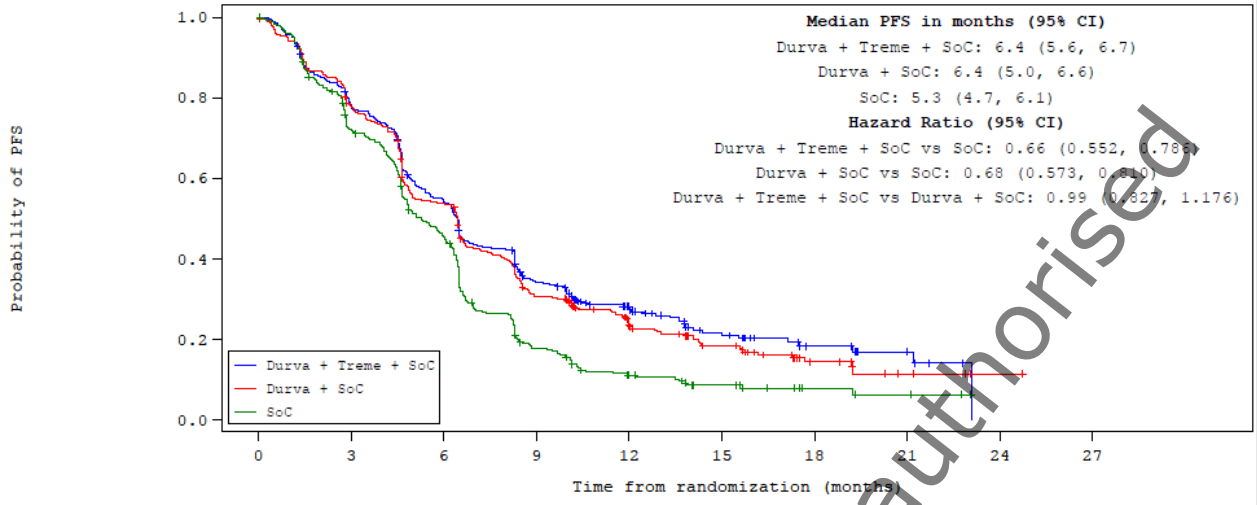
										Number of events/Number of randomized patients
Durva + Treme + SoC	338	243	161	94	56	32	13	5	0	238/338
Durva + SoC	338	246	158	88	53	35	11	4	0	253/338
SoC	337	219	121	43	23	12	3	2	0	258/337

Secondary endpoint: Progression free survival by investigator

Table 34. 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 22. 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 35. Disagreements between investigator and BIRC in the ITT, DCO 24-JUL-2019

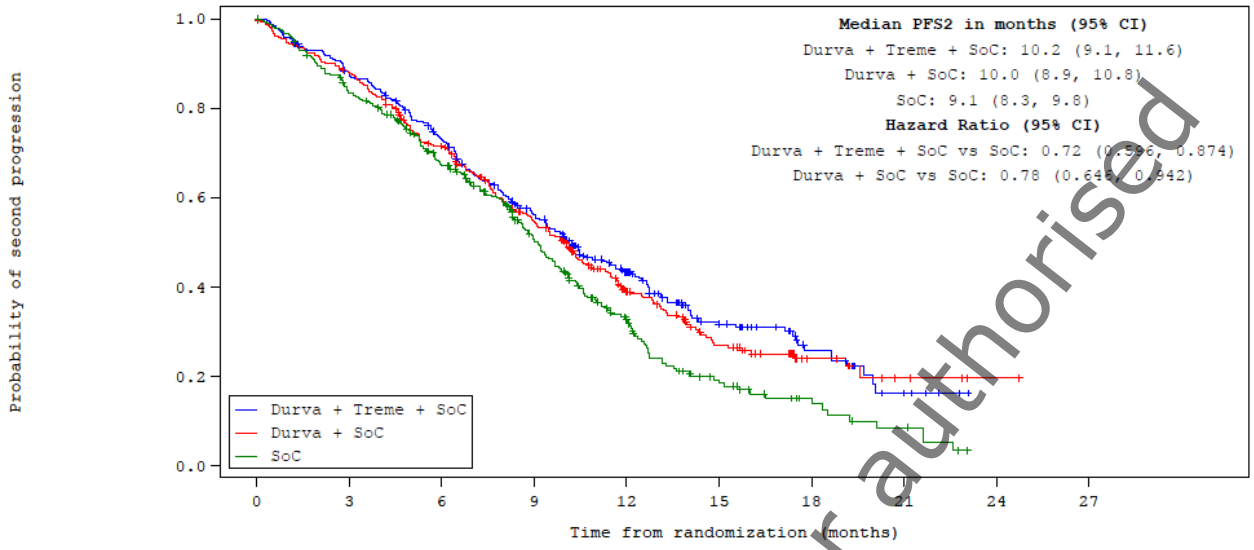
Progression	Durva + Treme + SoC (N=338)	Durva + SoC (N=338)	SoC (N=337)	Difference: Durva + Treme + SoC vs SoC	Difference: Durva + SoC vs SoC
RECIST progression [a] declared by, n (%)					
Investigator and central review	151 (44.7)	169 (50.0)	179 (53.1)	NA	NA
Progression date agreement (within 2 weeks)	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 36. 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 23. 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	36	12	6	0	0	232/337

Table 37. 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 38. 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.

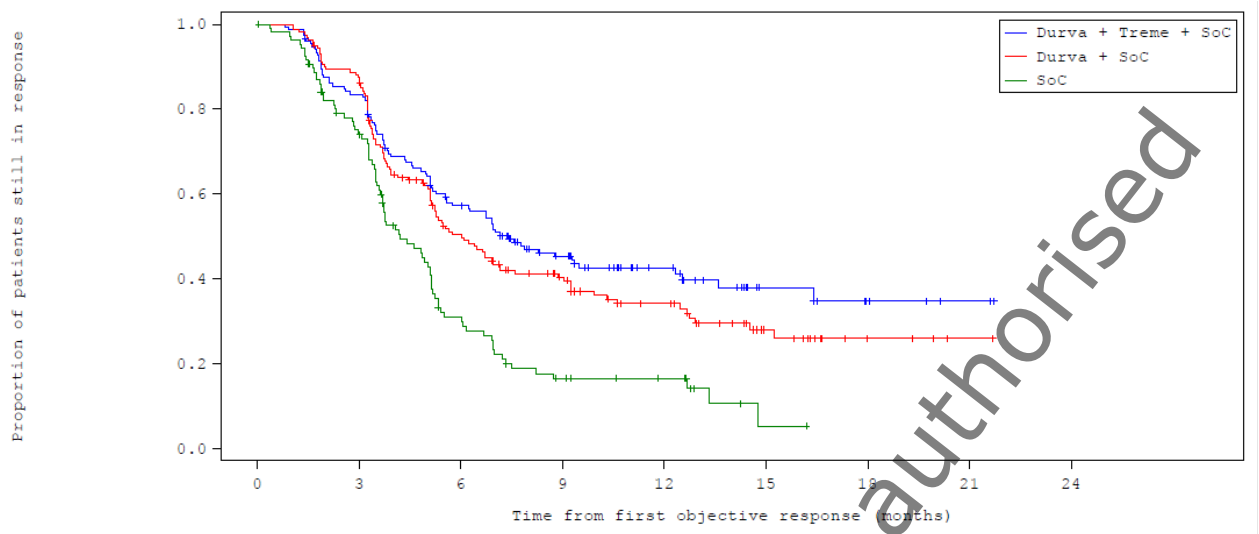
p In practice, considering '5 weeks' as threshold to allow for the 1-week permitted time-window.

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 24. 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 39: 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 40: 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 25: 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

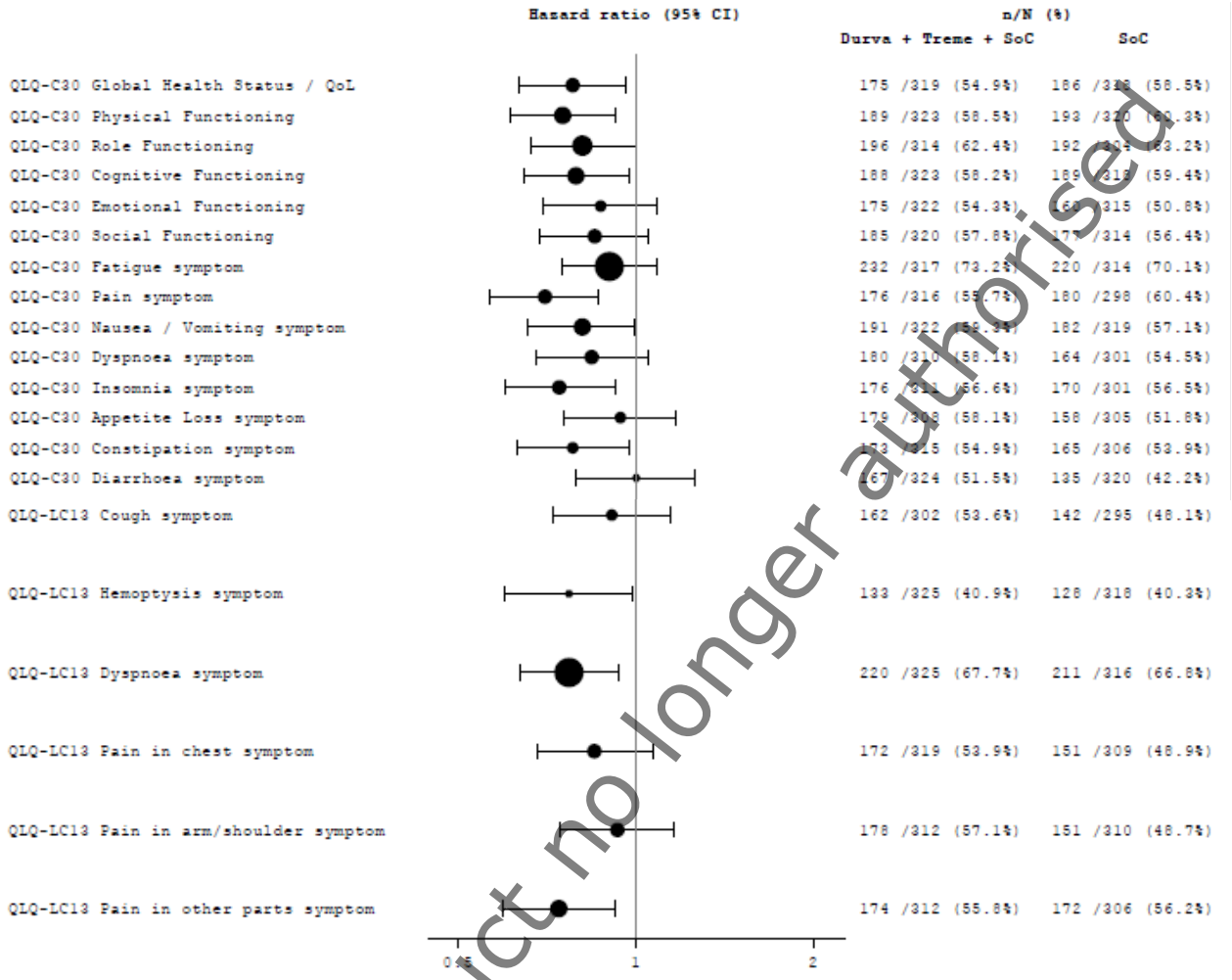
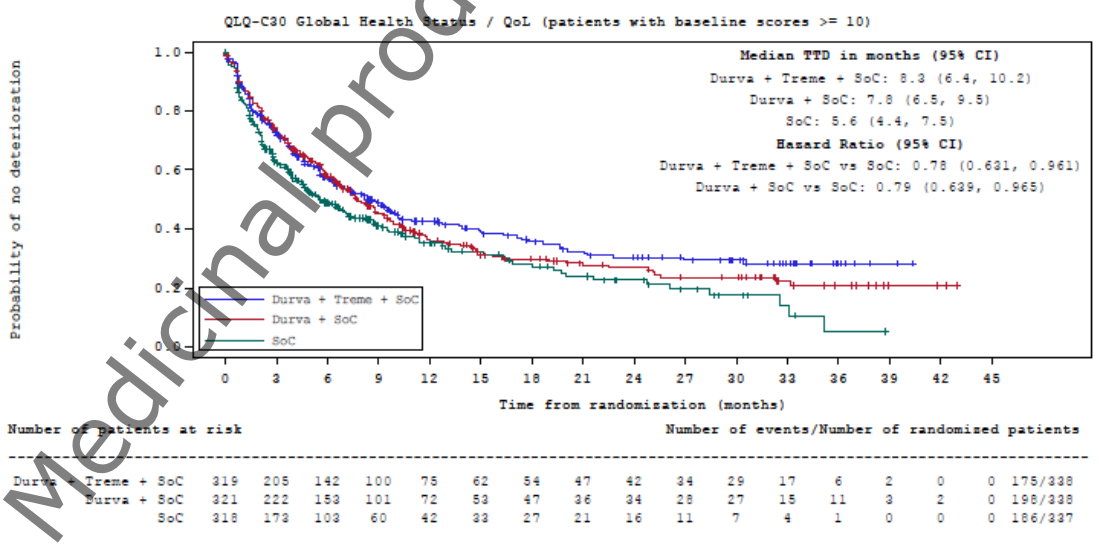


Figure 26: K-M plot of TTD in EORTC QLQ-C30 and QLQ-L13 in the ITT, DCO 12-MAR-2021



- **Ancillary analyses**

Subgroup analyses:

Figure 27. Forest plot of OS in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021

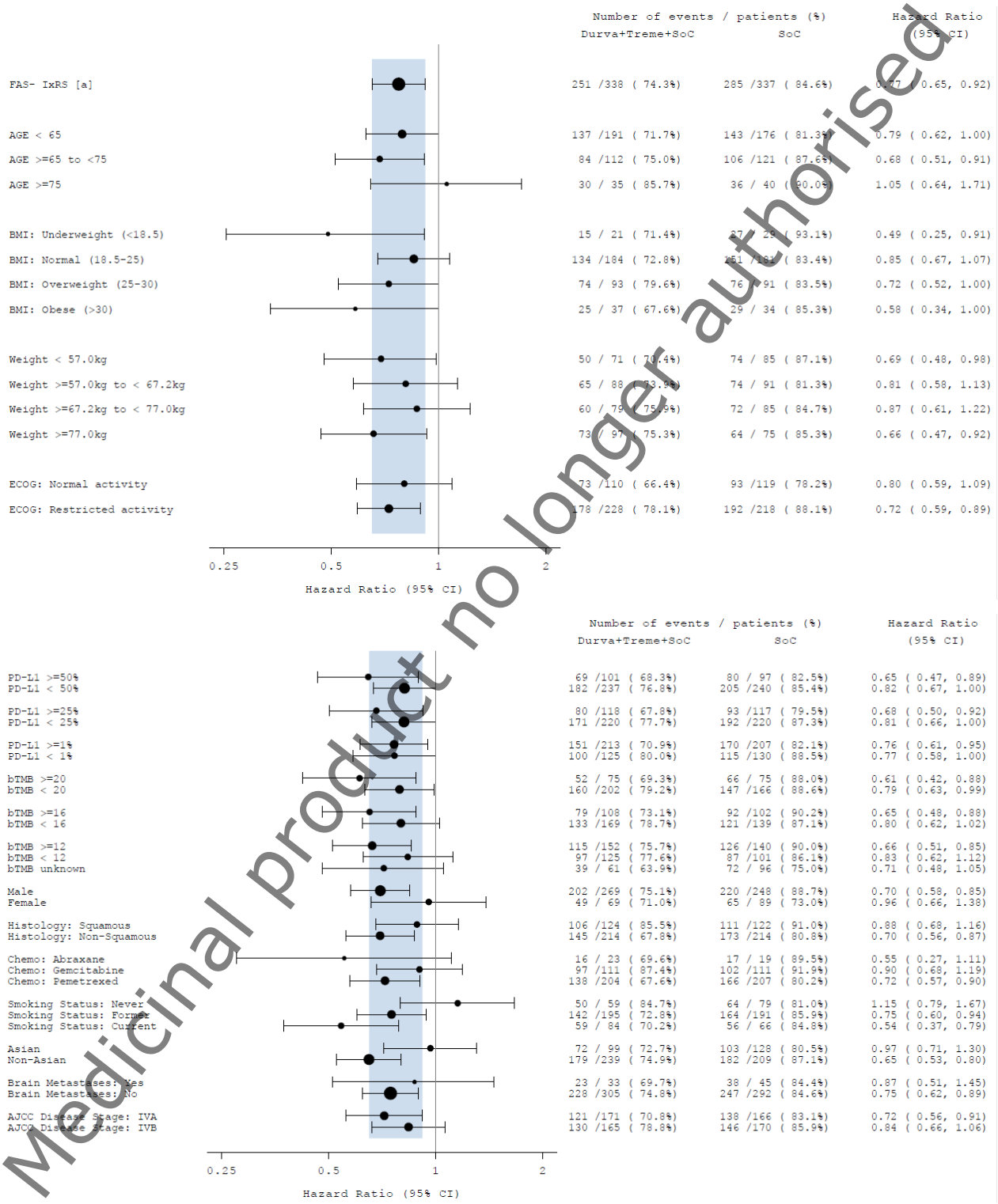
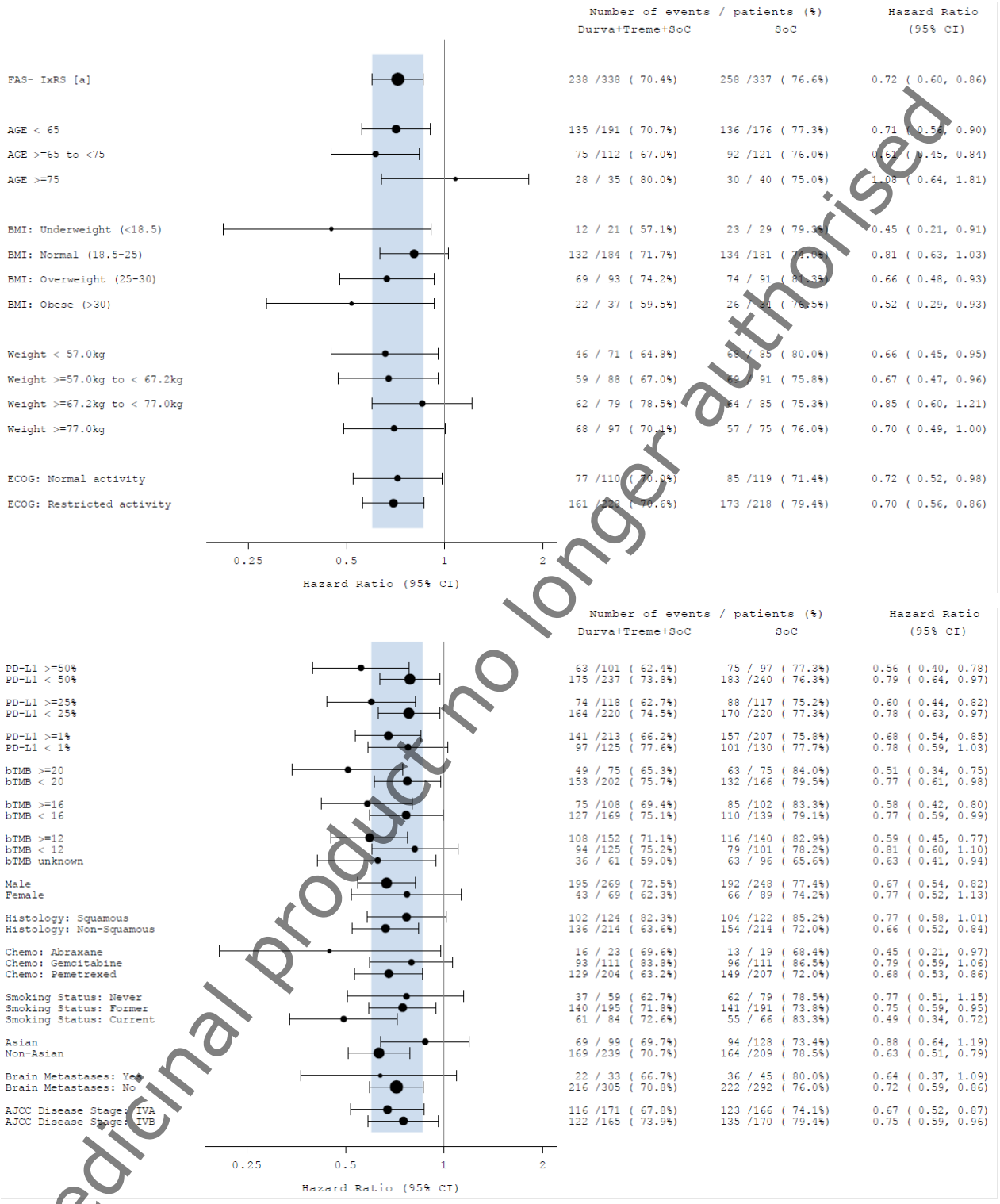


Figure 28. Forest plot of PFS by BICR in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021



Sensitivity analyses:

Table 41. 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, 1.013	0.0689
SoC	336	284 (84.5)	11.6			

Table 42. 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 43. 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 44. 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 45. 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.

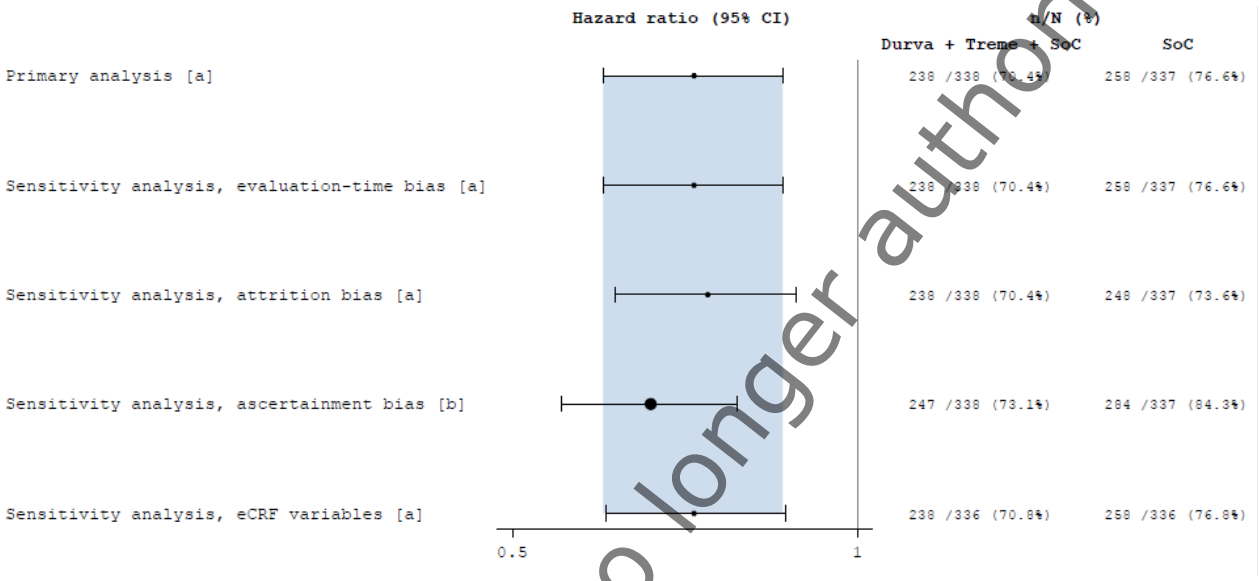
f The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) is analyzed.

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 29. 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 46. Contribution of components POSEIDON

	Treatment arm		
Efficacy measure	**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)
Median (months) [g] (95% CI) [g]	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 5.8)

Efficacy measure	Treatment arm		
	T + D + SoC	D + SoC	SoC
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 47. OS according to PD-L1 subgroups in the ITT, Durva + treme + chemo vs. chemo, DCO 12-MAR-2021

Analysis set	Number (%) of patients							
	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 30. Overall survival in the PD-L1 TC<1% population, DCO 12-MAR-2021

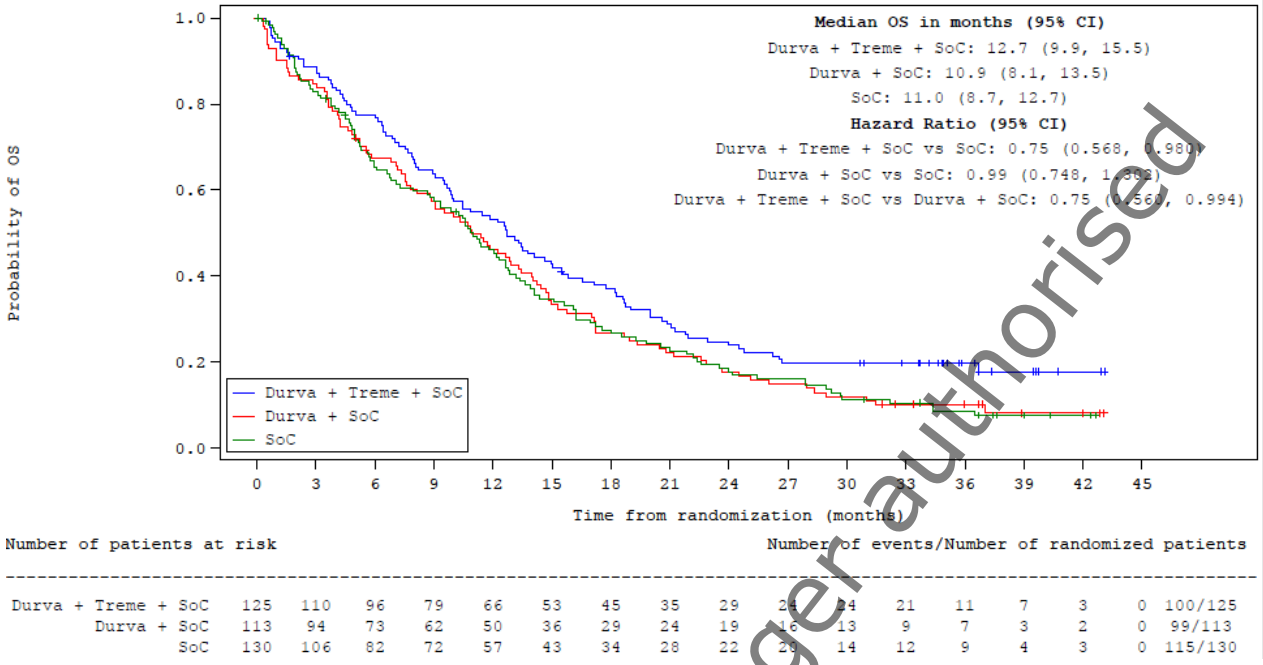


Figure 31. Overall survival in the PD-L1 TC≥1% population, DCO 12-MAR-2021

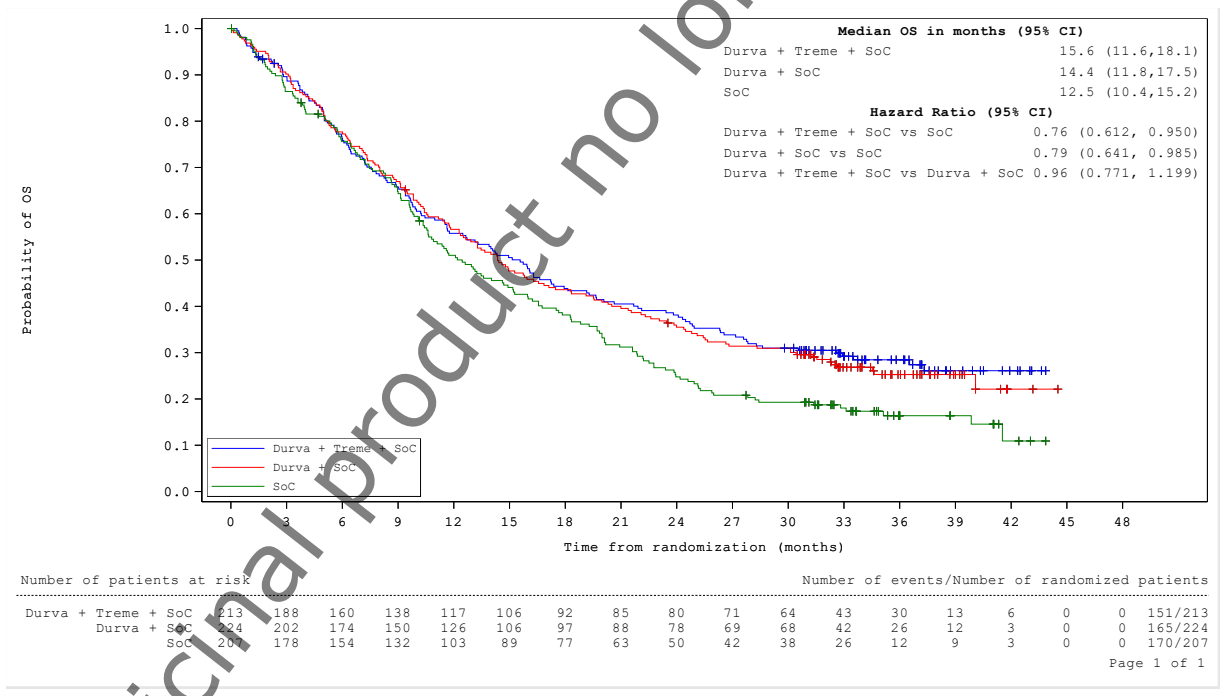


Table 48: Progression-free survival (BICR; RECIST 1.1), full analysis set and PDL1 analysis sets, T + D + SoC vs SoC, DCO 24-JUL-2019

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 efficacy results**

The following table summarises 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 49. 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.

2.6.5.3. Clinical studies in special populations

Table 50. 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

2.6.5.4. 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.

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

N/A

2.6.5.6. Supportive studies

Table 51 depicts the main similarities and differences among pivotal study POSEIDON and supportive studies MYSTIC and NEPTUNE.

Table 51. Key similarities and differences among POSEIDON, MYSTIC and NEPTUNE.

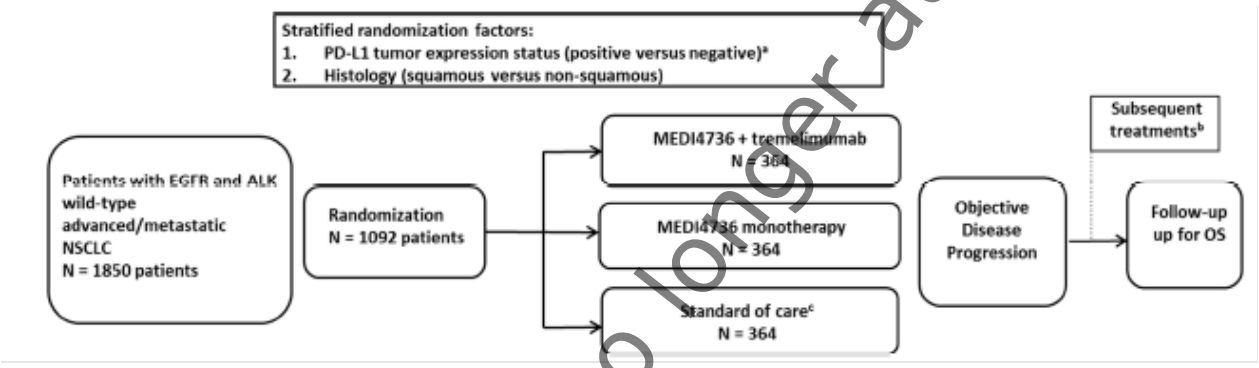
	POSEIDON	**MYSTIC**	**NEPTUNE**
Patient population	Advanced or metastatic NSCLC eligible for 1L treatment	Advanced or metastatic NSCLC eligible for 1L treatment	Advanced or metastatic NSCLC eligible for 1L treatment
Primary analysis set	All-comers	PD-L1 TC≥25%	bTMB>20 mut/megabase
Stratification	• Histology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

	POSEIDON	MYSTIC	NEPTUNE
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 M. Table MYS summarises OS and PFS results in the primary efficacy dataset (PD-L1 ≥25%).

Figure 32. 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).

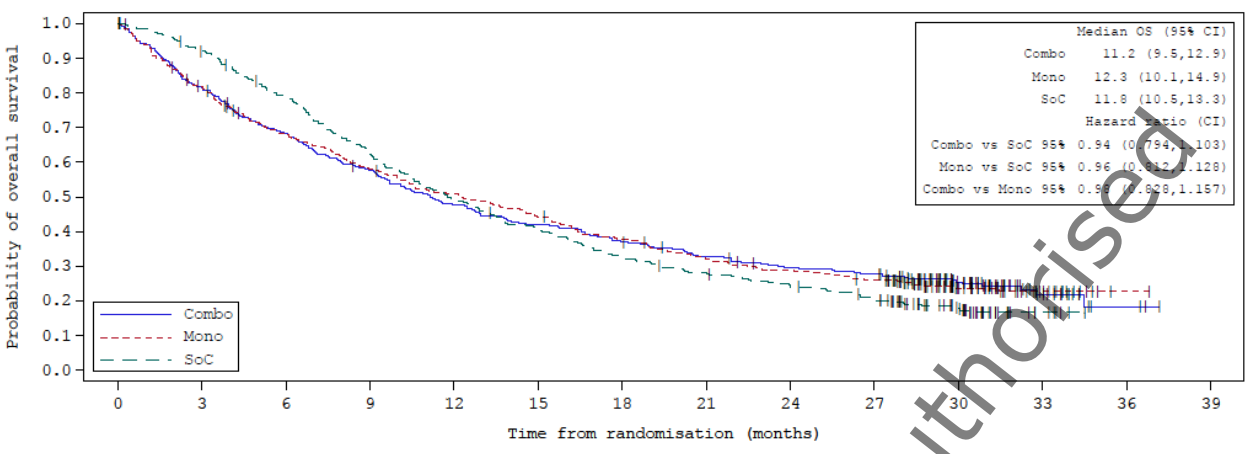
Table 52. OS and PFS in the PD-L1 ⩾25% analysis dataset of study MYSTIC

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		

Efficacy parameter	PD-L1 TC ≥25%		
	D + T	D	SoC
	N = 163	N = 163	N = 162
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 33. Kaplan-Meier plot of OS in the ITT of MYSTIC, DCO 04-OCT-2018



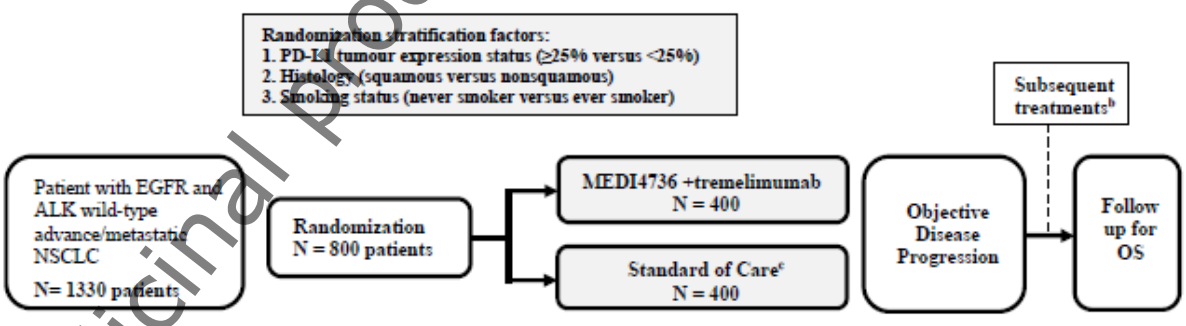
Number of patients at risk

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 N). A schematic diagram of the overall study design is shown in Figure R.

Figure 34. 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 53. OS in the bTMB≥20 analysis dataset of study NEPTUNE

Efficacy parameter	bTMB ≥20 analysis set	
	D + T	SoC
	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.

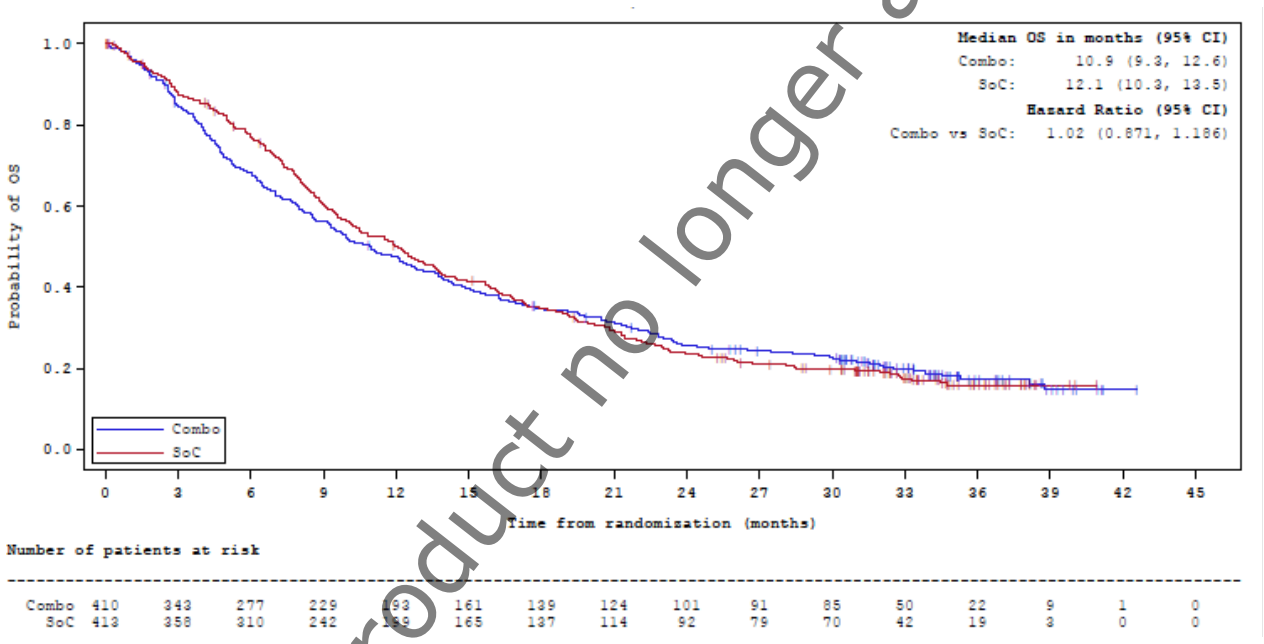
[b] The HR and CI were calculated using an unstratified Cox proportional hazards model, with ties handled by the Efron approach.

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



2.6.6. Discussion on clinical efficacy

The applicant has submitted a MAA for tremelimumab, an anti-CTLA-4 immune checkpoint inhibitor, for use in combination with durvalumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC without EGFR or ALK aberrations. The 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

The applicant held several regulatory interactions with the US FDA during the development of tremelimumab in NSCLC, but 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.

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 MAA for tremelimumab 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: 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.

2.6.7. 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.

2.6.8. Clinical safety

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 tremelimumab, 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 1). 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 54. 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 36, and the process of adjudicating imAEs is presented in detail in the imAE Charter.

Figure 36 The process for adjudicating imAEs

2.6.8.1. Patient exposure

Table 55. 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 56. 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 57. 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 58. 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.

2.6.8.2. Adverse events

Overview of all AEs:

Table 59. 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 60. 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 61. 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 62. 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 63. 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 64: 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:

Tremelimumabis associated with immune mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of tremelimumab.

Table 65. 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 66. 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 Tremelimumab AstraZeneca in combination with durvalumab:

- 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 Tremelimumab AstraZeneca in combination with durvalumab.

- 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 67. 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	83 (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 68. 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

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs:

Table 69. 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 70. 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 71. 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)

2.6.8.4. Laboratory findings

Table 72. 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 73. 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)

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
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)
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 74. 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)

Category	Number (%) of patients		
	POSEIDON		T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)	
Number of patients with at least one baseline and post-baseline TSH result	310 (93.9)	298 (89.5)	2070 (90.8)
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)

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Age:

Table 75. 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 (N1=45) (N2=295) (N3=198) (N4=58)	Chemo pool (N1=51) (N2=279) (N3=209) (N4=60)	T + D Pan-tumor pool (N1=259) (N2=1041) (N3=774) (N4=206)
		T + D + SoC (N1=29) (N2=158) (N3=108) (N4=35)	SoC (N1=31) (N2=143) (N3=120) (N4=39)			
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 76. 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)

	Number (%) of Patients [a]			
AE Group	Age < 65 n = 187	Age 65-74 n = 108	Age 75-84 n = 33	Age ≥ 85 n = 2
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)
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 77. 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 78: 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)

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)
	≥ Q1 to < Q2	2 (2.3)	3 (3.7)	3 (3.3)
	≥ Q2 to < Q3	2 (2.6)	3 (3.8)	3 (3.6)
	≥ 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 79. 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 80: 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 81. 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.

2.6.8.7. Immunological events

POSEIDON: Of the 286 durvalumab evaluable patients in the same arm, 42 (14.7%) tested positive for durvalumab at any visit. Of the 278 tremelimumab ADA-evaluable patients in the T + D + SoC arm, 44 (15.8%) tested positive for tremelimumab ADA 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 1379 durvalumab-evaluable patients, 86 (6.2%) tested positive for durvalumab at any visit. Of the 1337 tremelimumab ADA-evaluable patients, 171 (12.8%) tested positive for tremelimumab at any visit.

2.6.8.8. 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.

2.6.8.9. Discontinuation due to adverse events

Table 82: 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 83: 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 Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	
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.

2.6.8.10. Post marketing experience

Tremelimumab is not yet approved for use in any country.

2.6.9. Discussion on clinical safety

The requested indication is for tremelimumab in combination with durvalumab and chemotherapy. In order to understand the isolated safety profile of tremelimumab, an anti-CTLA4 antibody, a supplementary analysis of phase II and III trials in which it was administered as monotherapy was presented. The tremelimumab monotherapy pool contained 643 patients treated at 10 mg/kg or a fixed dose of 750 mg Q4W, regimens that do not compare to the dose intended for marketing authorisation (75 mg Q4W). Although tables for the most common PTs for each of the categories were not tabulated by frequency, it was determined that diarrhoea was the most common likely-related AE, with an incidence of 40% (any grade) and 13% of patients presenting ≥G3 diarrhoea. Of note, immune-mediated colitis is a well-known AE from anti-CTLA-4 treatment.

To evaluate the safety profile of tremelimumab in combination, safety results were also provided for all three arms of pivotal trial 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 one intended for approval. 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 Tremelimumab AstraZeneca in combination with durvalumab, 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 Tremelimumab AstraZeneca in combination with durvalumab. 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 AstraZeneca in combination with durvalumab 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 Tremelimumab AstraZeneca in combination with durvalumab 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.

There are no data on the use of tremelimumab in pregnant women. Based on its mechanism of action, tremelimumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. Tremelimumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

There is no information regarding the presence of tremelimumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG2 is excreted in human milk. Because of the potential for adverse reactions from tremelimumab in breast-fed infants, breast-feeding women are advised not to breast-feed during treatment and for at least 3 months after the last dose.

Tremelimumab has no or negligible influence on the ability to drive and use machines.

2.6.10. Conclusions on the 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.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 84: List of important risks and missing information

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

Table 85: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risks		
Immune-mediated adverse reactions	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.2, and 4.8 • PL Sections 2 and 4 • Prescription-only medicine **Additional risk minimisation measures**: • Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 2.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.10.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Labelling exemptions

A request to use minimum particulars on the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group. However the QRD Group would like the applicant to take note of the following remarks:

- Vial label: The short pharmaceutical form can be used as proposed on the multilingual label. However on the single language labels the full pharmaceutical form should be used. If not possible, 'after dilution' should be added next to the route of administration, i.e. "IV after dilution". Due to space constraints the QRD remarks could not be implemented.

- Outer carton: The statement "Keep out of the sight and reach of children" can be grey-shaded in Annex IIIA, and there is no need to print it on the actual carton as the product will be handled by healthcare professionals only. This will leave more space on the carton to improve readability of the rest of information.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tremelimumab AstraZeneca (tremelimumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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:

Tremelimumab AstraZeneca 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 aim of added tremelimumab in the targeted population is to prolong overall survival (OS) and progression-free survival (PFS).

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

Effects Table for Imfinzi (durvalumab) in combination with Tremelimumab AstraZeneca (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-2019 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 Tremelimumab AstraZeneca in combination with durvalumab 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, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to the launch of Tremelimumab AstraZeneca in each Member State the MAH will agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The additional risk miniminsation measure is aimed at increasing awareness and providing information concerning the symptoms of immune-mediated adverse reactions.

The MAH shall ensure that in each Member State where Tremelimumab AstraZeneca is marketed, all physicians who are expected to use Tremelimumab AstraZeneca have access to/are provided with the following to provide to their patients:

- Patient card

Key messages of the Patient Card include:

- A warning that immune-mediated adverse reactions (in lay terms) may occur and that they can be serious
- A description of the symptoms of immune-mediated adverse reactions
- A reminder to contact a healthcare professional provider immediately to discuss signs and symptoms
- Space for contact details of the prescriber
- A reminder to carry the card at all times.

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

Not applicable.

New Active Substance Status

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

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 15 December 2022