CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761270Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original BLA (tremelimumab); Supplemental BLA (durvalumab)
Application Number(s)	761270 (tremelimumab); 761069-S033 (durvalumab)
Priority or Standard	Standard
Submit Date(s)	November 15, 2021 (tremelimumab); January 13, 2022 (durvalumab)
Received Date(s)	November 15, 2021 (tremelimumab); January 13, 2022 (durvalumab)
PDUFA Goal Date	November 15, 2022 (tremelimumab); November 13, 2022 (durvalumab)
Division/Office	Division of Oncology 2
Review Completion Date	November 10, 2022
Established Name	Tremelimumab; Durvalumab
(Proposed) Trade Name	Imjudo; Imfinzi
Pharmacologic Class	Tremelimumab: anti-CTLA-4 inhibitor Durvalumab: anti-PD-L1 inhibitor
Code name	Tremelimumab: MEDI1123; formerly CP-675,206 (human IgG2 anti-CTLA-4 mAb) Durvalumab: MEDI4736; (human IgG1 anti-PD-L1 mAb)
Applicant	AstraZeneca AB (tremelimumab); AstraZeneca UK Limited (durvalumab)
Formulation(s)	Tremelimumab: concentrate for solution for infusion 20mg/mL Durvalumab: concentrate for solution for infusion (b) (4) mg/mL
Dosing Regimen	• Weight 30 kg and more: tremelimumab 75 mg every 3 weeks in combination with durvalumab 1,500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab 75 mg in combination with durvalumab dose 6 at week 16 • Weight less than 30 kg: tremelimumab 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy

	every 4 weeks, and a fifth dose of tremelimumab 1 mg/kg in combination with durvalumab dose 6 at week 16
Applicant Proposed Indication(s)/Population(s)	Tremelimumab in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Tremelimumab in combination with durvalumab and platinum-based chemotherapy is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations

Table of Contents

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Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Idara Ojofeitimi
Pharmacology/Toxicology Reviewer(s)	Melissa Pegues
Pharmacology/Toxicology Team Leader(s)	Claudia Miller
Office of Clinical Pharmacology Reviewer(s)	Yue Xiang; Ye Yuan
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao; Liang Li
Clinical Reviewer	Erica Nakajima
Clinical Team Leader	Nicole Drezner
Safety Analyst (if applicable)	Min Wang
Statistical Reviewer	Arup Sinha
Statistical Team Leader	Pallavi Mishra-Kalyani
Associate Director for Labeling (ADL)	Barbara Scepura
Cross-Disciplinary Team Leader	Nicole Drezner
Division Director (DHOT)	John Leighton
Division Director (OCP)	Nam Atiqur Rahman
Deputy Division Director (OB)	Yuan-li Shen
Division Director (OOD)	Harpreet Singh

Additional Reviewers of Application

OPQ	Xu Di/Ram Sihag; Vicky Borders-Hemphill/Virginia Carroll
Microbiology	Maria Scott/Zonglin Hu/Madu Dharmasena
OPDP	Rebecca Falter, Rachel Conklin
OSI	Lee Pai-Scherf, Karen Bleich
OSE/DEPI	Fang Tian, Steven Bird
OSE/DMEPA	Sali Mahmoud, Ashleigh Lowery
OSE/DRISK	Leah Hart, Carolyn Tieu
Other	(DMPP) Ruth Mayrosh, Barbara Fuller; (Safety) Maitreyee Hazarika, Stacie Woods

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

1L	First-line
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
bTMB	Blood Tumor Mutational Burden
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
E-R	exposure-response
eCTD	electronic common technical document
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
imAE	Immune-mediated adverse event
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NCA	non-compartmental analysis
NME	new molecular entity
NSCLC	Non small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Disease progression (used interchangeably with 'progressive disease')
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L1 TC <1%	PD-L1 expression on less than 1% of tumor cells
PD-L1 TC <25%	PD-L1 expression on less than 25% of tumor cells
PD-L1 TC <50%	PD-L1 expression on less than 50% of tumor cells
PI	prescribing information
PK	pharmacokinetics
PPK	population pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SoC	standard of care
TEAE	treatment emergent adverse event
TPS	Tumor proportion score
TMB	Tumor mutation burden

Executive Summary

Product Introduction

Tremelimumab (IMJUDO) is a fully human monoclonal IgG2 antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Blockade of CTLA-4 signaling can also inhibit T-regulatory cell function, which may lead to a general increase in T-cell responsiveness, including the anti-tumor immune response.

Tremelimumab in combination with durvalumab is approved for the treatment of unresectable hepatocellular carcinoma (HCC).

Durvalumab (IMFINZI) is a fully human monoclonal IgG1 kappa antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PDL1/ CD80 interactions releases the inhibition of immune responses.

Durvalumab is approved for the following indications:

- For the treatment of patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
- In combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

The Applicant's proposed indication is as follows:
Tremelimumab in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations

There are two recommended dosage regimens for the proposed indication according to body weight:

- Weight 30 kg and more: 75 mg every 3 weeks in combination with durvalumab 1,500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab 75 mg in combination with durvalumab dose 6 at week 16
- Weight less than 30 kg: 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab 1 mg/kg in combination with durvalumab dose 6 at week 16

Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this BLA is POSEIDON (Study D419MC00004), an international, multicenter, randomized (1:1:1), open-label trial comparing the combination of tremelimumab with durvalumab and platinum-based chemotherapy (T + D + SoC) and the combination of durvalumab and platinum-based chemotherapy (D + SoC) to platinum-based chemotherapy (SoC) in patients with previously untreated metastatic NSCLC without sensitizing EGFR or ALK genomic tumor aberrations. Patients were enrolled irrespective programmed death-ligand 1 (PD-L1) tumor expression status.

The dual primary endpoints were progression free survival (PFS) and overall survival (OS) for the comparison of D + SoC vs. SoC; key secondary endpoints were PFS and OS for the comparison of T + D + SoC vs. SoC. At the final analysis of OS, for the comparison of T + D + SoC vs. SoC, the hazard ratio (HR) for OS was 0.77 (95% confidence interval [CI] 0.65, 0.92; p-value: 0.00304) favoring the T + D + SoC arm. The median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC alone arm. The HR for PFS per blinded independent central review (BICR) was 0.72 (95% CI: 0.60, 0.86), with a median PFS of 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 4.8 months (95% CI 4.6, 5.8) in the SoC arm.

The submitted evidence meets the statutory evidentiary standard for regular approval. The combination of tremelimumab, durvalumab, and chemotherapy demonstrated a survival advantage over chemotherapy with a HR of 0.77 and a 2.3-month improvement in median OS, a statistically significant and clinically meaningful difference. This finding is supported by a statistically significant improvement in PFS and an improvement in overall response rate (ORR) (39% in the T + D + SoC arm compared to 24% in the SoC arm) and median duration of response (DOR) (9.5 months in the T + D + SoC arm compared to 5.1 months in the SoC arm. Therefore, the FDA review teams recommend granting approval to tremelimumab in combination with durvalumab for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations.

Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Tremelimumab is a monoclonal antibody that binds to that binds to the CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86, releasing CTLA-4-mediated inhibition of T-cell activation. Tremelimumab is approved in combination with durvalumab for the treatment of patients with unresectable HCC. Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80. Durvalumab is currently approved for the treatment of patients with unresectable Stage III NSCLC whose disease has not progressed after concurrent platinum-based chemotherapy and radiation therapy.

Metastatic NSCLC is a life-threatening disease with poor survival. Current standard of care, first-line treatment options for patients with metastatic NSCLC that does not harbor an EGFR or ALK mutation and regardless of PD-L1 tumor expression status include pembrolizumab (for non-squamous and squamous histology) or atezolizumab (for non-squamous histology) administered in combination with platinum-based chemotherapy. For patients with previously untreated NSCLC with PD-L1-positive NSCLC (tumor proportion score [TPS] ≥ 1%), pembrolizumab as a single agent, nivolumab in combination with ipilimumab, and nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy are FDA-approved treatment options (NCCN Guidelines, Version 5.2022).

The primary trial supporting this BLA is POSEIDON (Study D419MC00004), an international, multicenter, randomized, open-label trial comparing the combinations of tremelimumab with durvalumab and platinum-based chemotherapy (T + D + SoC) (n=338) and durvalumab and platinum-based chemotherapy (D + SoC) (n=338) to platinum-based chemotherapy (SoC) (n=337) in patients with previously untreated metastatic NSCLC without sensitizing EGFR or ALK genomic tumor aberrations. After completion of the 4 cycles of combination therapy, patients in the T + D + SoC and D + SoC arms continued durvalumab in combination with pemetrexed (if appropriate based on tumor histology) until disease progression or unacceptable toxicity. A fifth dose of tremelimumab was administered at week 16 to patients in the T + D + SoC arm. Patients in the SoC alone arm received pemetrexed maintenance if appropriate based on histology until disease progression or unacceptable toxicity.

The dual primary endpoints for POSEIDON were PFS and OS for the D + SoC vs. SoC comparison; key secondary endpoints were PFS and OS for the T + D + SoC vs. SoC comparison. For the T + D + SoC vs. SoC comparison, the HR for OS was 0.77 (95% CI 0.65, 0.92; p-value: 0.00304) favoring the T + D + SoC arm compared to the SoC arm. The median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC arm. The HR for PFS per blinded BICR was 0.72 (95% CI: 0.60, 0.86; p-value=0.00031), with a median PFS of 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 4.8 months (95% CI 4.6, 5.8) in the SoC alone arm. A post-hoc comparison of confirmed BICR-assessed ORR and median DOR also favored the T + D + SoC

arm over the SoC arm: ORR was 39% (95% CI 34, 44) and median DOR was 9.5 months (95% CI: 7.2, not reached [NR]) in the T + D + SoC arm and 24% (95% CI 20, 29) and 5.1 months (95% CI: 4.4, 6.0) in the SoC arm.

The pre-specified multiple testing procedure for POSEIDON did not include an alpha-controlled comparison between the T + D + SoC arm and the D + SoC arm. A small numeric improvement in median OS and PFS was observed in the T + D + SoC arm compared to the D + SoC arm: OS of 14.0 months (95% CI 11.7, 16.1) and 13.3 months (95% CI 11.4, 14.7) (HR 0.92 [95% CI 0.78, 1.10]) and PFS of 6.2 months (95% CI 5.0, 6.5) and 5.5 months (95% CI 4.7, 6.5) (HR 0.97 [95% CI 0.82, 1.17]) in the T + D + SoC and SoC arms, respectively. The assessment of the contribution of tremelimumab to the overall regimen is largely derived from this informal in-study comparison. Although OS was not formally tested between the T + D + SoC and D + SoC arms, there was an incremental improvement in median OS observed with the addition of tremelimumab to the combination. Furthermore, there is biologic rationale for the use of dual immune checkpoint blockade to improve survival outcomes in NSCLC, well as other tumor types. Dual checkpoint inhibitors have been approved in several tumor types, including NSCLC, melanoma, and HCC.

The primary safety population for this BLA was comprised of the 330 patients who received T + D + SoC in POSEIDON. To further evaluate the safety profile of T + D + SoC, data from patients enrolled in POSEIDON was pooled with data from patients with extensive-stage small cell lung cancer (ES-SCLC) who received tremelimumab in combination with durvalumab and platinum-based chemotherapy in the CASPIAN study (total pooled n=596).

The observed safety profile of tremelimumab in combination with durvalumab and platinum-based chemotherapy is acceptable when considered in the context of a life-threatening disease. The Warnings and Precautions section of the tremelimumab label provides information on immune-mediated adverse events (imAEs) and infusion-related reactions that can occur from treatment with tremelimumab. These adverse reactions are consistent with the known safety profile of immune checkpoint inhibitors.

The most common (≥ 20%) adverse reactions observed in patients enrolled on the T + D + SoC arm were nausea (42%), fatigue (36%), musculoskeletal pain (29%), decreased appetite (28%), rash (27%), and diarrhea (22%). Adverse reactions leading to treatment discontinuation of durvalumab or tremelimumab occurred in 17% patients who received T + D + SoC. The most common (≥ 2%) adverse reaction leading to treatment discontinuation was pneumonia.

Deaths considered related or possibly related to the combination of T + D + SoC occurred in 14 patients (4.2%); fatal adverse reactions included autoimmune hepatitis, autoimmune myocarditis, autoimmune nephritis, autoimmune pancreatitis (all of which occurred in a single patient), pneumonitis (2 patients), acute kidney injury (2 patients), sepsis (2 patients), febrile neutropenia, and ischemic stroke (1 patient each).
There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use.

The submitted evidence meets the evidentiary standard for regular approval and provides substantial evidence of the effectiveness of tremelimumab in combination with durvalumab and platinum-based chemotherapy. The reviewers recommend granting regular approval of the combination of tremelimumab, durvalumab, and platinum-based chemotherapy for the following indication: "for the first-line treatment of adult patients with metastatic NSCLC whose tumors do not harbor EGFR or ALK genomic tumor aberrations."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the US, with 80-85% of cases classified as NSCLC. • 85% of cases of NSCLC are diagnosed at later stages and for patients with metastatic disease, the 5-year survival rate is <10%.	Metastatic NSCLC is a life-threatening condition with poor survival.
Current Treatment Options	• When the primary trial (POSEIDON) supporting this BLA was initiated in 2017, platinum-based chemotherapy was the standard of care for patients with metastatic NSCLC that did not harbor a targetable mutation. • Standard of care treatment options for patients with previously untreated, metastatic NSCLC regardless of PD-L1 tumor expression include pembrolizumab (for non-squamous and squamous histology), atezolizumab with or without bevacizumab (for non-squamous histology) administered with platinum-based chemotherapy, and nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.	At the time that POSEIDON was designed, platinum-based chemotherapy, which is associated with a median OS of 8-11 months, was an appropriate comparator for the first-line treatment of patients with metastatic NSCLC. The combination of T + D +SoC would provide another treatment option for patients with NSCLC.
Benefit	• The primary trial supporting this BLA is POSIEDON, a randomized, multicenter, active-controlled, open-label clinical trial comparing durvalumab with tremelimumab in combination with platinum-based chemotherapy (Arm A, n=338) and durvalumab in combination with platinum-based chemotherapy (Arm C, n=338) to	The submitted evidence meets the statutory evidentiary standard for regular approval. The observed improvement in OS with a 2.3-month difference in median OS and a HR of 0.77 is clinically meaningful and statistically

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	platinum-based chemotherapy (Arm B, n=337). • The final analyses of PFS were conducted at a data cutoff (DCO) date of July 24, 2019. Analyses of PFS for the comparisons of D + SoC vs. SoC (dual primary endpoint) and T + D + SoC vs. SoC (key secondary endpoint) were statistically significant at the 1% alpha level. The final analyses of OS were conducted at a DCO date of March 12, 2021. For the comparison of D + SoC vs. SoC (dual primary endpoint), the OS HR did not cross the prespecified statistical threshold at the 4% alpha level. Therefore, the 1% alpha level from the analysis of PFS for the T + D + SoC vs. SoC comparison was recycled to test the comparison of T + D + SoC vs. SoC for OS (key secondary endpoint); for this comparison, the OS HR was statistically significant at the 1% alpha level. • At the final analysis of OS, POSEIDON demonstrated a HR for OS of 0.77 (95% CI: 0.65, 0.92) favoring the combination of durvalumab and tremelimumab with platinum-based chemotherapy over treatment with platinum-based chemotherapy alone. The median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC arm. • The HR for PFS per blinded independent central review (BICR) was 0.72 (95% CI: 0.60, 0.86), with a median PFS of 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 4.8 months (95% CI 4.6, 5.8) in the SoC arm. • A post-hoc comparison of confirmed BICR-assessed ORR and median DOR also favored the T + D + SoC arm over the SoC arm: ORR was 39% (95% CI 34, 44) and median DOR was 9.5 months (95% CI: 7.2,	significant. This finding is supported by a statistically significant improvement in PFS for the T + D + SoC arm compared to SoC. No direct statistical comparison was made between the T + D + SoC and D + SoC arms. The median OS was slightly longer in the T + D + SoC arm compared to the D + SoC arm (14.0 months vs. 13.3 months) with a HR favoring T + D + SoC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	not reached [NR]) in the T + D + SoC arm and 24% (95% CI 20, 29) and 5.1 months (95% CI: 4.4, 6.0) in the SoC arm.	
Risk and Risk Management	• The primary safety population included 330 patients enrolled in POSEIDON's Arm A who received T + D + SoC, supported by data from 266 patients with ES-SCLC enrolled on the T + D + platinum-based chemotherapy arm of the CASPIAN study (pooled n=596; unapproved regimen for ES-SCLC). • Based on the 330 patients who received T + D + SoC in POSEIDON, the most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue, decreased appetite, musculoskeletal pain, decreased appetite, rash, and diarrhea. Grade 3 or 4 laboratory abnormalities (≥ 10%) were neutropenia, leukopenia, lymphocytopenia, anemia, thrombocytopenia, increased lipase, and hyponatremia. • Adverse reactions leading to treatment discontinuation of tremelimumab or durvalumab occurred in 17% patients who received T + D + SoC. The most common (≥ 2%) adverse reaction leading to treatment discontinuation was pneumonia. Adverse reactions leading to dose interruption or delay of tremelimumab and durvalumab occurred in 41% of patients. • Serious adverse reactions (SARs) occurred in 44% of patients receiving T + D + SoC. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (11%), anemia (5%), diarrhea (2.4%), thrombocytopenia (2.4%), pyrexia (2.4%), and febrile neutropenia (2.1%).	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. No new significant safety signals were identified during FDA's review. The incidence of immune-related adverse events in patients treated with T + D + SoC was 15% higher to that amongst patients who received D + SoC, suggesting that the addition of tremelimumab may increase the risk of imAEs. The incidence of severe (Grade 3 or 4) imAEs was similar between the T + D + SoC and D + SoC arms. The risks of severe and serious adverse events, such as imAEs, are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of the tremelimumab and durvalumab prescribing information. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most commonly occurring immune-mediated adverse events (imAEs) (≥ 5%) were hypothyroidism (8%), dermatitis/rash (7%), and diarrhea/colitis (5%). • Deaths considered related or possibly related to the combination of T + D + SoC occurred in 4.2% of patients; fatal imAEs included autoimmune hepatitis, autoimmune myocarditis, autoimmune nephritis, autoimmune pancreatitis (all occurring in one patient) and pneumonitis (2 patients). • Additional supportive safety data was provided from the 266 patients with ES-SCLC who received tremelimumab in combination with durvalumab and standard of care chemotherapy in the study CASPIAN, for a total of 596 patients in a pooled safety population. Rates of imAEs were similar between the primary safety population and the pooled supportive safety population. • Permanent discontinuations of tremelimumab and durvalumab due to an adverse reaction occurred in 17% of the patients. Adverse reactions which resulted in permanent discontinuation of tremelimumab or durvalumab in > 2% of patients were pneumonia. • Adverse reactions that were included in the Warnings and Precautions section of the USPI are imAEs and infusion-related reactions.	Mitigation Strategy (REMS).

Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	

		x	Patient reported outcome (PRO)	Section 8.1.2 Study Results
		□	Observer reported outcome (ObsRO)	Not applicable
		□	Clinician reported outcome (ClinRO)	Not applicable
		□	Performance outcome (PerfO)	Not applicable
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Not applicable
	□	Patient-focused drug development or other stakeholder meeting summary reports		Not applicable
	□	Observational survey studies designed to capture patient experience data		Not applicable
	□	Natural history studies		Not applicable
	□	Patient preference studies (e.g., submitted studies or scientific publications)		Not applicable
	□	Other: (Please specify)		Not applicable
□	Patient experience data that was not submitted in the application, but was considered in this review.			

X

Nicole Drezner, MD
Cross-Disciplinary Team Leader

Therapeutic Context

Analysis of Condition

The Applicant's Position:

Metastatic non-small cell lung cancer (NSCLC)

Non-small cell lung cancer (NSCLC) is an aggressive, heterogenous, and life-threatening disease. It 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 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).

The pathophysiology of metastatic NSCLC is complex and the current treatment landscape continues to evolve. Approximately 25% of all lung cancer patients are alive 5 years after their initial diagnosis. In patients with metastatic NSCLC, the 5-year relative survival rate is even lower at around 6% in patients who receive cytotoxic chemotherapies (ESMO Guidelines Committee 2019; NCCN Clinical Practice Guidelines in Oncology Version 2.2021). Newer treatment options are required that will expand the potential of the existing therapeutic strategies and will benefit a broader patient population.

The FDA's Assessment:
FDA agrees with the Applicant's position. Long-term survival of patients with metastatic NSCLC remains limited to a small fraction of patients and additional treatment options are needed to improve outcomes.

Analysis of Current Treatment Options

In the past two decades, advances in molecular medicine have improved the understanding of NSCLC pathophysiology. As a result, the frontline treatment of metastatic NSCLC has undergone a fundamental change. Biomarker targeted therapies provide significant long-term clinical benefits in patients whose tumors harbor oncogenic driver mutations. However, driver mutations are detected in up to one-third of all NSCLC patients. As such, the majority of NSCLC patients cannot avail these options, and in these patients, immunotherapy based treatments are the backbone of frontline treatment.

Immune checkpoint inhibitors, specifically those targeting PD 1 or PD L1, have demonstrated durable efficacy in advanced or metastatic NSCLC. After first being approved for use in relapsed or refractory setting, immune-checkpoint inhibitors have moved rapidly in the frontline setting where they are now the established standard of care (NCCN Clinical Practice Guidelines in Oncology Version 2.2021).

Current immunotherapies approved in the 1L advanced/metastatic NSCLC setting are broadly classified

into either immunotherapy only regimens or immunotherapy chemotherapy combinations (Table 1). Since all immunotherapy-based treatments have gained regulatory approvals by demonstrating superiority over platinum doublet chemotherapy, head-to-head prospective comparisons of efficacy are currently lacking. Nonetheless, general recommendations exist (NCCN Clinical Practice Guidelines in Oncology Version 2.2021).

The Applicant's Position:

Notwithstanding the therapeutic breakthroughs in this treatment setting, the available treatment strategies extend long-term survival in only a minority of patients (Peters et al 2019; Grant et al 2021). The response rate to immune checkpoint inhibitors varies depending on the regimen and setting. The highest response rates occur in patients with PD-L1 levels ≥50% in the first-line setting and no actionable molecular biomarkers (approximately 40% response rate to single-agent immunotherapy; approximately 60% to immunotherapy-chemotherapy combination). However, only approximately 30% of patients with metastatic NSCLC have PD-L1 levels ≥50%. Although PD-L1 expression level is widely used as an immune biomarker, some patients with low PD-L1 expression levels respond to immunotherapy and others with high levels do not respond to immunotherapy (NCCN Clinical Practice Guidelines in Oncology Version 2.2021).

Newer treatment options are therefore required that can explore the potential of immunotherapy strategies and benefit a broader patient population. The complex pathophysiology of the NSCLC disease and the challenging 1L treatment landscape have led to the investigation of combination immunotherapy strategies. The combination of biologically distinct yet synergistic immunotherapies offers the likelihood of increasing antitumour immune response and achieving the goal of more patients experiencing durable responses relative to the response rates achieved with the same agents as monotherapy (Hellman et al [CheckMate-227] 2019). Furthermore, the addition of upfront chemotherapy might enable rapid disease control in a higher percentage of patients, thereby avoiding the early mortality observed with immunotherapy-only treatments in certain clinical trials, which manifests as an initial crossing of the survival curve (Hellman et al [CheckMate-227] 2019; Paz-Ares et al [Checkmate 9LA] 2021).

The FDA's Assessment:

In general, FDA agrees with the Applicant's position and summary of available therapies.

When the primary trial (POSEIDON) supporting this BLA was initiated in May 2017, platinum-based chemotherapy was the standard of care for patients with metastatic NSCLC that did not harbor a targetable mutation; no immune checkpoint inhibitors had regular FDA approval in the first-line setting. While platinum-based chemotherapy in combination with an immune checkpoint inhibitor is the current standard of care for patients with treatment-naïve, advanced NSCLC that does not harbor a targetable mutation, platinum-based chemotherapy was an appropriate control arm when POSEIDON was initiated.

Table 1 Summary of Treatment Armamentarium Relevant to Proposed Indication

Product Name	Relevant indication	Year of Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Subjects with Tumor PD-L1 Unselected Patient Population					
Nivolumab + Ipilimumab + platinum-doublet chemotherapy	In combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.	2020; Full	Nivolumab 360 mg every 3 weeks with Ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy; IV	mOS: 15.6 vs 10.9 m HR (96.71% CI) 0.66 (0.55, 0.80)	Immune-mediated adverse events
Pembrolizumab + pemetrexed and/or platinum chemo	in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	2017 accelerated; 2018 Full	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks; IV	mOS: 22.0 vs 10.6 m HR (95% CI): 0.56 (0.46, 0.69)	Immune-mediated adverse events
Pembrolizumab + carboplatin and paclitaxel or nab-paclitaxel	In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC with no EGFR or ALK genomic tumor aberrations	2018; Full	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks; IV	mOS: 17.1 vs 11.6 m HR (95% CI): 0.71 (0.58, 0.88)	Immune-mediated adverse events
Atezolizumab + bevacizumab + paclitaxel + carboplatin	In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	2018; Full	Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks; IV	mOS: 19.2 vs 14.7 m HR (95% CI): 0.78 (0.64, 0.96)	Immune-mediated adverse events

Product Name	Relevant indication	Year of Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Atezolizumab + carboplatin + nab-paclitaxel	In combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	2019; Full	Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks; IV	mOS: 18.6 vs 13.9 m HR (95% CI): 0.79 (0.64, 0.98)	Immune-mediated adverse events
Subjects with Tumor PD-L1 Expressing Patient Population					
Cemiplimab	for the first-line treatment of patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations	2021; Full	350 mg IV every 3 weeks; IV	mOS 22.1 vs 14.3m HR 0.68 (0.53, 0.87)	Immune-mediated adverse events
Pembrolizumab	As a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test	2016, Full 2019; Full	200 mg every 3 weeks; IV	TPS ≥ 1%: mOS: 16.7 vs 12.1 m HR (95% CI): 0.81 (0.71, 0.93) TPS ≥ 50%: mOS: 22.0 vs 10.7 m HR (95% CI): 0.56 (0.45, 0.70)	Immune-mediated adverse events
Nivolumab + Ipilimumab	in combination with ipilimumab, for first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	2020; Full	Nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks; IV	mOS 17.1 vs 14.9m HR 0.79 (0.67, 0.94)	Immune-mediated adverse events

Regulatory Background

U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tremelimumab is not currently approved in any region.

Durvalumab received accelerated approval on 01 May 2017 from the US DFA for the treatment of urothelial carcinoma (UC). Subsequently, durvalumab was approved for Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy, for the 1L ES-SCLC in combination with standard of care chemotherapy. On 07 May 2021, the Applicant voluntarily withdrew the urothelial carcinoma indication for durvalumab.

Combination of tremelimumab and durvalumab is not approved in the US or any other region globally.

The FDA's Assessment:

Since the November 15, 2021, submission of the current BLA for the treatment of patients with NSCLC, tremelimumab in combination with durvalumab received regular FDA approval for the treatment of patients with unresectable HCC.

Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2 Summary of key regulatory interactions with the US FDA

Date	Summary
29-May-2015	IND 124702 for durvalumab + tremelimumab for lung cancer was opened
24-Mar-2017	Protocol for POSEIDON study was submitted to IND124702
12-Jun-2018	FDA issued advice/information request for CSP version 1 of POSEIDON Study. This communication provided advice regarding evaluation of contribution of components and study population subgroups and exclusion criteria. The applicant was requested to modify the informed consent process and eligibility criteria.
11-Jan-2019	The sponsor received Type C written responses for structure and content of the tremelimumab BLA and durvalumab sBLA
30-Jan-2019	The sponsor received written advice regarding an integrated summary of immunogenicity for a potential tremelimumab BLA
01-Feb-2019	The sponsor received agreement from FDA on the durvalumab iPSP; Plan to request waiver for pediatric studies was acknowledged for durvalumab in combination with platinum based chemotherapy for 1L metastatic NSCLC
11-Feb-2019	The sponsor received written advice on integrated summary of efficacy and safety pool for potential tremelimumab BLA

26-Jun-2019	The sponsor received agreement from FDA on the tremelimumab iPSP; Plan to request waiver for pediatric studies was acknowledged
23-Mar-2021	The amended tremelimumab iPSP was agreed by FDA; (b) (4)
30-Jul-2021	Pre-BLA meeting; High level study results for POSEIDON, contribution of components, and structure and content for the tremelimumab BLA were discussed

The FDA's Assessment:
FDA agrees with the regulatory history provided by the Applicant.

Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Office of Scientific Investigations (OSI)

Clinical data from Study D419MC00004 (POSEIDON) were submitted to the Agency in support of a Biological License Application (BLA) 761270 for tremelimumab. Two clinical investigators (CI), Dr. Chul Byoung Cho in Seoul, Korea and Dr. Melissa Johnson in Nashville, TN, were selected for clinical inspection.

Based on FDA's inspections of Drs. Cho and Johnson, the data generated by Drs. Cho and Johnson appear acceptable in support of the proposed indication in the BLA.

In addition, the European Medicines Agency (EMA) shared with the Office of Scientific Investigations (OSI) the inspection findings from routine inspections of the CI Schim Rittmeyer (site # E2605), the Contract Research Organization (CRO) (b) (4) and the Sponsor AstraZeneca. The OSI reviewed the inspection reports provided by the EMA and summarized the GCP findings in this Clinical Inspection Summary (CIS). (b) (4) .

For additional details, see the Clinical Inspection Summary by Dr. Lee Pai-Scherf.

Product Quality

The Office of Biotechnology Products, OPQ, CDER, recommends approval of BLA 761270 for tremelimumab manufactured by (b) (4) (drug substance) and (b) (4) (drug product), for AstraZeneca Pharmaceutical. The data submitted in this application are adequate to support the conclusion that the manufacture of tremelimumab is well-controlled and leads to a product that is pure and potent. It is recommended that this product be

approved for human use under conditions specified in the package insert.

See the full review by Dr. Xu Di for further details.

Clinical Microbiology

See the CMC review from the current BLA submission. No clinical microbiology concerns were identified.

Devices and Companion Diagnostic Issues

Not applicable.

Nonclinical Pharmacology/Toxicology

Executive Summary

Tremelimumab (CP-675,206, MEDI1123) is an IgG2 monoclonal antibody directed against cytoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 and CD28 are receptors expressed on T cells and share the ligands CD80 (B7.1) and CD86 (B7.2). The interaction of CD28 with CD80/86 results in T cell activation and proliferation; however, CTLA-4 is an inhibitory receptor and binds CD80/86 with higher affinity than CD28, thus limiting T cell activity by preventing CD28-mediated T cell co-stimulation (Alegre et al., 2001). Tremelimumab binds to CTLA-4 and blocks binding to its ligands CD80 and CD86, thereby blocking an inhibitory signal and enhancing T cell-mediated immune responses. The established pharmacologic class for tremelimumab is a CTLA-4 blocking antibody.

The Applicant proposes to use tremelimumab 75 mg once every three weeks in combination with durvalumab and platium-based chemotherapy. Durvalumab (IMFINZI®) is a human IgG1 monoclonal antibody targeting human programmed death ligand 1 (PD-L1) and is approved for the treatment of non-small cell lung cancer (NSCLC), small cell lung cancer, and metastatic biliary tract cancer. Programmed cell death ligand-1 (PD-L1) is expressed on tumor cells and immune cells in the tumor microenvinronment and inhibits T cell activation through its interaction with programmed death protein 1 (PD-1) on activated T cells. Durvalumab binds PD-L1 and blocks its binding to PD-1, releasing inhibition of immune responses, including anti-tumor immune responses, without inducing antibody-dependent cellular cytotoxicity (ADCC). Because durvalumab is approved for multiple oncology indications, the focus of this review is the pharmacology and toxicology of tremelimumab.

As assessed by surface plasmon resonance, tremelimumab bound human and cynomolgus CTLA-4 with K_Ds of 0.29 nM and 0.98 nM, respectively. Tremelimumab also bound CTLA-4 expressed on human and cynomolgus T cells stimulated to express CTLA-4, but did not bind stimulated mouse, rat, hamster, or rabbit T cells; tremelimumab demonstrated minimal binding to unstimulated CD3 T cells from humans

or monkeys. Tremelimumab demonstrated >500-fold higher selectivity for CTLA-4 than CD28, CD86 or IgG1. Tremelimumab blocked CTLA-4 binding to CD80 and CD86 in an enzyme-linked immunosorbent assay (ELISA) with IC_{50}s of 0.78 nM and 0.46 nM, respectively and enhanced IL-2 and IFNγ release from primary human T cells co-cultured with Raji human lymphoma cells endogenously expressing CD80 and CD86. At a concentration of 30 µg/mL, tremelimumab enhanced activation of T cells in peripheral blood mononuclear cells (PBMC) and whole blood samples stimulated with an anti-CD3 antibody and staphylococcal enterotoxin A (SEA); tremelimumab similarly enhanced IL-2 release (up to 460% higher than an isotype control antibody) in PBMC and whole blood samples from healthy donors and patients with different types of cancer, including solid tumors and lymphomas. Additionally, tremelimumab enhanced IL-2 release from monkey T cells stimulated with SEA. In an in vitro co-culture assay, tremelimumab did not reverse the ability of human peripheral regulatory T cells (Tregs) to suppress activity and proliferation of stimulated human effector T cells. Aggregated or surface bound tremelimumab did not inhibit T cell activation in SEA-stimulated human PBMC or whole blood cultures at concentrations ≤100 µg/mL. Tremelimumab did not bind FcγRs in an competitive in vitro binding assay or mediate ADCC against activated human T cells. Tremelimumab did not mediate release of TNF-α, IL-6, or IL-1β from unstimulated human PBMCs in an in vitro cytokine release assay or reduce platelets in a separate in vitro assay.

A surrogate tremelimumab anti-CTLA-4 antibody prolonged survival in multiple subcutaneous mouse tumor models when administered alone and demonstrated increased response rates when administered in combination with an anti-mouse PD-L1 antibody. Additionally, administration of a surrogate anti-mouse CTLA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody reduced Tregs in tumors in mice implanted with CT26 mouse colon cancer tumors and increased proliferating intratumoral T cells in multiple syngeneic mouse tumor models at doses ≥20 mg/kg.

The Applicant evaluated the safety of tremelimumab administered intravenously, the intended route of administration, using cynomolgus monkeys in GLP-compliant 1- and 6-month repeat-dose toxicology studies. In consultation with the FDA clinical pharmacology team, animal to human exposure multiples were calculated using human pharmacokinetic (PK) parameters of C_{max} and area under the curve (AUC) values of 24.4 µg/mL and 245 µg·day/mL (AUC was multiplied by 24 hours to determine a value of 5880 µg·hour/mL for use in comparisons to animal data), respectively, at steady state after multiple doses of 75 mg tremelimumab. These values were derived from aggregated data from multiple clinical trials evaluating administration of 75 mg tremelimumab once every three weeks or once every four weeks; because clinical PK values were similar for both dosing regimens, FDA considers these values representative of human exposure to tremelimumab at the recommended dose. Mortalities occurred in the 6-month toxicology study in monkeys administered 50 mg/kg/week due to persistent diarrhea that correlated with minimal to moderate inflammation in the small and large intestines. Gastrointestinal (GI) toxicity occurred in both 1- and 6-month studies at doses ≥5 mg/kg (approximately ≥0.5 times the clinical AUC after multiple doses of 75 mg tremelimumab [referred as clinical AUC for the remainder of the Nonclinical Pharmacology/Toxicology review]) with signs of loose stools and decreased food consumption; weight loss occurred at 50 mg/kg (approximately 6.3 times the clinical AUC) in the 6-month study. Liver findings occurred at doses ≥15 mg/kg in the 1-month study and at doses ≥5 mg in the 6-month study (approximately ≥0.5 times the clinical AUC) and included increased AST in some animals and increased liver weight that correlated with minimal to mild periportal mononuclear cell infiltrates.

Decreased red blood cells, hemoglobin, and hematocrit occurred at doses ≥5 mg/kg in the 1-month study and at doses ≥15 mg/kg in the 6-month study (approximately ≥0.5 times the clinical AUC).

Tremelimumab-related effects on the immune system included histological findings of hyperplasia in multiple lymphoid organs (spleen, lymph nodes, bone marrow, gut-associated lymphoid tissue [GALT]) at doses ≥15 mg/kg in the 1-month study and ≥5 mg/kg in the 6-month study (approximately ≥0.5 times the clinical AUC) and correlated with increases in circulating leukocytes, lymphocytes, and T cells at doses ≥50 mg/kg (approximately ≥4.5 times the clinical AUC) in both studies. Clinical signs of swollen lymph nodes and histological findings of mononuclear cell infiltration with inflammation in multiple organs occurred at doses ≥5 mg/kg (approximately ≥0.5 times the clinical AUC) in the 6-month study. These findings improved after a drug-free period of 2 or 3 months in the 1- and 6-month studies, respectively.

Additional target organs in the 6-month study were the skin with clinical signs of abrasion, open sores, and/or rash in animals administered 50 mg/kg (approximately 6.3 times the clinical AUC) and the thyroid with findings of decreased T3/T4, increased TSH, and marked atrophy at doses ≥15 mg/kg (approximately ≥0.7 times clinical AUC). Tremors were observed in individual animals at doses ≥15 mg/kg (approximately ≥0.7 times the clinical AUC), but lacked any correlates. Consistent with nonclinical findings, diarrhea, decreased appetite, rash, hypothyroidism, and anemia have been seen clinically and the IMJUDO (tremelimumab) label includes warnings for immune-mediated adverse events and infusion reactions.

The Applicant did not conduct carcinogenicity or genetic toxicology studies as they are generally not appropriate for antibody therapies. In addition, the Applicant did not conduct dedicated studies to assess fertility. In general, these studies are not needed to support a marketing application for a drug intended to treat patients with advanced cancer. There were no adverse or notable effects on the male or female reproductive organs in the 1- and 6-month repeat-dose toxicology studies conducted in sexually mature cynomolgus monkeys.

Based on mechanism of action of tremelimumab and data from a literature-based risk assessment, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the label for IMJUDO. In animal models, the CTLA-4 signaling pathway is important for the maintenance of pregnancy through induction of maternal-fetal immune tolerance and immune regulation in newborns. Once weekly IV administration of tremelimumab to pregnant monkeys during the period of organogenesis did not result in maternal toxicity or embryo-fetal development toxicity at doses ≤30 mg/kg (approximately ≤4 times the clinical AUC); however, CTLA-4 blockade resulted in increased resorptions and fewer live fetuses in a mouse model. Additionally, studies using genetically engineered mice demonstrated that CTLA-4 deficient mice died from lymphoproliferative disorders 3 to 4 weeks after birth. Human immunoglobulin G2 (IgG2) is known to cross the placenta; therefore, tremelimumab has the potential to be transmitted from the mother to the developing fetus. Consistent with the recommendation for non-genotoxic drugs that are teratogenic or embryo-fetal lethal as described in the FDA Guidance for Industry Oncology Pharmaceticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the half-life of 18.2 days for tremelimumab, FDA recommends advising females of reproductive potential to use effective contraception during treatment with IMJUDO and for 3 months

after the last dose. The Applicant did not evaluate the presence of tremelimumab in milk; however, maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemice exposure in the breastfed child to IMJUDO are unknown. Because of the potential adverse effects of IMJUDO on a breastfed child, the review team recommends advising patients not to breastfeed during treatment with IMJUDO and for 3 months after the last dose.

Recommendation
There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of IMJUDO in combination with IMFINIZI and platinum-based chemotherapy.

Referenced NDAs, BLAs, DMFs

The Applicant's Position:
There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology.

The FDA's Assessment:

BLA 761069 was referenced for the nonclinical data for durvalumab.

Pharmacology

Primary pharmacology

Table 3 Primary Pharmacology Studies Supporting Mechanism of Action of Tremelimumab

Study Number/ eCTD Location	Study Objective(s)	Test System	Test Methods	Noteworthy Findings
06-CP-675,206 /Module 4.2.1.1	Selectivity of binding of tremelimumab to rhCTLA-4-Ig relative to rhCD28-Ig, rhCD86 (B7.2)-Ig, and hIgG1	rhCTLA-4-Ig, rhCD28-Ig, rhCD86-Ig, and hIGg1 coated onto plates (at a concentration of 1 µg/mL); Tremelimumab and HRP-conjugated anti-human IgG2	ELISA	Tremelimumab demonstrated > 500-fold higher selectivity for rhCTLA-4-Ig over rhCD28-Ig, rhCD86-Ig, and hIgG1
14-CP-675,206 /Module 4.2.1.1	Binding affinity of tremelimumab for rhCTLA-4 and rcynoCTLA-4	rhCTLA-4 or rcynoCTLA-4 (at a concentration of 50 µg/mL); Tremelimumab (666 nM to 0.01 nM)	SPR	Tremelimumab binds to: • rhCTLA-4 with KD of 0.28 nM • rcynoCTLA-4 with K_D of 0.98 nM

Study Number/ eCTD Location	Study Objective(s)	Test System	Test Methods	Noteworthy Findings
03-CP-675,206 /Module 4.2.1.1	Ability of tremelimumab to inhibit the binding of rhCTLA-4-Ig to rhCD80 (B7.1)-Ig and rhCD86 (B7.2)-Ig	rhCD80-Ig (4 nM) and rhCD86-Ig (3 nM); rhCTLA-4-Ig (0.3 nM); Tremelimumab (15.5 to 0.02 nM); HRP-conjugated anti-human IgG4	ELISA	Tremelimumab inhibits the binding of rhCTLA-4-Ig to: • rhCD80 in a concentration-dependent manner with an IC_{50} of 0.78 nM • rhCD86 in a concentration-dependent manner with an IC_{50} of 0.46 nM

CTLA-4 = cytotoxic T-lymphocyte antigen 4; cyno = cynomolgus monkey; ELISA = enzyme-linked immunosorbent assay; h = human; HRP = horse radish peroxidase; IC_{50} = half-maximal inhibitory concentration; Ig = immunoglobulin; IL = interleukin; KD = equilibrium dissociation constant; KLH = keyhole limpet hemocyanin; PBMC = peripheral blood mononuclear cell; PHA = phytohemagglutinin; rcyno = recombinant cynomolgus monkey; rh= recombinant human; SA = streptavidin; SPR = surface plasmon resonance; T-reg = regulatory T cell.

Table 4 Complete Responses in Antitumor Efficacy Studies Conducted with EMT6, CT26 or MCA205 Syngeneic Tumor Lines Adminstered anti-mouse CTLA-4 monoclonal antibody as Monotherapy or in Combination with an Anti-mouse PD-L1

Study Number/eCTD location: ONC1123-0001/4.2.1.1		**Anti-mouse PD-L1 clone 80**		**Anti-mouse CTLA-4 clone 9D9 mIgG1**		**Anti-PD-L1 clone 80 + Anti-mouse CTLA-4 clone 9D9 mIgG1**	
Tumor model	**Mouse strain**	**Experiment 1**	**Experiment 2**	**Experiment 1**	**Experiment 2**	**Experiment 1**	**Experiment 2**
EMT6 breast cancer	Balb/c	7 of 12 (58%)	10 of 12 (83%)	7 of 12 (58%)	7 of 12 (58%)	10 of 12 (83%)	11 of 12 (92%)
CT26 colon cancer	Balb/c	2 of 12 (17%)	2 of 12 (17%)	1 of 12 (8.3%)	2 of 12 (17%)	9 of 12 (75%)	6 of 12 (50%)
MCA205 sarcoma	C57BL/6	0 of 11 (0%)	4 of 11 (36%)	0 of 12 (0%)	0 of 11 (0%)	2 of 12 (17%)	4 of 11 (36%)

The anti-mouse CTLA-4 monoclonal antibody clone 9D9 mIgG1 (tremelimumab surrogate) was administered to mice engrafted with syngeneic tumors either as monotherapy or in combination with an anti-mouse programmed cell death ligand-1 (PD-L1) murine surrogate antibody.

The FDA's Assessment:

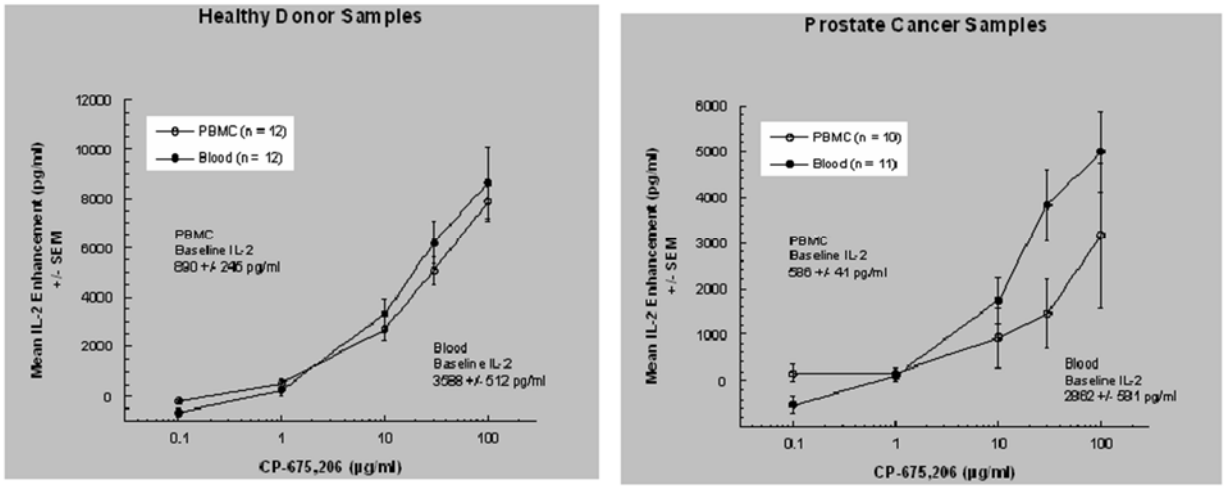
The FDA generally agrees with the Applicant's summary. In addition to these findings, the FDA notes the following results:

At a concentration of 10 µg/mL, tremelimumab bound human and cynomolgus T cells treated with phytohemagglutinin (PHA) to stimulate expression of CTLA-4, but did not bind mouse, rat, hamster, or rabbit PHA-stimulated T cells (Study# 15-CP-675,206). Tremelimumab demonstrated minimal surface or intracellular binding to unstimulated T cells from monkeys or humans. These results support the monkey as the only pharmacologically relevant species.

The Applicant assessed the ability of tremelimumab to enhance T cell responses by co-culturing, PHA-stimulated human T cells with Raji human B lymphoblast cells endogenously expressing CD80 and CD86 in the presence of 30 µg/ml tremelimumab or an isotype control. After 72 hours, treatment with 30 µg/mL tremelimumab resulted in higher IL-2 (510%) and IFNγ (54%) release than co-cultures treated with an isotype control (Study# 02-CP-675,206).

To evaluate the ability of tremelimumab to enhance T cell activation in vitro, the Applicant designed an assay in which T cell activity is dependent upon CD80 and CD86 signaling through CD28, an activating receptor expressed on T cells. In this assay, PBMCs or whole blood were cultured in the presence of staphylococcal enterotoxin A (SEA) and an immobilized anti-CD3 antibody, then IL-2 release into the supernatant was measured by ELISA to assess T cell activation. The addition of CTLA-4-Ig, an anti-human CD80 antibody, or an anti-human CD86 antibody inhibited IL-2 release, suggesting that activating signals mediated by CD80/CD86 interaction with CD28 is needed for T cell activation. In contrast, the addition of tremelimumab increased IL-2 release compared to an isotype control antibody, suggesting that blocking competitive CTLA-4 binding to CD28 allows for increased activiating signals mediated through CD80/86 interactions with CD28 (Study# 08-CP-675,206). Using this assay the Applicant evaluated the ability of tremelimumab to enhance activation of human T cells from healthy donors and donors with multiple types of cancer. Compared to an isotype control, treatment with 30 µg/mL tremelimumab resulted in 120% and 400% higher IL-2 release in whole blood and PBMCs from healthy donors, respectively (Study# 01-CP-675,206). Using PBMCs and whole blood from patients with different types of cancers, including solid tumors and lymphomas, tremelimumab resulted in 180% to 460% higher IL-2 release than controls for all types of cancer evaluated, indicating that tremelimumab can similarly enhance activation of T cells from healthy donors and patients with cancer (Figure 1, Study# 13-CP-675,206). Additionally, in a similar assay using whole monkey blood, tremelimumab resulted in 91% higher IL-2 release compared to samples treated with an isotype control (Study# 04-CP-675,206).

Figure 1: Effect of Tremelimumab on IL-2 Release from PBMC and Whole Blood from Healthy Donors and Patients with Cancer (FDA review)



(Applicant Figure reproduced from Study# 13-CP-675,206)

To evaluate the effect of tremelimumab on regulatory T cell (Treg)-mediated suppression of conventional T cells, $CD4^+CD25^-$ conventional T cells were co-cultured with $CD4^+CD25^+$ Tregs in the presence of 30 or 100 µg/ml tremelimumab or an isotype control antibody. Co-culture of conventional T cells with Tregs reduced IFNγ release and proliferation compared to culture of conventional T cells alone; however, the addition of tremelimumab to co-cultures did not result in increased IFNγ release or proliferation. This finding suggests that tremelimumab does not reverse the ability of human peripheral Tregs to suppress activity and proliferation of stimulated peripheral human conventional T cells (Study# 11-CP-675,206).

The Applicant investigated the potential of aggregated (plate-bound) tremelimumab to inhibit T cell activation through high-level aggregation of CTLA-4 on T cells using SEA-stimulated human PBMC and whole blood cultures treated with immobilized tremelimumab. After 72 hours, treatment with plate-bound tremelimumab did not result in increased IL-2 production compared to isotype control, suggesting that aggregated or surface bound tremelimumab does not inhibit T cell activation in SEA - stimulated human PBMC or whole blood cultures at concentrations ≤100 µg/mL (Study# 07-CP-675,206).

In an in vitro cytokine release assay, treatment of unstimulated human PBMCs or whole blood cultures with soluble tremelimumab for up to 48 hours did not result in release of TNF-α, IL-6, or IL-1β compared to untreated controls (Study# 05-CP-675,206). Treatment with tremelimumab for up to 24 hours did not reduce platelet counts in whole blood from healthy human donors in an in vitro assay (Study# 10-CP-675,206).

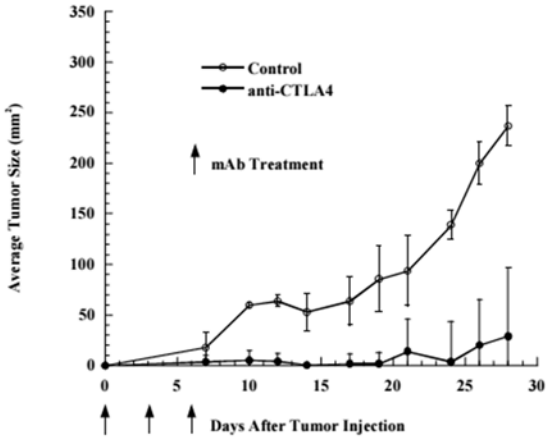
The ability of tremelimumab to bind FcγRs was assessed in a competitive binding assay using human PBMCs from healthy donors or patients with prostate cancer treated with unlabeled and/or radio-labeled tremelimumab or an isotype control antibody. Treatment with unlabeled and radio-labeled tremelimumab did not result in reduced binding of radio-labeled tremelimumab as assessed by counts

per minute (CPM) compared to treatment with radio-labeled tremelimumab alone. In comparison, treatment with a radio-labeled isotype control antibody and unlabeled isotype control antibody resulted in ≤ -53.3% binding of the radio-labeled isotype compared to treatment with the radio-labeled isotype control antibody alone. This result indicated that tremelimumab does not bind to human FcγRs (Study# 16-CP-675,206).

The Applicant investigated the ability of tremelimumab to mediate antibody-dependent cellular cytotoxicity (ADCC) using activated human NK cells as effector cells and naïve T cells or CD3/CD28-stimulated T cells from the same donor as target cells. Tremelimumab did not result in increased cytotoxicity of either target cell compared to untreated and isotype treated controls, suggesting that tremelimumab does not mediate ADCC (Study# 09-CP-675,206).

In addition to the mouse tumor studies described by the Applicant, administration of a surrogate anti-mouse CTLA-4 antibody inhibited growth of SA1N murine fibrosarcoma tumors when administered as a 200 µg injection on Days 0, 3, and 6 after tumor innoculation. (Figure 2, Study# 12-CP-675,206).

Figure 2: Effect of An Anti-Mouse CTLA-4 Surrogate Antibody on SA1N Mouse Fibrosarcoma Tumors (FDA review)



(Applicant Figure reproduced from Study# 12-CP-675,206)

In mice bearing CT26 tumors, treatment with an anti-mouse CLTA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody reduced the percentage of $Foxp3^+$ Tregs in the tumors, but not draining lymph nodes or spleens. Additionally, higher percentages of $Ki\text{-}67^+$ proliferating T cells were identified in EMT6, CT26, and MCA205 tumors from mice administered a surrogate anti-CTLA-4 antibody alone or in combination with an anti-mouse PD-L1 antibody (Study# ONC1123-0001).

Secondary Pharmacology

The Applicant's Position:
Secondary pharmacodynamics (PD) studies of tremelimumab were not conducted.

The FDA's Assessment:

The FDA agrees.

Safety Pharmacology

Stand-alone studies evaluating safety pharmacology of tremelimumab have not been conducted. However, safety pharmacology parameters including neurological, cardiovascular and respiration rate were evaluated following IV administration of tremelimumab in the acute single-dose (Study 99-1985-01), the 1-month (Study 00-1985-04) and the 6-month (Study 2004-0150) repeat-dose toxicity studies in cynomolgus monkeys.

The FDA's Assessment:
The FDA agrees that there were no tremelimumab-related effects on cardiovascular, respiration, or central nervous system parameters in male and female cynomolgus monkeys at doses up to 50 mg/kg administered once weekly for up to 6 months.

ADME/PK

The Applicant's Position:

The PK of tremelimumab was characterized in cynomolgus monkeys following a single IV administration at a dose level of 0.75 mg/kg of both clonally and nonclonally derived tremelimumab in PBS (pH 7.4) and NaAc buffer (pH 5.5), respectively. The PK of clonally and nonclonally derived tremelimumab was characterized by low plasma clearance (CL = 4.4 to 4.9 mL/day/kg) and small steady state volume of distribution (Vss = 54 to 71 mL/kg), resulting in a long mean elimination half-life (t½) of 9.1 to 11 days. Differences in the PK of clonally and non clonally derived tremelimumab were not statistically significant. In addition, the observed anti-drug antibody (ADA) responses were similar between clonally and non clonally derived tremelimumab. The mean SC bioavailability of tremelimumab was moderate (54.2%).

The toxicokinetics of tremelimumab was evaluated in cynomolgus monkeys following IV administrations of tremelimumab in a single-dose (10, 30, and 100 mg/kg), 1 month (5, 15, and 50 mg/kg/week;) and 6 month (5, 15, and 50 mg/kg/week) toxicologic studies, and an embryofoetal development (5, 15, and 30 mg/kg/week) toxicologic study. In the toxicologic studies with tremelimumab in cynomolgus monkeys, systemic exposures to tremelimumab, as assessed by mean maximal concentration (Cmax) and mean area under the concentration-time curve (AUC), increased dose proportionally within the dose ranges examined following single or multiple IV administrations. In the 6-month repeat-dose study, the steady state Cmax and cumulative AUC were 2030 µg/mL and 776000 µg·h/mL, respectively, following weekly (6 or 7 weeks) IV administrations of 50 mg/kg tremelimumab. No evidence of non linearity and gender-related differences in exposures were observed in any of the studies. Mean accumulation of tremelimumab was less than expected in these studies. This is probably due to the development of ADA in seven animals resulting in accelerated CL and decreased systemic exposures. All of ADAs were neutralizing Abs..

The FDA's Assessment:

The FDA generally agreed with the Applicant's summaries of the nonclinical ADME/PK data; however, see the FDA's additional noteworthy results and comments below.

Table 5: Summary and comments of nonclinical ADME/PK data (FDA review)

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Pharmacokinetics of CP-675,206 in Cynomolgus Monkeys Following Subcutaneous Administration/ DM2001-675206-009</td><td>
Monkeys (2/sex) were administered a single subcutaneous dose of 5 mg/kg tremelimumab
No sex differences, thus data was combined
PK Parameters in Monkeys:
<table>
<tr><td>C_{max} (µg/mL)</td><td>33.39</td></tr>
<tr><td>AUC_{last} (µg·hr/mL)</td><td>15200</td></tr>
<tr><td>T_{max} (hr)</td><td>84.0</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>Plasma Concentrations of CP-675,206 in Cynomolgus Monkeys Following a Single IV Dose in the Acute Toxicity Assessment/ DM2000-675206-001</td><td>
Monkeys (3/sex) were administered a single IV dose of 10, 30, or 100 mg/kg tremelimumab
No sex differences
PK Parameters in Monkeys:
<table>
<tr><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{last} (µg·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>10</td><td>190.84</td><td>311.48</td><td>27600</td><td>30500</td><td>2.0</td><td>0.8</td></tr>
<tr><td>30</td><td>755.74</td><td>620.99</td><td>75100</td><td>58600</td><td>0.08</td><td>8.05</td></tr>
<tr><td>100</td><td>2265.41</td><td>3669.19</td><td>213000</td><td>206000</td><td>0.08</td><td>0.08</td></tr>
</table>
Hr = hours
</td></tr>
<tr><td>Distribution</td><td>Not conducted</td></tr>
<tr><td>Metabolism</td><td>Not conducted</td></tr>
<tr><td>Excretion</td><td>Not conducted</td></tr>
<tr><td>TK data from general toxicology studies
1 Month Intravenous Toxicity Study with 2 Month Post-Dose Observation in Cynomolgus Monkeys (Study# 00-1985-04)</td><td>
Monkey
$T_{1/2}$: Not calculated; T_{max}: 0.5-5.0 hours
Dose proportionality: C_{max} and AUC increased increased approximately dose-proportionally on Days 1 and 29.
Accumulation: None
Sex differences: None
Anti-drug antibodies (ADA): ADAs were detected at all dose levels
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{0-24} (µg·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>5</td><td>111</td><td>103</td><td>1930</td><td>1690</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>330</td><td>384</td><td>6070</td><td>6940</td><td>0.5</td><td>2.0</td></tr>
<tr><td>50</td><td>1140</td><td>1050</td><td>19980</td><td>19700</td><td>0.5</td><td>0.5</td></tr>
<tr><td rowspan="3">29</td><td>5</td><td>148</td><td>180</td><td>2850</td><td>3660</td><td>0.5</td><td>5.0</td></tr>
<tr><td>15</td><td>483</td><td>383</td><td>8640</td><td>6240</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1530</td><td>1430</td><td>29800</td><td>26700</td><td>0.5</td><td>0.5</td></tr>
</table>
Hr = hours
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>6-Month Intravenous Toxicity Study of CP-657,206 in Monkeys (Study# 2004-0150)</td><td>Monkey
$T_{1/2}$: Not calculated; T_{max}: 0.5-3.0 hours
Dose proportionality: C_{max} increased less than dose proportionally and AUC_{0-24} decreased from 5 mg/kg to 15 mg/kg for males on Day 176.
Accumulation: None
Sex differences: At 15 mg/kg, AUC_{0-24} was 3.0-fold higher in females compared to males on Day 176.
Anti-drug antibodies (ADA): ADAs were detected at 5 mg/kg (1F), 15 mg/kg (3M, 1F), and 50 mg/kg (1M, 1F) as early as Day 22 and remained elevated throughout the remainder of the study.

<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{0-24} (µg·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>5</td><td>141</td><td>149</td><td>2590</td><td>2950</td><td>0.5</td><td>2.4</td></tr>
<tr><td>15</td><td>421</td><td>415</td><td>7510</td><td>7830</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1390</td><td>1410</td><td>27700</td><td>25700</td><td>3.0</td><td>1.8</td></tr>
<tr><td rowspan="3">29</td><td>5</td><td>221</td><td>247</td><td>4350</td><td>4900</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>431</td><td>579</td><td>5840</td><td>10500</td><td>0.5</td><td>0.5</td></tr>
<tr><td>50</td><td>1920</td><td>2140</td><td>36900</td><td>41800</td><td>0.5</td><td>1.8</td></tr>
<tr><td rowspan="2">176</td><td>5</td><td>247</td><td>137</td><td>5040</td><td>2700</td><td>0.5</td><td>0.5</td></tr>
<tr><td>15</td><td>309</td><td>579</td><td>3860</td><td>11800</td><td>0.5</td><td>0.5</td></tr>
</table>
Hr = hours</td></tr>
</table>

Toxicology

General Toxicology

Overall, the Nonclinical Toxicology program adequately assessed the nonclinical safety and tolerability profile of tremelimumab.

The toxicology profile of tremelimumab was assessed following IV administration in cynomolgus monkeys in two single dose studies (Study Nos. 00-1985-06 and 99-1985-01) and repeat dose studies of 1-month (Study No. 00-1985-04) and 6-months (Study No. 2004-0150) duration (see Module 4.2.3.1 and 4.2.3.2, respectively).

Local tolerance of IV administered tremelimumab was assessed following single dose administration at doses up to 100 mg/kg and following repeat administration at doses up to 50 mg/kg. No adverse tremelimumab-related changes were observed at the site of injection.

Following repeat administration at doses up to 50 mg/kg for either 1-month (5 doses) or 6-months (26 doses), signs comprised intermittent diarrhea which in some animals at 50 mg/kg in the 6-month repeat dose study became persistent and was associated with weight loss and inappetence, resulting in the cessation of dosing and/or euthanasia of these animals and termination of the group following 6 or 7 weekly doses. Target tissues for tremelimumab-induced toxicity included secondary lymphoid tissues of the gastrointestinal tract, the skin, spleen, lymph nodes, and thyroid tissues and the hematologic system. Most toxicities observed were either reversible or showed a trend towards reversibility

following a 10-week treatment-free period following the 1-month or 6-month dosing period. A dose of 5 mg/kg was considered to be the no-observed effect level (NOAEL) following 1-month of dosing and following 6-months of dosing a NOAEL was not established but 15 mg/kg was considered to be the maximum tolerated dose.

Table 6 6-Month Intravenous Toxicity Study of CP-675,206 in Monkeys

Species / Strain: Cynomolgus monkey		**Duration of dosing:** Once weekly for up to 6 months					**Study number:** 2004-0150		
Age at start of dosing: 2.5 – 5 years		**Duration of post-dose:** 99 days					**GLP compliance:** Yes		
Date of first dose: 20 July 2004		**Method of administration:** Bolus intravenous injection					**eCTD Location:** Module 4.2.3.2		
Special features: Assessments of lymphocyte immunophenotyping and of the development of primate anti-CP-675,206 human antibodies (PAHA) were also conducted.				**Vehicle / Formulation:** Solution in 20 mM Na acetate, 140 mM NaCl, 0.2 mg/mL polysorbate 80, pH 5.5					
No observed adverse-effect level: Not determined									
Daily Dose (mg/kg)		**0 (Vehicle)**		**5**		**15**		**50[a]**	
Number of Animals **Main Recovery**		**M: 4** **M: 2**	**F: 4** **F: 2**	**M: 4** **M: 0**	**F: 4** **F: 0**	**M: 4** **M: 0**	**F: 4** **F: 0**	**M: 4** **M: 2**	**F: 4** **F: 2**
Toxicokinetics [b]:	Day 29 $AUC_{(0\text{-}24h)}$ (µg.h/mL) C_{max} (µg/mL) Day 176 $AUC_{(0\text{-}24h)}$ (µg.h/mL) C_{max} (µg/mL)			 4350 221 5040 247	 4900 247 2700 137	 5840 431 3860 309	 10500 579 11800 579	 36900 1920	 41800 2140
Noteworthy Findings	**Died or Sacrificed Moribund**	0	0	1 [c]	1 [c]	0	0	4 [d]	4 [d]
Clinical Observations [e]		+	+	+	+	+	+	+++	+++
Haematology (Day 15)	Lymphocytes (10^3/µL) (% change from control) WBCs (10^3/µL) (% change from control)	6.763 11.000	5.233 8.517	7.423 (+9.8) 10.805 (-1.8)	6.908 (+32.0) 11.563 (+35.8)	8.848* (+30.8) 13.000* (+18.2)	7.793 (+48.9) 11.900* (+39.7)	11.512* (+70.2) 17.400** (+58.2)	9.455** (+80.7) 15.000** (+76.1)

Immunophenotyping (Day 15)	CD3+ (10^3/µL)	4.392	3.585	4.940	4.543	6.263*	5.790*	9.072**	6.887**
	(% change from control)			(+12.5)	(+26.7)	(+42.6)	(+61.5)	(+107)	(+92.1)
	CD3+CD4+ (10^3/µL)	2.428	1.990	3.085	2.548	3.768*	3.280	6.445*	5.057**
	(% change from control)			(+27.1)	(+28.0)	(+55.2)	(+64.8)	(+65.4)	(+154)
	CD3+CD8+ (10^3/µL)	1.453	1.242	1.553	1.690	1.890	2.123*	1.660	1.490
	(% change from control)			(+6.9)	(+36.1)	(+30.1)	(+70.9)	(+14.2)	(+20.0)
Serum Chemistry	**Day 15**								
	A/G ratio	1.20	1.17	1.20	1.13	1.20	1.00*	1.13	1.10
	(% change from control)			(0)	(-3.4)	(0)	(-14.5)	(-5.8)	(-6.0)
	Albumin (g/dL)	4.10	4.07	4.05	3.98	4.15	3.95	4.12	4.02
	(% change from control)			(-1.2)	(-2.2)	(+1.2)	(-2.9)	(+0.5)	(-1.2)
	Globulin (g/dL)	3.48	3.53	3.35	3.55	3.53	4.03	3.67	3.77
	(% change from control)			(-3.7)	(+0.6)	(-1.4)	(+14.2)	(+5.5)	(+6.8)
	Day 170								
	Thyroid stimulating hormone (UIU/mL)	0.5398	0.9055	0.3543	0.6443	0.8783	39.0393	ND	ND
	(% change from control)			(-34.4)	(-28.8)	(+62.7)	(+4211)		
	Thyroxine (T4) (ng/dL)	6.23	8.88	5.97	6.40	9.45**	<6.20		
	(% change from control)			(-4.2)	(-27.9)	(+51.7)	(30.2+)		
	Total T3 (ng/dL)	199.0	194.8	207.0	236.0	203.0	125.5		
	(% change from control)			(+4.0)	(+21.1)	(+2.0)	(-35.6)		
Organ Weights (g) [f]	Brain	75.83	67.73	76.03	65.87	70.90	59.98*	ND	ND
	(% change from control)			(+0.3)	(-2.7)	(-6.5)	(-11.4)		
	Liver	74.58	59.80	88.17	74.07**	81.23	66.83		
	(% change from control)			(+18.2)	(+23.9)	(+8.9)	(+11.8)		
Histopathology Number examined		4	4	4	4	4	4	4	4

Cecum	Inflammation								
	Minimal	0	0	0	0	0	1	2	2
	Mild	0	0	0	0	0	0	0	1
Colon	Inflammation								
	Minimal	0	0	0	0	0	1	3	0
	Mild	0	0	0	0	0	0	1	2
	Moderate	0	0	0	0	0	0	0	1
Duodenum	Inflammation								
	Mild	0	0	0	0	0	0	0	1
Kidney	Infiltration, mononuclear cells								
	Minimal	2	1	1	2	1	1	0	2
	Mild	0	0	1	0	0	0	0	0
	Inflammation, mononuclear cells								
	Minimal	1	0	2	1	2	1	2	1
	Mild	0	0	0	0	0	1	1	1
	Moderate	0	0	0	0	0	0	1	0
Liver	Infiltration, mononuclear cells								
	Minimal	0	0	0	1	0	0	0	0
	Infiltration, mononuclear cells, periportal								
	Minimal	3	2	3	3	4	3	0	2
	Mild	0	0	1	1	0	0	2	1
	Moderate	0	0	0	0	0	0	1	0
Lymph node, axillary	Lymphoid hyperplasia								
	Minimal	0	0	0	1	1	2	0	1
	Mild	0	0	0	0	0	0	2	0
	Moderate	0	0	1	0	0	0	0	0

Lymph node, mesenteric	Lymphoid hyperplasia								
	Minimal	0	0	1	2	0	1	0	0
	Mild	0	0	1	0	2	0	0	0
Pancreas	Atrophy, acinar								
	Mild	0	0	0	0	0	0	0	1
	Infiltration, mononuclear cells								
	Minimal	1	0	0	2	1	2	3	1
	Mild	0	0	0	0	0	1	0	0
	Inflammation, mononuclear cells								
	Minimal	0	0	0	0	1	0	0	0
	Mild	0	0	0	0	0	0	0	1
Parathyroid	Infiltration, mononuclear cells								
	Minimal	0	0	2	1	2	1	1	0
	Mild	1	1	1	0	0	1	2	0
Salivary gland	Infiltration, mononuclear cells								
	Minimal	0	1	2	1	1	0	2	1
	Mild	0	0	0	1	0	1	0	0
	Inflammation, mononuclear cells								
	Minimal	0	0	2	0	1	0	0	0
	Mild	0	0	0	0	0	2	2	1
	Moderate	0	0	0	1	1	0	0	0
	Marked	0	0	0	0	0	0	0	2

Skin	Atrophy, follicular								
	Moderate	0	0	0	1	0	0	0	0
	Infiltration, mononuclear cells								
	Minimal	2	3	3	3	0	4	0	3
	Mild	0	0	0	1	2	0	0	0
	Moderate	0	0	0	0	0	0	2	0
	Marked	0	0	0	0	0	0	2	0
Spleen	Lymphoid hyperplasia								
	Minimal	0	0	0	0	1	1	2	3
	Mild	0	0	0	0	0	1	1	1
Stomach	Inflammation								
	Minimal	0	0	0	0	0	1	0	0
	Mild	0	1	0	0	0	0	1	1
	Inflammation, mononuclear cells								
	Minimal	0	0	0	0	0	0	1	0
	Mild	0	0	0	0	0	0	0	1
Thyroid	Atrophy								
	Moderate	0	0	0	0	0	0	1	0
	Marked	0	0	0	0	0	1	0	0
	Infiltration, mononuclear cells								
	Minimal	1	1	2	2	2	2	2	2
	Mild	0	0	0	0	1	0	1	0
	Moderate	0	0	0	0	0	1	0	0
	Inflammation, mononuclear cells								
	Mild	0	0	1	0	0	0	0	0
	Moderate	0	0	0	0	0	0	1	0
Post-dose Evaluation:	**Number Evaluated**	2	2	0	0	0	0	2	2
Noteworthy findings									

Histopathology	**Number examined**	2	2					2	2
Salivary gland	Infiltration, mononuclear cells Minimal	0	0					1	1
	Inflammation, mononuclear cells Minimal	0	0					1	0
Skin	Inflammation, mononuclear cells Minimal	1	0					1	2

F = female; M = male, ND = no data (animals deceased prior to observation point); - No noteworthy findings; + Mild; ++ Moderate; +++ Marked; * p<0.05; ** p<0.01.

[a] Due to the development of severe adverse effects, 50 mg/kg/week monkeys only received 6 or 7 weekly doses (one male was last dosed on Day 37 and the rest of the group was last dosed on Days 43/44 for females and males, respectively) with dosing being suspended to see if the animals would improve.

[b] The plasma concentration of tremelimumab collected from the control group animals (0 mg/kg) at 0.5 hour postdose on treatment Days 1, 29 and 176 and recovery Day 99 were less than the LLOQ (0.156 µg/mL).

[c] Male 9 from the 5 mg/kg/week group was found dead on Day 52 due to severe, peracute diarrhea. Because the microscopic changes in the intestine of this animal were those of acute suppurative inflammation with ulcerations typical of an infectious process, instead of the chronic inflammation typically observed in other monkeys dosed with tremelimumab, the diarrhea and mortality of this animal were not considered directly related to treatment. In addition, Female 27 of the 5 mg/kg/week group was euthanized on Day 94 due to a non-treatment-olrelated compound fracture of the arm.

[d] After approximately 5 weeks of dose cessation and administration of palliative treatment, the 50 mg/kg/week animals failed to improve and several of these monkeys were euthanized due to poor condition. At this point, it was decided to begin the recovery phase early, beginning on Day 79, for the surviving high-dose monkeys along with the control monkeys originally designated as recovery monkeys (for comparison purposes).

[e] Adverse clinical observations included diarrhea in 5/12, 4/8, 6/8 and 10/12 animals of the control, 5, 15, and 50 mg/kg groups¼/4 M an¼/4 F in 5 mg/kg group and 3/6 M and 3/6 F in 50 mg/kg group required supportive care; dose-dependent decrease in appetite in 1/12, 3/8, 4/8, and 8/12 animals in the control, 5, 15, and 50 mg/kg groups; treatment-related adverse skin conditions in 1/8, 1/8, and 9/12 animals in 5, 15, and 50 mg/kg groups; skin conditions in animals in 5 and 15 mg/kg groups appeared during second half of dosing phase, and lasted for approximately 2 months; incidence and severity of skin conditions were less severe (small bumps and scabs on all the limbs, pruritus, wrinkled skin, and generalized scabbing) than those observed in the animals in the 50 mg/kg group; animals in 50 mg/kg group developed open sores along with lower incidences of swollen eyelids; dry, cracked, scaly or crusty skin; rash or reddened skin; scabbed areas; and yellowish skin; skin findings in 50 mg/kg group first manifested on Day 33 (after 5th dose), several other animals in the same group developed adverse skin observations by the 7th dose leading to discontinuation of dosing; palliative treatment did not improve diarrhea/skin conditions but affected recovery animals appeared normal by the end of the recovery period; dose-related enlarged lymph nodes in axillary and/or inguinal areas in 1/12, 6/8, 7/8, and 11/12 animals in the control, 5, 15 and 50 mg/kg group, respectively; affected animals were clinically normal at the end of the recovery period.

[f] Both absolute and relative weights differed from controls in the direction indicated. Displayed figures are for the absolute organ weight effects.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summaries of the repeat-dose toxicology studies in monkeys. Findings described by the Applicant were generally present in both the 1-month and 6-month toxicology studies. In the 6-month toxicology study, tremors occurred in one female at 15 mg/kg and one female at 50 mg/kg, however, no clear histologic correlates were identified in either animal.

Hematologic changes, including decreased red blood cells (RBC), hematocrit, and hemoglobin, occurred at doses ≥5 mg/kg in the 1-month study and at doses ≥15 mg/kg in the 6-month study. In the 6-month study, changes in RBC parameters generally peaked by Day 30 then trended toward improvement. These findings completely recovered after a drug-free period in both studies.

Slight increases in liver enzymes were observed in both studies but were transient or lacked a clear dose-response. Increased aspartate aminotransferase (AST) occurred in females at 15 mg/kg on Day 30 in the 1-month study. In the 6-month study, one female (#29) at 5 mg/kg had a transient increase in AST on Day 30 that improved by Day 92 and correlated with slight, but statistically significant increased liver weight in 5 mg/kg females. While periportal mononuclear cell infiltrates occurred in the liver of males and females at doses ≥5 mg/kg in both studies, there were no additional microscopic findings correlating to increased liver enzymes.

In addition to the histologic findings described by the Applicant, findings of minimal to mild hyperplasia were noted in several lymphoid tissues and signs of inflammation in multiple organs were noted at doses ≥5 mg/kg in the 6-month study (Table 7). There was also an increased incidence of minimal to mild mononuclear cell infiltration at dose levels ≥ 5 mg/kg in the adrenal glands, heart, skeletal muscle, prostate, uterus, pituitary, and brain. There were no notable findings in reproductive organs in either the 1-month or 6-month repeat-dose toxicology studies in monkeys.

Table 7: Selected Histopathology Findings (6-Month Study; Monkeys) (FDA review)

			Male				Female			
		Dose (mg/kg)	0	5	15	50*	0	5	15	50*
Organ/Tissue	Finding	# Animals examined	6	4	4	6	6	4	4	6
Lymph node, mandibular	Lymphoid hyperplasia	Mild				1				
	Foamy macrophages	Mild				1				
Bronchial node	Lymphoid hyperplasia	Min		1		1				
		Mild			1				1	

Organ/Tissue	Finding		Male				Female			
		Dose (mg/kg)	0	5	15	50*	0	5	15	50*
		# Animals examined	6	4	4	6	6	4	4	6
Bone marrow, sternum	Lymphoid hyperplasia	Min		1	2	2	1R	1	1	2, 1R
		Mild							1	
	Hypocellularity	Mild				1				
GALT	Lymphoid hyperplasia	Min		1	1	1R				1
		Mild			1					
Sciatic nerve	Degernation, axon	Mild								1R
Eye	Inflammation, mononuclear cells	Min						1		1
Heart	Inflammation, mononuclear cells	Mild				1				
Lung	Hyperplasia, Type II pneumocytes	Mild							1	
Adrenal glands	Mineralization	Mod			1					
	Hemorrhage	Mild				1				
	Hypertrophy	Mild		1						
	Inflammation, mononuclear cells	Min				1				
		Mod								1
		Marked				1			1	
Skeletal muscle	Inflammation, mononuclear cells	Min				1				
		Mild				1				
		Mod			1			1		
		Marked								2
Seminal vesicle	Inflammation, mononuclear cells	Min				1				

Organ/Tissue	Finding		Male				Female			
		Dose (mg/kg)	0	5	15	50*	0	5	15	50*
		# Animals examined	6	4	4	6	6	4	4	6
Testis	Hypoplasia	Mild			1					
	Inflammation	Mild				1				
Prostate	Inflammation, mononuclear cells	Mild		1						
		Mod				1				
Mammary gland	Inflammation, mononuclear cells	Mild								2
		Mod								1

R denotes recovery; *50 mg/kg animals were euthanized on Days 44 to 79

Similar findings were observed in a one-month repeat-dose toxicology study (previously reviewed under IND (b) (4)) in monkeys evaluating once weekly IV administration of 0, 5, 15, or 50 mg/kg tremelimumab. There were no mortalities or changes in body weight, food consumption, ophthalmology, or ECG parameters. Clinical signs were limited to loose stools at doses ≥5 mg/kg. Immunophenotyping identified increased total CD3 T cells, CD4 T cells, and B cells and decreased $CD16^{+}$ myeloid cells in animals administered 50 mg/kg tremelimumab. Changes in immune cell populations correlated to minimal to mild lymphoid hyperplasia in the spleen at doses ≥15 mg/kg and mesenteric lymph nodes at 50 mg/kg. Minimal to mild mononuclear cell infiltrates occurred in multiple organs, including the kidney, pancreas, salivary gland, heart, thyroid, brain, peripheral nerve, and bone marrow. Additional histologic findings in individual animals at doses ≥15 mg/kg include minimal tubular dilation in the kidney, minimal inflammation in lung, and increased cellularity in the stomach.

Genetic Toxicology

The Applicant's Position:
No studies were conducted in accordance with ICH S6(R1).

The FDA's Assessment:
The FDA agrees.

Carcinogenicity

The Applicant's Position:
No studies were conducted in accordance with ICH S6(R1).

The FDA's Assessment:
The FDA agrees.

Reproductive and Developmental Toxicology

Assessment of embryofetal development with tremelimumab was performed following IV treatment of pregnant cynomolgus monkeys (Study No. 2501-001) during the period of organogenesis (from confirmation of pregnancy on Gestation Day 20 [GD20] to GD50) at dose levels of 0 (vehicle), 5, 15 or 30 mg/kg/wk. After the final dose on GD48, animals were maintained until GD100 ± 1, when caesarean sections were carried out and fetuses assessed. There were no unscheduled deaths during the course of the study and no tremelimumab-mediated effects on clinical signs, body weights, vaginal smears, placental weights and appearance, or abortion rates/prenatal losses in the pregnant dams. No effects of tremelimumab were observed on fetal weights, or external, visceral and skeletal abnormalities, or weights of selected organs. Therefore, tremelimumab did not elicit maternal toxicity, developmental toxicity or teratogenicity and the NOAEL was considered to be 30 mg/kg.

Table 8 Design of Study 2501-001, Endpoints Evaluated, and Noteworthy Findings

Study Number: 2501-001		**Test Article:** Tremelimumab	**Test Article Lot:** E 5 644 LO 05 (61002D)	**Number of Doses:** 5
Control Article: L-histidine (0.0564%), L-histidine HCl (0.0343%), trehalose dihydrate (8.4%), polysorbate 80 (0.02%)				**Species:** Cynomolgus monkey
Route of Administration: Intravenous bolus		**Duration of Post-dose Treatment-free Period:** 52 days		**GLP Compliance:** Yes
Study Type: Reproductive toxicity/embryo-foetal development				**eCTD Location:**Module 4.2.3.5.2
Study Objective: To investigate the embryonic and teratogenic effects when administered to pregnant cynomolgus monkey during the period of organogenesis				
GRP	**Test Article**	**Number of Pregnant Females**	**Dose Level (mg/kg)**	**Number of Animals with Cesarean section on GD 100**
1	Vehicle	16	0	13
2	Tremelimumab	16	5	12
3	Tremelimumab	16	15	14

4	Tremelimumab	16	30		12
Toxicokinetics (group mean value)					
Dose Level (mg/kg)		**0**	**5**	**15**	**30**
AUC_{0-24} (µg·h/mL)	GD 20	NA	2830 ± 530	9050 ± 1190	18600 ± 6540
	GD 48	NA	3680 ± 977	12900 ± 3750	23800 ± 4720
$AUC_{Days\ 20-49}$ (µg·h/mL)		NA	76800 ± 17200	208000 ± 59900	454000 ± 75000
C_{max} (µg/mL)	GD 20	NA	154 ± 32.2	498 ± 78.4	954 ± 345
	GD 48	NA	187 ± 42.8	707 ± 144	1230 ± 210
ADA incidence (number of M/F) and percentage positive		NA	NA	NA	NA
Endpoints Evaluated (Dams): mortality, clinical signs, body weight, food consumption, pregnancy outcome (pre-implantation loss/abortions, foetal/embryonic death, placental weights). **Endpoints Evaluated (Fetuses)**: mortality, body weight, foetal body measurements, organ weights, and external, visceral, and skeletal examinations.					
Noteworthy Findings					
There were no noteworthy tremelimumab-related findings.					

ADA = anti-drug antibody; AUC = area under the concentration-time curve; C_{max} = maximal concentration; GD = Gestation Day; NA = not applicable.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion. Under the conditions tested, there were no effects on maternal toxicity or embryo-fetal mortality or malformations at doses up to 30 mg/kg administered once weekly during the period of organogenesis from GD20 to GD48 in an embryo-fetal toxicity study in cynomolgus monkeys. Additionally, there were no signs of toxicity to male or female reproductive organs in the general toxicology studies. Although the cynomolgus monkey is a pharmacologically relevant species for the evaluation of tremelimumab, non-human primate models of pregnancy can present challenges for evaluating human reproductive risks due to multiple factors such as low numbers of pregnant animals, low fertility, variable abortion rates, and low numbers of offspring (Cauvin et al., 2015). In humans and monkeys, transfer of IgG antibodies from mother to fetus across the placenta is mediated by the neonatal Fc receptor (FcRn) and FcRn expression in the placenta is highest during the second and third trimesters in humans and during approximately the last 50 days of pregnancy in cynomolgus monkeys; thus, IgG transfer is highest after the period of organogenesis in both species (Cauvin et al., 2015; Pentsuk and van der Laan, 2009). Tremelimumab is an IgG2 antibody and is anticipated to be transferred across the placenta; however, it is difficult to assess the potential risk to the fetus due to in-utero exposure to tremelimumab in this study given that tremelimumab was administered to pregnant cynomolgus monkeys only during the period of organogenesis.

Maternal immune tolerance of the semi-allogeneic fetus is critical for maintenance of pregnancy. CTLA-4 regulates immune responses by controlling T cell activation and contributing to the immunosuppressive effects of Tregs. CTLA-4 may also contribute to immune tolerance in pregnancy considering Tregs constitutively expressing CTLA-4 are essential for regulating immune responses at the maternal-fetal interface by maintaining an anti-inflammatory environment necessary for implantation and placental development (Robertson et al., 2018). Given that disruption of CTLA-4-mediated immunosuppression may abrogate maternal immune tolerance to fetal antigens, the FDA performed a literature-based assessment (reviewed by Dr. Melissa A. Pegues and Dr. Brian Christmas) of the potential for blockade of

CTLA-4 to cause reproductive and embryofetal toxicity.

In an animal model, administration of an anti-mouse CTLA-4 antibody to pregnant CBA/J female mice on GD 4.5, 6.5, and 8.5 resulted in lower maternal body weight gain, increased resorptions, and reduced number of live fetuses compared to mice administered an isotype control antibody (Wang et al., 2019). Additionally, analysis of decidual CD4 T cells from these mice demonstrated that treatment with an anti-CTLA-4 antibody resulted in an increase in the percentage of cells expressing the Th1 associated cytokines TNF-α and IFNγ and a decrease in the percentage of cells expressing the Th2 associated cytokines IL-4 and IL-10 compared to controls (Wang et al., 2019). In humans, CTLA-4 expression positively correlated with production of Th2 cytokines, IL-4 and IL-10, and negatively correlated with expression of Th1 cytokines, IL-2 and IFNγ, in samples from normal pregnancies; however, CTLA-4 expression was lower on decidual T cells from miscarriages and was associated with lower frequency of cells expressing IL-4 or IL-2 and an increase in cells expressing IL-2 or IFNγ, suggesting a shift towards a pro-inflammatory Th1 expression profile (Jin et al., 2011). Taken together, these findings suggest that disruption of CTLA-4 signaling may lead to alterations in tolerogenic T cell responses, which in turn may be associated with pregnancy loss.

Further, studies using genetically engineered mice suggest that CTLA-4 may be important for the development of neonatal immune tolerance. Homozygous CTLA-4 deficient (CTLA-$4^{-/-}$) mice resulting from mating mice heterozygous for CTLA-4 (CTLA-$4^{+/-}$) develop a lymphoproliferative disorder characterized by a systemic accumulation of T cell blasts in multiple organs, including liver, heart, lungs, and lymphoid organs, that results in death due to heart failure 3 to 4 weeks after birth (Waterhouse et al., 1995; Tivol et al., 1995; Araki et al., 1998). These findings suggest that fetal exposure to tremelimumab may increase the risk of developing immune-mediated disorders or of altering normal immune responses.

The proposed indication for tremelimumab is in combination with durvalumab, an anti-PD-L1 antibody, and platinum-based chemotherapy; both of these therapies can also cause fetal harm. Based on the mechanism of action of tremelimumab and nonclinical findings from animal models, FDA recommends advising females of reproductive potential to use effective contraception during treatment with tremelimumab and for 3 months after the last dose.

Other Toxicology Studies

The Applicant's Position:

In vitro tissue cross-reactivity studies were conducted in both monkey (IM645; Module 4.2.3.7.7) and human (IM676; Module 4.2.3.7.7). Tremelimumab bound only to cells in tissues expected to contain CTLA-4 expressing cells and were considered similar between species. In cynomolgus monkey tissues -positive staining was specific for lymphocytes in lymphoid tissues including tonsil, lymph node, spleen, and thymus. Positive staining was noted on rare to occasional lymphocytes in mucosa-associated lymphoid tissue in stomach and colon. In human tissues -positive staining was specific for lymphocytes in lymphoid tissues including tonsil, lymph node, spleen, and non involuted thymus. Positive staining was noted on rare to occasional lymphocytes in mucosa-associated lymphoid tissue in the small intestine and colon, and rare lymphocytes in lymphoid nodules of one thyroid gland.

The FDA's Assessment:
The FDA generally agrees with the Applicant's conclusion. Additionally, the placenta was noted for positive staining in humans, but not monkeys.

X X

Melissa A. Pegues, PhD
Primary Reviewer

Claudia P. Miller, PhD
Acting Supervisor

Clinical Pharmacology

Executive Summary

Tremelimumab is a human IgG2 monoclonal antibody (mAb) directed against CTLA-4. Combined durvalumab and tremelimumab target PD-L1 and CTLA-4 to block complementary immunosuppressive pathways acting at initial T-cell priming and activation and later at the effector T-cell response.

The Applicant seeks approval for the combination of tremelimumab with durvalumab and platinum-based chemotherapy in patients with previously untreated metastatic NSCLC without sensitizing EGFR or ALK genomic tumor aberrations.The proposed dosage regimen is tremelimumab 75 mg in combination with durvalumab 1500 mg and platinum-based chemotherapy every 3 weeks (Q3W) for four cycles followed by (b) (4)

The proposed dosage regimen of tremelimumab in combination with durvalumab and platinum-based chemotherapy (T+D+SOC) achieved a 2.3-month longer median overall survival (OS) in the pivotal trial Study D419MC00004 (POSEIDON) compared to the SOC control and is supported by the dose finding study, Study 06 (D4190C00006). The incidence of AEs and of Grade 3 or 4 AEs in T+D+SOC arms was comparable with the control arm, 97.3% vs 96.1 %, and 53.3% vs 51.7%, respectively. The incidence of AEs leading to discontinuation of study treatment and leading to dose delay/interruption was 22.1 % vs 15.3% and 57.3% vs 42.9%, respectively. Serious AEs including events with outcome of death were higher in T+D+SOC arms compared to the control arm (44.2% vs 35.1%).

This BLA includes reports describing the population pharmacokinetic (PPK) and exposure-response (E-R) analyses and immunogenicity evaluation. The PPK analyses found that the following factors have no clinically relevant effet on the PK parameters of tremelimumab: body weight (34 to 149 kg), age (18 to 87 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or American Indian), serum albumin level (0.3 to 396 g/L), lactate dehydrogenase level (12 to 5570 U/L), soluble PD-L1 level (67 to 349 pg/mL), creatinine clearance (22.5 to 299 mL/min), and mild to moderate hepatic impairment (bilirubin <3x ULN and any AST). The E-R analyses found no evidence indicative of relationship for safety of both durvalumab and tremelimumab. No clear correlations were identified for the efficacy endpoints of OS and PFS vs. the durvalumab PK exposures. For tremelimumab, both Kaplan-Meier (KM) plots and Cox proportional hazard (CPH) model analyses suggested potential exposure-response relationships between tremelimumab PK exposures and efficacy endpoints. However, tremelimumab PK exposures were found to be associated with other disease covariates, e.g. albumin and neutrophil-to-lymphocyte ratio (NLR), suggesting the identified exposure-exponse relationships for tremelimumab were potentially confounded.

In the POSEIDON study, 38 of the 278 (13.7%) anti-drug-antibody (ADA) evaluble patients who were treated with T+D+SOC tested positive for treatment-emergent anti-tremelimumab antibodies and neutralizing antibodies (Nab) against tremelimumab were detected in 31 of the 38 (81.6%) patients at

any visit. The presence of ADAs against tremelimumab had no apparent effect on tremelimumab exposure. For durvalumab, 29 of the 286 (10%) patients tested positive for anti-durvalumab antibodies and 3 of the 29 (10.3%) patients tested positive for Nab. Geometric mean concentrations of durvalumab at week 3 predose decreased in ADA positive patients compared to that in ADA negative patients. There is no observed impact of ADAs against durvalumab or tremelimumab on safety. The effect of ADAs on efficacy of trelimumab and durvalumab is unknown due to low occurrence of ADA incidences.

6.1.1 Recommendations

Table 9: Clinical Pharmacology Review and Recommendations (FDA review)

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of tremelimumab, durvalumab in combination with platinum-based chemotherapy (T + D + SOC) in patients with NSCLC was established in pivotal study POSEIDON. Compared with control arm, T + D + SoC achieved a statistically significant OS benefit of 2.3 months compared to the control arm with a hazard ratio of 0.77 (95% CI: 0.650, 0.916; p=0.00304). E-R analyses suggested generally flat relationships for safety with either tremelimumab or durvalumab PK exposures at the recommended dosing regimen. For efficacy, no clear exposure-response relationships were identified for durvalumab. KM plots and CPH model analyses suggested potential correlations between tremelimumab PK exposures and clinical efficacy endpoints (OS and PFS). However, the potential E-R relationship for tremelimumab was confounded by other disease covaraites, e.g. albumin and neutrophil-to-lymphocyte ratio (NLR).
General dosing instructions	*Body weight ≥30 kg*: 75 mg tremelimumab in combination with durvalumab 1,500 mg and chemotherapy Q3W for 4 cycles followed by (b) (4) *Body weight <30 kg:* (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic factors)	*Dose based on 30 kg body weight cutpoint* Body weight ≥ 30kg: The proposed adult flat dosing regimen is acceptable given that (1) minimal impact of body weight in the

	range of 34 to 149 kg on tremelimumab exposure, and (2) flat E-R relationships for safety. Body weight < 30 kg: A weight-based dosing regimen is appropriate. Although no clinical data available, approved durvalumab regimen has a body weight dosing cutoff at 30 kg. This is an acceptable general approach to prevent overexposure in patients with lower body weight.
Immunogenicity	*Tremelimumab* During 16 weeks of treatment in study POSEIDON with T + D + SoC, 13.7% (38/278) patients tested positive for ADA against tremelimumab. Neutralizing antibodies against tremelimumab (Nab) were detected in 81.6% (31/38) of patients. The presence of ADAs against tremelimumab had no apparent effect on PK or safety. Due to the low occurrence of ADA, the effect of the ADA on OS is unknown. *Durvalumab* During the initial 16 weeks of treatment in study POSEIDON with T + D + SoC, 10% (29/286) of patients tested positive for ADA against durvalumab and, Nabs were detected in 10.3% (3/29) of the patients. The geometric mean of durvalumab concentrations in the ADA positive patients was 46 mcg/mL compared to 89 mcg/mL in the patients with ADA negative at week 3. There was no clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab. Because of the low occurrence of anti-durvalumab antibodies, the effect of the ADAs on OS is unknown.
Labeling	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements on the FDA recommended labeling revisions.

6.1.2 Post-Marketing Requirements and Commitments

The FDA's Assessment:
Not applicable.

Summary of Clinical Pharmacology Assessment

Pharmacology and Clinical Pharmacokinetics

Data:

Table 10 Clinical pharmacology and pharmacokinetics data

Pivotal	Supportive
Summary of observed **tremelimumab** and **durvalumab PK** concentrations in the POSEIDON study. **Population PK analyses:** • Tremelimumab: PK modelling using tremelimumab PK data from Study 002, Study 006, Study 010, DETERMINE, D4884C00001, and POSEIDON. • Durvalumab: Update existing durvalumab population PK model (PK data from Study 1108, ATLANTIC, PACIFIC, CASPIAN) via adding POSEIDON durvalumab PK data. • Evaluation of the impact of intrinsic/extrinsic factors (demographics, renal/hepatic impairment, ADA, monotherapy vs combination therapy, smoking, tumor type and other disease-related factors) on tremelimumab or durvalumab PK.	Exposure-response analyses: • **Exposure-efficacy analysis:** The relationship between tremelimumab (C_{max}, C_{trough}, and AUC at Cycle 1/Dose 1 and Cycle 5/Dose 5) and durvalumab PK exposure (C_{max}, C_{trough}, and AUC at Cycle 1 and steady state) and key efficacy endpoints (e.g., OS, PFS, ORR) is evaluated within the exposure range of tremelimumab 75 mg Q3W and durvalumab 1500 mg Q3W in the POSEIDON study. • **Exposure-safety analysis:** The relationship between tremelimumab (C_{max}, C_{trough}, and AUC at Cycle 1/Dose 1 and Cycle 5/Dose 5) and durvalumab PK exposure (C_{max}, C_{trough}, and AUC at Cycle 1 and steady state) and key safety endpoints (eg, Grade 3+ AE, AESI, AE leading to discontinuation) is evaluated within the exposure range of tremelimumab 75 mg Q3W and durvalumab 1500 mg Q3W in the POSEIDON study. Immunogenicity: • **Tremelimumab immunogenicity analysis:** An ISI for tremelimumab is submitted to support the BLA review of tremelimumab in combination with durvalumab and chemotherapy in the proposed patient population. Summary of ADA data against tremelimumab is briefly described in Module 2.7.2.4 section. • **Durvalumab immunogenicity analysis:** Summary of ADA data for durvalumab in the POSEIDON study as well as comparison with historical durvalumab ADA data is described in Module 2.7.2.4 section.

Clinical Pharmacokinetics (PK) of tremelimimab:

Tremelimumab monotherapy exhibited a biphasic and approximately dose-proportional PK profile following single and multiple dose IV infusion ranging from 0.1 to 15 mg/kg in patients with advanced solid tumor. Multiple dosing PK of tremelimumab monotherapy were investigated in patients mainly at doses of 10 mg/kg or 750 mg administered Q4W for 7 doses followed by Q12W for 2 doses [studies D4884C00001 and D4880C00003 (DETERMINE) monotherapy arm]. The fixed dose (750 mg) PK data were similar to those weight-based (10 mg/kg) for tremelimumab monotherapy, and tremelimumab concentrations appeared similar across multiple tumor types studied (see Module 2.7.2.2.2). Accumulation ratios for C_{max} and C_{trough} were around 1.3-1.6 (at Week 12), and steady state was achieved

at approximately 12 weeks.

The PK of tremelimumab in combination with durvalumab is similar to the PK in monotherapy. D4190C00006 (Study 06) collected intensive PK samples for the first dose of tremelimumab in combination with durvalumab. NCA analysis was performed based on a total of 353 subjects for the tremelimumab data. Following the first IV dose, an approximately dose-proportional increase in PK exposure (C_{max} and area under the serum concentration-time curve from Day 1 to Day 29 [AUC_{0-28}]) of tremelimumab was observed over the doses of 1, 3, and 10 mg/kg tremelimumab Q4W as assessed by dose normalized PK parameters. Mean accumulation ratios of tremelimumab ranged from 0.861 to 1.69 and from 1.50 to 1.87 for C_{max} and C_{trough}, respectively. The steady state was achieved around Day 85 (after 3 Q4W doses) (see Table 53, Study 06 CSR, Module 5.3.5.2.).

For pivotal Phase 3 POSEIDON study (75 mg Q3W T + D + chemo), Table 11 summarized tremelimumab C_{max} and C_{trough} concentrations in comparison with pan-tumor pool (1 mg/kg Q4W T + D, without chemo). Following the first dose, the geometric mean C_{max} at 75 mg Q3W was similar (approximately 12% higher) to that at 1 mg/kg Q4W in the D + T pan-tumor pool at end of infusion. The geometric mean steady state C_{trough} (week 12) at 75 mg Q3W in POSEIDON was approximately 86% higher than at 1 mg/kg Q4W in the D + T pan-tumor pool, due to the different dosing frequency Q3W vs. Q4W.

Table 11 Summary of Serum Tremelimumab Concentrations (PK-evaluable Population)

Visit, timepoint	Geometric mean, µg/mL (geometric %CV) [n]	
	POSEIDON	T + D Pan-Tumor Pool
	T + D + SoC 1500 mg Q3W D + 75 mg Q3W T (N = 327)	20 mg/kg Q4W D + 1 mg/kg Q4W T (N = 2056)
Week 0, post-infusion	23.2 (65.62) [294]	20.7 (38.19) [1849]
Week 3, pre-infusion	4.2 (80.83) [285]	- (-) [0]
Week 12, pre-infusion	7.8 (75.68) [183]	4.2 (88.82) [815]

BLQ, below the lower limit of quantification; CV, coefficient of variation; D, durvalumab; N, number of patients; n, sample size; Source: Table 20, Module 2.7.2.3.1

Population PK (PPK) analysis of tremelimumab:

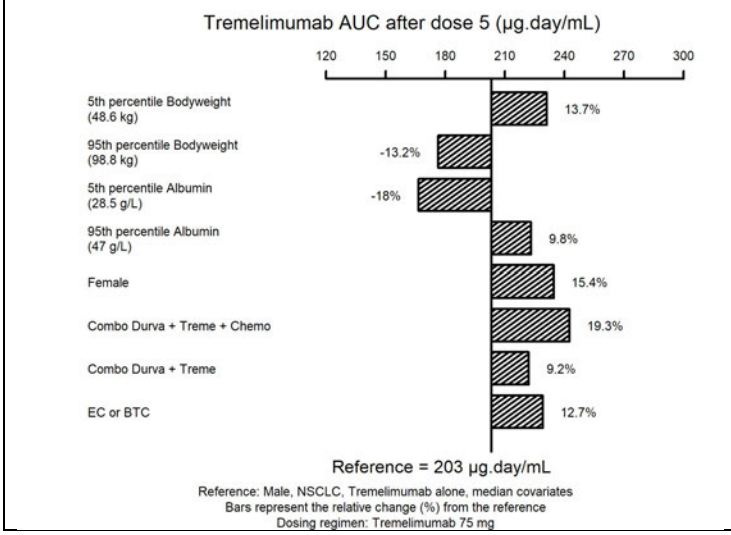
The PPK analysis were performed based on data from Japan Study 02, Study 06, Study 10, DETERMINE, and D4884C00001 following tremelimumab monotherapy or tremelimumab in combination with durvalumab, as well as POSEIDON (tremelimumab in combination with durvalumab and chemo). Tremelimumab PK was best described by a linear 2-compartment model with time-varying clearance.

For tremelimumab in combination with durvalumab and chemo (based on POSEIDON post-hoc parameters), the geometric mean (% coefficient of variation [CV%]) for central (V1) and peripheral (V2) volume of distribution was 3.45 (27.3%) L and 2.47 (43.3%) L, respectively. Tremelimumab clearance decreases over time in combination with durvalumab and chemo, with a mean maximal reduction (CV%) from baseline values of approximately 22.7% (26.1%) resulting in a geometric mean (CV%) steady state

clearance (CLss) of 0.202 L/day (19.2%); the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life was approximately 20.4 (34.7%) days.

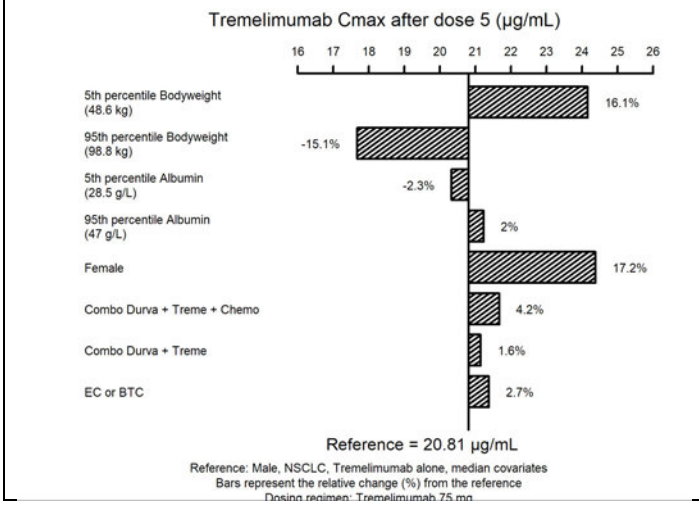
Several covariates were statistically significant on tremelimumab CL and V1: body weight, ALB, sex, combination therapy and primary indication on CL; and body weight and sex on V1. However, their impact on the tremelimumab exposure (Figure 3, Figure 4) can be regarded of minimal clinical relevance (less than 20%).

Figure 3 Univariate Impact of Covariates on Tremelimumab AUC



Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual CL values between the 5th and 95th percentiles, respectively, of the median observed covariate values.
AUC, area under the serum concentration-time curve; BTC, biliary tract carcinoma; Chemo, chemotherapy; CL, clearance; Combo, combination; Durva, durvalumab; EC, esophagus carcinoma; NSCLC, non-small cell lung cancer; PK, pharmacokinetic(s); Treme, tremelimumab.
Source: Figure 51, Population PK and Exposure-Response Report, Module 5.3.3.5.

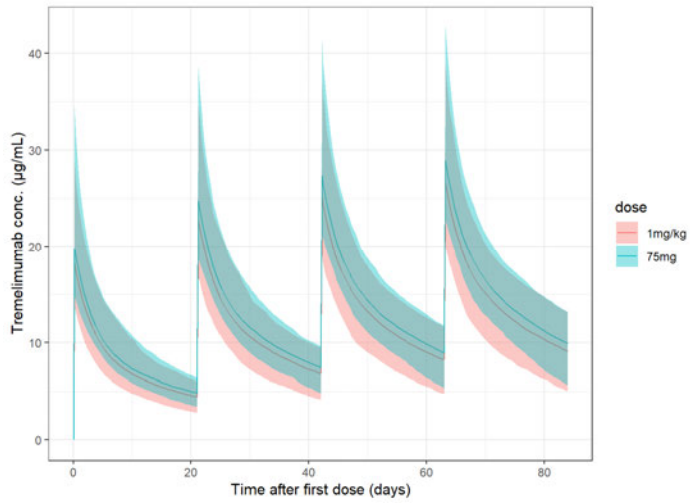
Figure 4 Univariate Impact of Covariates on Tremelimumab C_{max}



Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual CL values between the 5th and 95th percentiles, respectively, of the median observed covariate values.
BTC, biliary tract carcinoma; Chemo, chemotherapy; CL, clearance; Cmax, maximum serum concentration; Combo, combination; Durva, durvalumab; EC, esophagus carcinoma; NSCLC, non-small cell lung cancer; PK, pharmacokinetic(s); Treme, tremelimumab.
Source: Figure 52, Population PK and Exposure-Response Report, Module 5.3.3.5.

The simulated concentration profiles (Figure 5) showed a good overlap between flat dosing (75 mg Q3W) and body-weight based (1 mg/kg Q3W) dosing regimens, while graphically a flat dosing may exhibit less variability (narrower shaded band and less patients with low exposure) as compared to weight based dosing. The exposure difference was small (< 20%) for all metrics (AUC, C_{max}, C_{min}), with a large overlap between body weight brackets. A flat dosing regimen of tremelimumab seems therefore justifiable.

Figure 5 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.
Source: Figure 67, Population PK and Exposure-Response Report, Module 5.3.3.5

The Applicant's Position:

Pharmacology:

Tremelimumab is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell priming and amplifying T-cell proliferation, resulting in memory T-cell expansion and increased antitumor immune activity.

Combined durvalumab and tremelimumab targets PD-L1 and CTLA-4 to block complementary immunosuppressive pathways acting at initial T-cell priming and activation and later at the effector T-cell response.

Dual blockade of PD-L1 and CTLA-4 resulted in an increased and sustained antitumor activity nonclinically (murine syngeneic tumor models) and clinically (preliminary efficacy data in patients with advanced NSCLC from study D4190C00006). Addition of these IO combination to SoC chemo (early disease control) was to broaden the antitumor responses and provide long-term survival benefits in first line NSCLC.

Clinical PK:

Tremelimumab PPK analysis evaluated tremelimumab monotherapy PK and in durvalumab combinations with or without chemo in multiple tumor types. Based on the PPK analysis, tremelimumab

PK was well described by a linear 2-compartment model with time varying CL (for monotherapy, elimination was linear only). Several statistical significant covariates were identified but their impact on the tremelimumab exposure can be regarded of minimal clinical relevance (less than 20%). There was no clinically relevant impact of age, race, renal function, hepatic function, and smoking on the PK of tremelimumab. Hence, there is no need to adjust the dose of tremelimumab based on these intrinsic and extrinsic factors. The flat dosing (75 mg Q3W) and body-weight based (1 mg/kg Q3W) dosing regimens had similar concentration profiles and exposure metrics based on simulations.

Durvalumab PPK model was updated by adding POSEIDON data, and consistent with the previous submitted (BLA761069/Original and BLA761069/S-002) PPK analysis of 2-compartment, linear PK model with time-varying CL. There were no clinically relevant effects of baseline patient characteristics of body weight, age, race, renal function, and hepatic function and other intrinsic/extrinsic factors on PK of durvalumab. Albumin levels, CRCL, ECOG status, LDH, sex, body weight, and combination therapy had a statistically significant impact on CL; sex and body weight were significant covariates on V1. However, their impact on the durvalumab exposure remained minor (less than 20%) in patients treated with durvalumab in the POSEIDON study. Overall, there were no clinically relevant effects of baseline patient characteristics of body weight, age, race, renal function, and hepatic function and other intrinsic/extrinsic factors on PK of durvalumab. (Source: Population PK and Exposure-Response Report, Module 5.3.3.5).

The FDA's Assessment:

FDA agrees with the Applicant's position that based on PPK model assessment dose adjustments for durvalumab or tremelimumab in specific populations are not needed as the PPK analysis showed no clinically relevant effects of baseline patient characteristics of body weight, age, race, renal or hepatic function on PK of durvalumab and tremelimumab.

FDA agrees with Applicant's position that fixed dose regimen and BW-based dose have similar exposures of durvalumab and tremelimumab according to PPK stimulation.

FDA agrees with Applicant's position that ADAs against tremelimumab have no impact on the PK or safety of tremelimumab as the results showed no difference in tremelimumab concentrations and no identifiable trend of infusion related reactions (IRR) between ADA positive patients and ADA negative patients. See Table 16 and Table 17 for additional details.

FDA disagrees with the Applicant's position that ADAs against durvalumab have no impact on the PK of durvalumab as a lower geometric mean durvalumab concentration at week 3 predose was observed in ADA positive patients. See Figure 11 for additional details.

General Dosing and Therapeutic Individualization

General Dosing

Data:

Tremelimumab 1 mg/kg Q4W in combination with durvalumab 20 mg/kg Q4W was selected in the dose finding study (Study 06) in which it was sufficient to achieve the significant elevation in proliferating T cell quantities with acceptable tolerability profile. In this study, tremelimumab 3 or 10 mg/kg exceeded MTDs (SAEs frequently attributed to immunotherapy, pneumonitis, colitis, and other immune mediated events were more commonly seen compared to the 1 mg/kg dose cohorts), thus not recommended for future studies.

A fixed dose of tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W for an average body weight of 75 kg) is 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 the PPK model for tremelimumab. Q3W regimen was selected to conform to the chemotherapy schedule (Q3W), and PK modeling reveals no meaningful differences in drug levels between Q3W and Q4W dosing.

Tremelimumab 75 mg Q3W and durvalumab 1500 mg Q3W in combination with chemo (combination therapy for 4 cycles, with the option of receiving additional 1 cycle or another full 4 cycles) was then evaluated in BR.34 (CCTG Phase 1, NCT02537418) and D419SC00001 (Phase 1b) studies. Dose selection for tremelimumab (combination with durvalumab and chemo) in POSEIDON study was aligned with efficacy and safety results from the above mentioned studies as well as CASPIAN study in SCLC. The dose regimen tested in POSEIDON study was justified and deemed appropriate for 1L treatment of mNSCLC, based on totality of the data on clinical PK, PPK, efficacy, safety, and E-R relationship analyses (see Section 0 data).

Durvalumab dose regimen was justified from the approvals as monotherapy in UC (withdrawed) and Stage III NSCLC at 10 mg/kg Q2W or fixed 1500 mg Q4W; or as combinations with etoposide platinum based chemotherapy for SCLC in many global regions. The approved dosing regimen is in agreement with the dose rationale based on clinical and nonclinical data to demonstrate appropriate clinical benefit:risk profiles in efficacy and safety in these disease populations. Dose selection for durvalumab (combination with tremelimumab and chemo) in POSEIDON study was aligned with efficacy and safety results from the above mentioned studies with Q3W regimen to conform to chemo schedule.

The Applicant's Position:

Based on prior clinical trials in NSCLC including Study 06 and BR.34, the observed clinical activity coupled with a manageable safety profile, as well as the PPK and E-R analysis, support the proposed dose of durvalumab 1500 mg Q3W with tremelimumab 75 mg Q3W in combination with SoC for 4 cycles, with (b) (4) for the first-line treatment of patients (with body weight greater than 30 kg) with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations.

The tremelimumab first dose C_{max} and week 12 C_{trough} levels in POSEIDON study at 75 mg Q3W dose regimen were similar or slightly higher when compared to those at tremelimumab 1 mg/kg Q4W based on observed pooled PK data across supportive studies, or simulations from PPK model. This confirms

that tremelimumab target exposure associated with pharmacodynamic response following tremelimumab 1 mg/kg Q4W was maintained at tremelimumab 75 mg Q3W.

No clinically meaningful exposure-efficacy and exposure-safety relationships were identified for this dose regimen, indicating that no dose optimization for NSCLC is necessary. No dose adjustment is necessary based on body weight (>30 kg) or other intrinsic or extrinsic factors based on covariate analysis in the PPK modelling. No apparent relationship between body weight and efficacy or safety was observed, suggesting that the fixed doing regimen used in the study was appropriate.

It is to be noted that given that the body weight of all of the patients was above 30 kg in the POSEIDON study, the safety profile of the fixed dose regimen in patients with extremely low body weight (less than or equal to 30 kg) is unknown. Therefore, in order to prevent over-exposure in these patients, it is recommended that patients with a body weight of 30 kg or less receive weight-based dosing, equivalent to durvalumab 20 mg/kg Q3W with tremelimumab 1 mg/kg Q3W in combination with SoC Q3W for 4 cycles, with (b) (4) until weight increases to greater than 30 kg.

The FDA's Assessment:

The effectiveness of current regimen of tremelimumab 75 mg and durvalumab 1500 mg Q3W in combination with chemotherapy for 4 cycles followed by (b) (4) is supported by dose finding Study 06 and pivotal study POSEIDON. FDA agrees with Applicant's position on dose recommendation based on efficacy and safety data from these studies. See Section 6.3 for justification on dose selection.

Therapeutic Individualization

Data:
The effect of intrinsic factors (ie, race, age, renal impairment, hepatic impairment, sex, and body weight) on the PK of tremelimumab have been evaluated in the PPK analysis. The final PPK modelling indicated that the baseline patient characteristics of age, race, renal function, and hepatic function had no effect on the PK of tremelimumab. While the PPK analysis identified several covariates that were statistically significant for 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 can thus be regarded of minor clinical relevance.

The previous durvalumab PPK modeling results have been summarized in previous submissions (BLA761069/Original and BLA761069/S-002) for durvalumab registration (as applicable) and are reflected in the current prescribing information. The effect of intrinsic factors (ie, race, age, renal impairment, hepatic impairment, sex, and body weight) on the PK of durvalumab have also been evaluated in an updated PPK model with addition of POSEIDON data. In the final PPK model, ALB, CRCL, ECOG status, LDH, sex, body weight, and combination therapy were identified as statistically significant covariates on CL. Similarly, body weight and sex had a statistically significant impact on V1. When further investigating the impact of the covariates through either a univariate analysis or based on a multivariate approach using individual patient characteristics, none of the covariates had a significant

impact on the durvalumab exposure metrics in patients treated with durvalumab in the POSEIDON study.

The Applicant's Position:
Therapeutic individualization is not recommended for tremelimumab or durvalumab based on these intrinsic and extrinsic factors for patients with body weight over 30 kg. Patients with a body weight of 30 kg or less receive weight-based dosing (see Section 18).
There was no clear exposure safety relationship for either durvalumab or tremelimumab exposure in POSEIDON. Additionally, there was no apparent relationship between body weight and efficacy or safety risk in these patients.

The FDA's Assessment:
FDA agrees with Applicant's position that dose adjustments are not needed for durvalumab or tremelimumab for the intrinsic and extrinsic factors including body weight, age, sex, race, serum albumin level, lactate dehydrogenase level, soluble PD-L1, tumor type, mild to moderate renal impairment, and mild to moderate hepatic impairment, as the PPK analyses showed no clinically relevant effect of these covariates on the PK of both tremelimumab and durvalumab. No clear E-R relationships can be concluded for efficacy, and a flat E-R relationship was observed for safety at the recommended dosing regimen.

Outstanding Issues

Data:
None.

The Applicant's Position:
There are no outstanding issues to report.

The FDA's Assessment:
FDA agrees with the Applicant's position that there are no outstanding issues from the clinical pharmacology perspective.

Comprehensive Clinical Pharmacology Review

General Pharmacology and Pharmacokinetic Characteristics

Data:

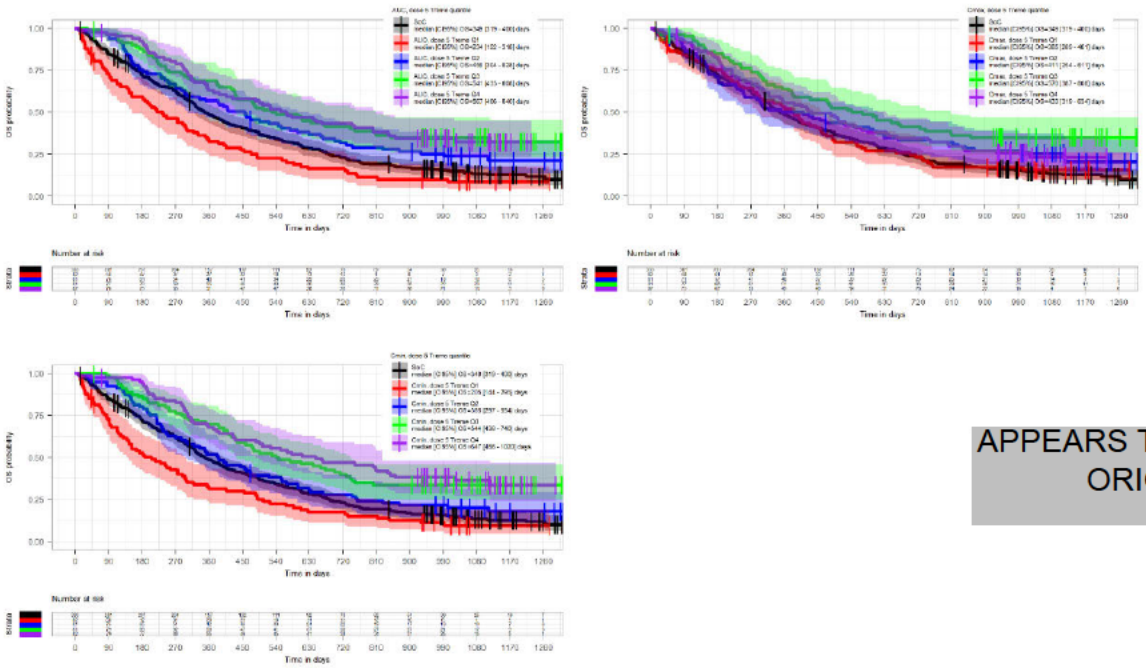
Pharmacology and clinical PK of tremelimumab and durvalumab was summarized in Section 0 and Module 2.7.2 in this BLA submission.

Figure 6 and Figure 7 are representative exposure-efficacy and exposure-safety analyses results in the T + D + SoC arm of POSEIDON respectively, with a case-matching analysis summarized in Table 12. The

immunogenicity data of tremelimumab and durvalumab for POSEIDON study are summarized in Table 13.

In addition, the concentration-QTc analysis were performed on ECG data from 379 patients who received at least one dose of tremelimumab in combination with durvalumab in Study 06.

Figure 6: OS Kaplan-Meier Plots for Tremelimumab Exposure Metrics by Quartiles at Dose 5 (FDA review)



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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; Cmax maximum serum concentration; Cmin 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.
Source: Figure 74, Population PK and Exposure-Response Report, Module 5.3.3.5.

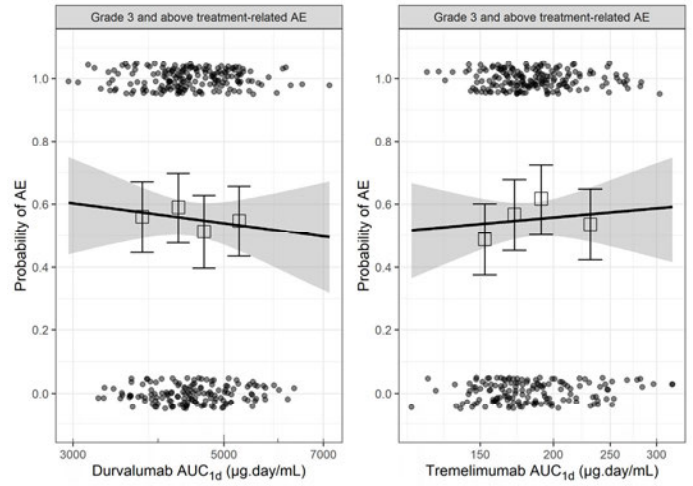
Table 12: Case Matching Analysis: HR for OS and PFS in Patients of Cmin, Dose 5 Treme Q1 Subgroup and SoC Group (FDA review)

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)

Endpoint	Analysis	Median survival (days)		HR (95% CI)
		SoC	$C_{min, Dose\ 5\ Treme}$	
PFS	Matched with disease-related covariates	n = 82 133	n = 82 128	0.99 (0.72-1.36)

CI, confidence interval; Cmin, 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.
Source: Table 30, Population PK and Exposure-Response Report, Module 5.3.3.5

Figure 7: Relationship Between the Probability of Having Grade 3 and Above Treatment-related AEs and AUC after the First Dose of Durvalumab and Tremelimumab (FDA review)



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).
Source: Figure 96, Population PK and Exposure-Response Report, Module 5.3.3.5

Table 13: Summary of ADA Responses to Tremelimumab and Durvalumab (FDA review)

	POSEIDON 75 mg Q3W T + 1500 mg Q3W D + SoC	
ADA category	**ADA to Tremelimumab (N = 330) n (%)**	**ADA to Durvalumab (N = 334) n (%)**
ADA-evaluable patients	278 (84.2)	285 (85.3)
ADA prevalence[a] Median of maximum titer	44 (15.8) 16.0	33 (11.6) 4.0
ADA incidence[b] Median of maximum titer	38 (13.7) 16.0	19 (6.7) 4.0
ADA-positive post-baseline and positive at baseline Median of maximum titer	5 (1.8) 32.0	2 (0.7) 5.0
ADA-positive post-baseline only, or treatment-induced ADA Median of maximum titer	35 (12.6) 16.0	18 (6.3) 4.0
ADA-positive at baseline only Median of maximum titer	4 (1.4) 4.5	13 (4.6) 2.0

	POSEIDON 75 mg Q3W T + 1500 mg Q3W D + SoC	
Treatment-boosted ADA[c] Median of maximum titer	3 (1.1) 256.0	1 (0.4) 8.0
Persistently positive ADA[d] Median of maximum titer	22 (7.9) 16.0	7 (2.5) 2.0
Transiently positive ADA[e] Median of maximum titer	18 (6.5) 12.0	13 (4.6) 8.0
nAb positive at any visit Median of maximum titer	31 (11.2) 16.0	3 (1.1) 4.0

ADA prevalence is the proportion of ADA-evaluable patients who were ADA-positive at any time. ADA incidence is the proportion of ADA-evaluable patients who were treatment-emergent ADA-positive. Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥ 4-fold during the study period. Persistently positive is defined as having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA-positive result at the last available assessment. The category may have included patients meeting these criteria who were ADA-positive at baseline. Transiently positive is defined as having at least one post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive. The category included patients meeting these criteria who were ADA-positive at baseline.

Note: N is the number of patients in the safety analysis set in the treatment group. The denominator for calculation of percentage for all categories is the number of ADA-evaluable patients (defined as the patients in the safety analysis set who had a non-missing baseline ADA and at least one non-missing post-baseline result) in the treatment group. The denominator for ADA-evaluable patients category is N.

Note: If a patient had more than one titer result, the maximum titer result was used whether it was baseline or post baseline. Titer results < 1 were excluded; Source: Table 2.7.4.9.1.2, Module 5.3.5.3

The Applicant's Position:

The following validated methods were used in POSEIDON:

PK concentration measurement: a validated bioanalytical method IC-P-1354 using indirect enzyme-linked immunosorbent assay for tremelimumab, and electrochemiluminescence (ECL) assay methods IC-P-1284, (b) (4) 17-078-230 for durvalumab
Detection of anti-drug ant es (ADA): method ICDIM 153 for tremelimumab and method ICDIM 166 for durvalumab
Detection of neutralizing ADA in human serum: methods ICDIM 189 for tremelimumab and method ICDIM 324 for durvalumab

The effect of tremelimumab on durvalumab quantification in human serum has been examined and no interference was observed. Also the presence of a 10-fold excess of durvalumab did not affect quantitation of tremelimumab. The bioanalytical methods for measuring PK concentrations of tremelimumab and durvalumab were appropriately cross-validated and in compliance with all regulatory requirements in the clinical trials pooled in the PPK analysis.

The durvalumab clinical pharmacology profiles, including PK, PD, and E-R relationships (safety and efficacy) across multiple tumor types have been previously characterized, both as monotherapy and in combination with chemotherapy. The updated PPK analysis on durvalumab are consistent with the previous PPK analyses across tumor types. PK was well characterized using a 2-compartment PPK model with a time-dependent CL. There were no clinically relevant effects of baseline patient characteristics of

body weight, age, race, renal function, and hepatic function and other intrinsic/extrinsic factors on PK of durvalumab, therefore no dose adjustment is needed.

Tremelimumab PK was well characterized using a 2-compartment PPK model with linear and time-dependent elimination (for monotherapy, elimination was linear only). Based on the PPK analysis, there was no clinically relevant impact of age, race, renal function, hepatic function, and smoking on the PK of tremelimumab. Hence, there is no need to adjust the dose of tremelimumab based on these intrinsic and extrinsic factors.

No relationship between durvalumab exposure and OS or PFS (assessed by BICR) was identified in the POSEIDON T + D + SoC arm. The Cmin after tremelimumab dose at Cycle 5 was the most significant exposure matrix that influenced OS and PFS in patients enrolled in the POSEIDON study; however, case-matching analysis suggested that the observed relationship with tremelimumab exposure is possibly confounded by disease related covariates.

Exposure response analysis demonstrated that in addition to tremelimumab exposure, the following covariates also influence OS and PFS: the risk of death was higher with tumor histology type of squamous (both OS and PFS), higher NLR (PFS), lower PD-L1 (<=25%) T cells (PFS) and lower tumor mutational burden (<12) (PFS). None of the durvalumab and tremelimumab exposure metrics in a logistic regression analysis was identified to have any impact on the unconfirmed ORR (assessed by BICR) in the T + D + SoC arm. None of the durvalumab and tremelimumab exposure metrics in a logistic regression analysis was identified to have an influence on safety events defined as Grade 3+ treatment-related AEs, Grade 3+ AESI, AEs leading to durvalumab treatment discontinuation and AEs leading to tremelimumab treatment discontinuation in the T + D + SoC arm.

Based on efficacy, safety, PK, and exposure-response relationships in POSEIDON, 75 mg Q3W IV tremelimumab in combination with 1500 mg Q3W IV durvalumab and SoC for 4 cycles, with (b) (4) to disease progression or unacceptable toxicity is the appropriate dose regimen for the 1L treatment of patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations. No dose adjustment is necessary based on body weight (> 30 kg) or other intrinsic or extrinsic factors based on covariate analysis in the tremelimumab or durvalumab popPK modeling.

In POSEIDON, of 278 tremelimumab ADA-evaluable patients, 44 tested positive for tremelimumab ADA at any visit (tremelimumab ADA prevalence was 15.8%). A total of 38 ADA-evaluable patients tested positive for treatment-emergent ADA (tremelimumab ADA incidence was 13.7%). nAb prevalence was 11.2% (31 of 278 ADA-evaluable patients). These are consistent with across studies results (10.7%, 143 and 8.9%, 119 out of 1137-evaluable patient respectively). The presence of tremelimumab ADA did not impact tremelimumab PK. There was no clear evidence that the presence of tremelimumab ADA had any potential impact on the efficacy or safety in the POSEIDON study. Overall, these results support a low immunogenicity risk of tremelimumab. (Integrated summary of immunogenicity for tremelimumab, Module 5.3.5.3).

Immunogenicity risk of Durvalumab remains low in POSEIDON study as compared to previous studies. Of 286 durvalumab ADA-evaluable patients in POSEIDON 42 tested positive for durvalumab ADA at any visit (durvalumab ADA prevalence was 14.7%). A total of 29 ADA evaluable patients tested positive for treatment-emergent ADA (durvalumab ADA incidence was 10.1%). nAb prevalence was 1.0% (3 of 286 ADA-evaluable patients). Across studies it has been consistently demonstrated that the durvalumab ADA

incidence ranges from 0% to 10.1% and the occurrence of nAb-positive patients was low.

The concentration-QTc modeling results did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF. (see Table 33, Appendix 16.1.13, Study 06 CSR, Module 5.3.5.2.).

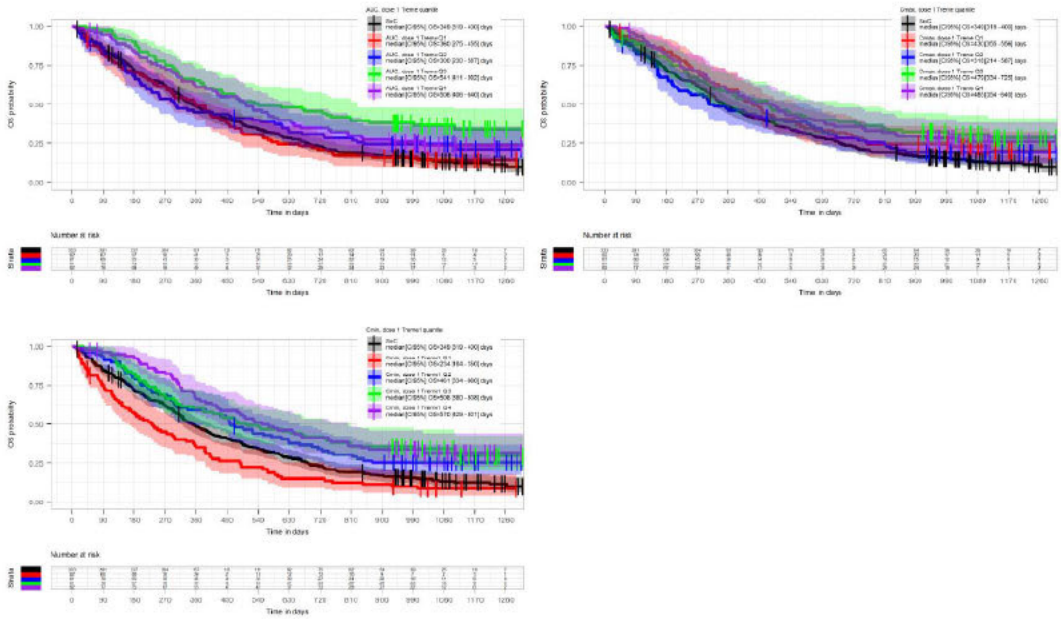
The FDA's Assessment:

FDA agrees with Applicant's position that no relationship between durvalumab exposure and OS or PFS was identified in the T + D + SoC arm.

FDA agrees with Applicant's position that no significant correlation between PK exposures of durvalumab or tremelimumab and safety events was found, including treatment-related AEs, Grade 3+ AESI, and treatment discontinuation. KM plots and CPH model analyses suggested potential correlations between tremelimumab PK exposures and clinical efficacy endpoints (OS and PFS). However, the potential E-R relationship for tremelimumab was confounded by other disease covaraites, e.g. albumin and neutrophil-to-lymphocyte ratio (NLR). Of note, the E-R analysis is limited by only one dose level being studied in POSEIDON.

For efficacy, KM plot suggested increased tremelimumab PK exposures was related to increased OS (Figure 8). In addition, CPH modeling suggested that tremelimumab PK exposures were associated with OS and PFS. However, the tremelimumab PK exposure was found to be correlated with other disease-related covariates, e.g. albumin and NLR (Figure 9), suggesting the potential E-R relationship for tremelimumab was confounded. KM plot also appeared that the patients with low tremelimumab exposures (Quantile 1) had no or worse OS compared to patients receiving SOC only (Figure 6Figure 8). This finding was confirmed with increased HR for OS in patients from quantile 1 of Cmin after first dose of tremelimumab compared to patients in SOC group (Table 14). However, the case-matching analysis showed a comparable HR for OS between the two populations, suggesting the detrimental effect of tremelimumab observed in patients with low PK exposures was confounded (Table 14). As shown in Table 14, within each quartile, no significant HR difference was observed between unmatched vs. matched results, except for OS HR in Q1 subgroup. After case matching, in Q1, the HR of OS reduced from 1.42 (CI 95% 1.10-1.84) to 1.19 (CI 95% 0.86-1.64), suggesting no significant difference in OS between Cmin, dose1 Q1 and SOC. HRs are generally similar across tremelimumab Q2, Q3 and Q4 of Cmin (Table 14).

Figure 8: OS Kaplan-Meier Plots for Tremelimumab Exposure Metrics by Quartiles at Dose 1 (FDA review)



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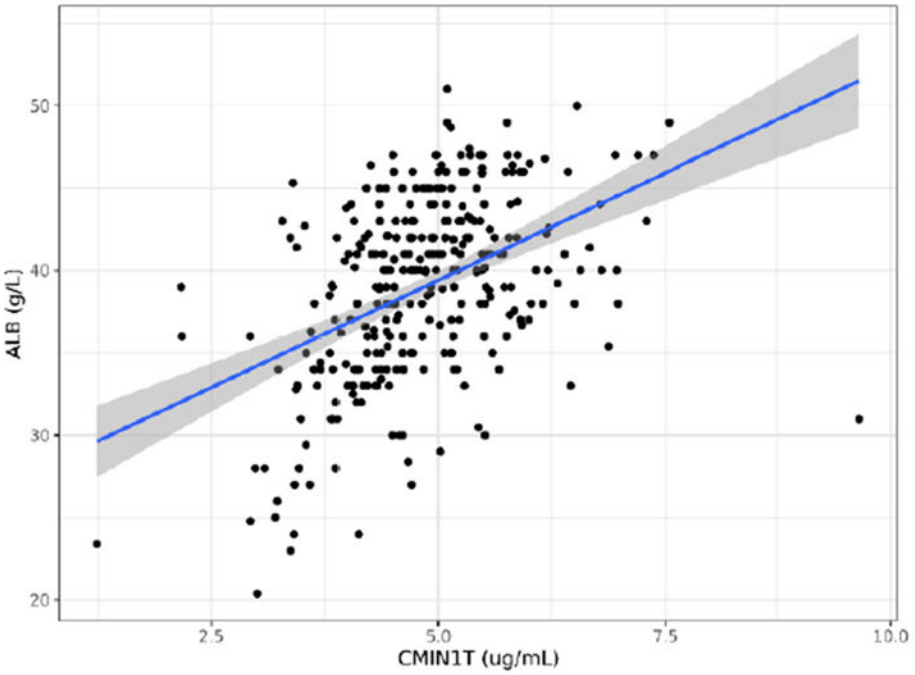
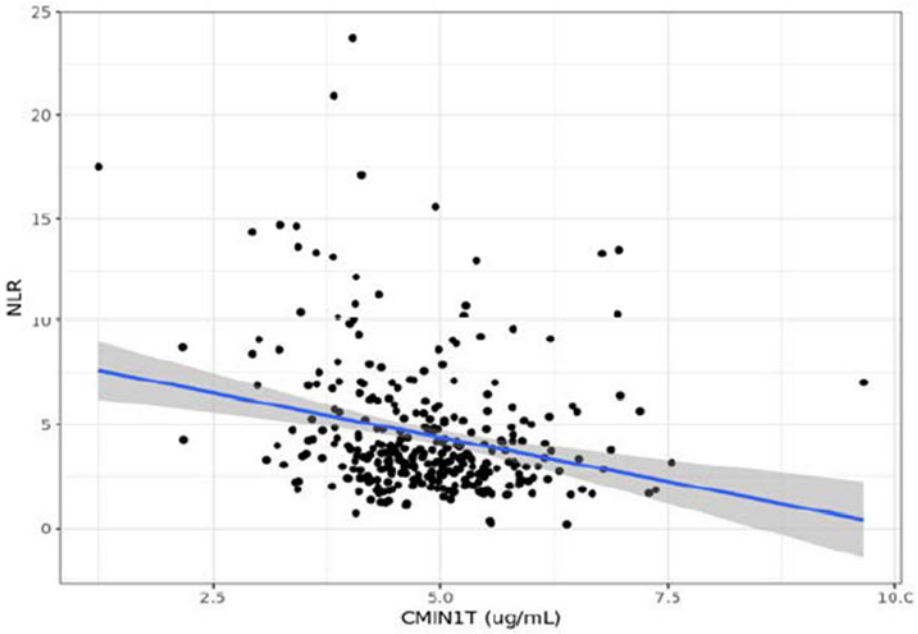
Source: az-durvalumab-os-triplet-v25.Rmd, Reference: f8e6f3:8d65e0
Note: Shaded areas are the 95% confidence interval around the KM curves. Vertical ticks represent the right censoring.
Abbreviations: OS=overall survival, Cmin=minimum serum concentration, Cmax=maximum serum concentration, AUC=area under the serum concentration-time curve, SOC=Standard of Care

Data source: Figure 73, Population PK and Exposure-Response Report, Module 5.3.3.5

Figure 9: Correlation between ALB, NLR vs. Cmin, cycle 1 Tremelimumab (FDA review)





ALB: albumin; NLR: neutrophil-to-lymphocyte ratio, CMIN1T: Cmin, cycle 1 Treme.

Data source: Figure 1, Applicant's response to information request on 17 February 2022.

Table 14: HR for OS in Patients of Cmin, cycle 1 Tremelimumab Q1, Q2, Q3, Q4 Subgroup and SoC Group (FDA review)

	Median overall survival (days)				Median overall survival (days)		
Comparison	Control	Treatment	HR (CI 95%)	Comparison	Control	Treatment	HR (CI 95%)
Q1 vs. SoC	n=333 349	n=82 234	1.42 (1.10-1.84)	Q1 vs. Matched Control	n=82 321	n=82 234	1.19 (0.86-1.64)
Q2 vs. SoC	n=333 349	n=81 461	0.71 (0.54-0.94)	Q2 vs. Matched Control	n=81 315	n=81 461	0.59 (0.42-0.83)
Q3 vs. SoC	n=333 349	n=81 506	0.60 (0.45-0.80)	Q3 vs. Matched Control	n=81 323	n=81 506	0.58 (0.41-0.83)
Q4 vs. SoC	n=333 349	n=82 570	0.56 (0.42-0.75)	Q4 vs. Matched Control	n=82 394	n=82 570	0.66 (0.46-0.95)

HR=hazard ratio; OS=overall survival; Q=quartile; SoC=standard of care; CI= confidence interval
OS DCO: 12 March 2021; a hazard ratio <1 favors Durva + Treme + SoC over SoC alone

Data source: Applicant's response to information request on 17 February 2022.

ADA Evaluation

- FDA agrees with Applicant's position that ADA against tremelimumab has no impact on the PK, or safety of tremelimumab. Table 15 below shows that ADAs have no impact on PPK model predicted $AUC_{0\text{-}INF}$ or CL,ss.

- Figure 10 shows that PK concentrations at week 4 predose of ADA positive patients coincide with the concentrations of ADA negative patients with 90% confidence interval (CI), geometric mean ratio (GMR) of tremelimumab concentrations in ADA positive vs ADA negative patients mostly ranging between 0.75 and 1and closing to 1. The results showed no difference for tremelimumab concentrations in ADA positive patients vs ADA negative patients. For safety , there is also no identifiable trend of IRR occurrence vs ADA incidence (Table 15). Due to the low occurrence of ADAs, no formal analysis has been conducted to assess the impact of ADAs on effectiveness of tremelimumab.

Table 15: CL_{ss} and AUC0-INF derived from tremelimumab PPK models for ADA positive and ADA negative individuals who received a single dose of tremelimumab 300 mg (FDA review)

Parameter Geometric Mean	Number of observations (N)	Mean of Predicted $AUC_{0\text{-}INF}$ (µg/mL*day)	Mean of CLss (L/day)
ADA+ tremelimumab	38	1114	0.20
ADA- tremelimumab	240	1111	0.20

Data Source: FDA analysis

Figure 10: By sample analysis for ratio of tremelimumab concentrations in patients who tested ADA positive vs who tested ADA negative (FDA review)

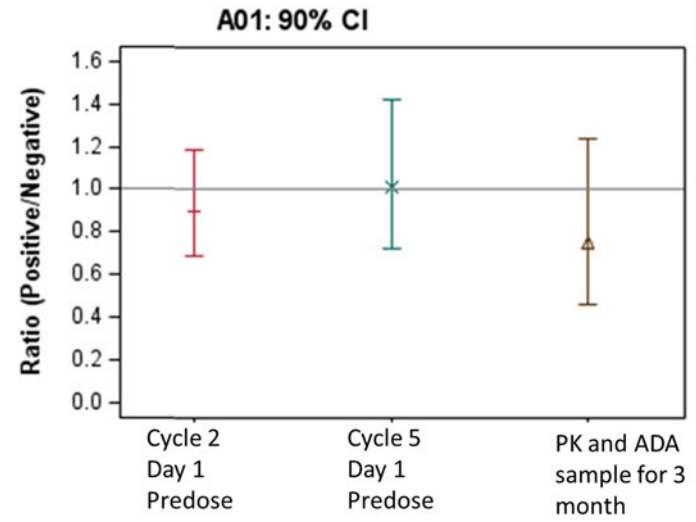


Table 16: Infusion reaction in patients with tremelimumab ADA positive vs ADA negative (FDA review)

Patient # (%)	T + D + SoC	
	ADA + (N=38)	ADA- (N=240)
IRR AEs	1(3.2%)	13 (5.4%)
≥ grade 3 IRR	0	1 (0.5%)

Data Source: BLA Table 14.2.12.3

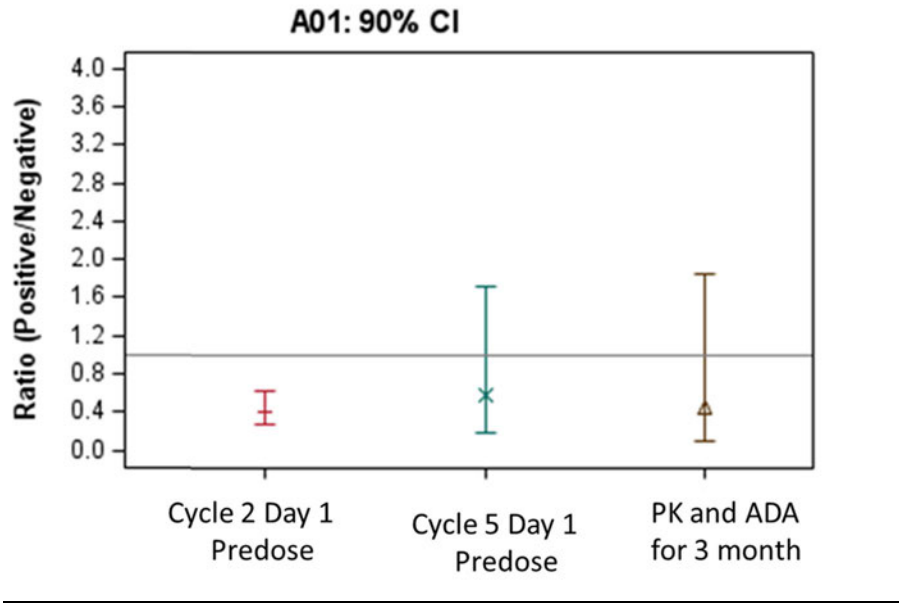
- FDA disagrees with the Applicant's position that ADAs against durvalumab have no impact on the PK of durvalumab. A lower durvalumab concentrations at week 4 predose was observed in patients who developed ADA with 90% CI of GMR of durvalumab median concentration of 0.1 and 0.4 (Figure 11) as compared to ADA negative patients. Due to low ADA incidence of 10% (29/286), the insufficient data prevent the assessment whether observed the ADA-associated exposure decrease reduced effectiveness. There was no infusion reactions of any grade observed in ADA positive patients (Table 17).

Table 17: Infusion reactions in durvalumab's ADA positive vs ADA negative patients (FDA review)

Patient # (%)	T + D + SoC	
	ADA positive (N=29)	ADA negative (N=257)
IRR AEs	0	1 (0.4)

Data Source: BLA table 14.3.9.2

Figure 11: Reduction of durvalumab concentrations on week 4 pre-dose in patients with ADA positive status compared to patients with ADA negative status (FDA review)



Data Source: FDA analysis

Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

See Section 0 on efficacy results and Section 18 on general dosing.

The Applicant's Position:

Yes, the clinical pharmacology program provides evidence that the selected dose and schedule of 75 mg Q3W IV tremelimumab in combination with 1500 mg Q3W IV durvalumab and SoC for 4 cycles, with (b) (4) offers benefit for the 1L treatment of patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations based on statistically significant improvements in OS (hazard ratio [HR] = 0.77 [95% CI: 0.650, 0.916], p=0.00304), PFS (HR = 0.72 [95% CI: 0.600, 0.860], p=0.00031), and ORR (46.3% vs 33.4%, p < 0.001) with Tremelimumab+Durvalumab+SoC relative to SoC chemotherapy in Study POSEIDON.

Tremelimumab PPK analysis showed that several covariates including body weight, ALB, sex, primary indication, and combination therapy (with durvalumab and chemotherapy) had statistically significant effects on tremelimumab CL; however, the magnitude of this difference was not considered to be clinically relevant (< 20% impact on tremelimumab exposure). In addition, from durvalumab PPK analysis, ALB levels, CRCL, ECOG status, LDH, sex, body weight, and combination therapy (with tremelimumab and chemotherapy) had a statistically significant impact on durvalumab CL. Again these covariates' impact on the durvalumab exposure remained minor and not clinically relevant (< 20%).

Exposure-response (efficacy) analyses for 1L NSCLC subjects in POSEIDON study demonstrated that the risk of death was not associated with tremelimumab or durvalumab exposures within the dosing regimen of durvalumab 1500 mg Q3W and tremelimumab 75 mg Q3W in combination with SoC, with (b) (4) (b) (4)

The FDA's Assessment:

FDA agrees with Applicant's position that for safety, no significant correlation was found between PK exposures of either durvalumab or tremelimumab and safety events, including treatment-related AEs, Grade 3+ AESI, and treatment discontinuation. For efficacy, E-R analyses found no significant relationship between durvalumab exposures and efficacy (OS and PFS). There appears a correlation between tremelimumab PK exposure and OS; however, this apparent exposure-response relationship was confounded by other disease-related covariates such as albumin and neutrophil-to-lymphocyte ratio.

FDA agrees with Applicant's position that fixed dose regimen and BW-based dose have similar exposures of durvalumab and tremelimumab. This conclusion is supported by PK stimulation, where similar Cmax and Ctrough were observed following the weight-based and the equivalent fixed dosing regimen of durvalumab and tremelimumab.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

See section 6.2.2.1 general dosing and Section 0 general pharmacology and PK characteristics.

The Applicant's Position:
Yes, the dosing regimen of durvalumab 1500 mg Q3W and tremelimumab 75 mg Q3W in combination with SoC, (b) (4) is appropriate as 1L treatment of patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations, the indication being sought in this submission. This combination dose regimen was selected based on the observed safety and efficacy data from study D4190C00006 (dose finding study 06), D419SC00001 and BR.34 studies (dose regimen selection in chemo combination), and CASPIAN study (see Section 18). Additionally, this dosing regimen was further supported by the clinical efficacy and safety data from metastatic NSCLC subjects in POSEIDON (1L Phase 3 study), and PPK and E-R analyses that included data from POSEIDON (see Section 18).

The FDA's Assessment:
FDA agrees with Applicant's position that the dosing regimen of T + D + SoC was supported by data from dose finding Study 06 .

Regarding tremelimumab dose selection

- In Study 06, tremelimumab was studied in patients with metastatic NSCLC at doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg once every 4 weeks (Q4W). A dose level 1mg/kg or tremelimumab 75 mg in combination with durvalumab Q4W (T75+D) was selected given that the tremelimumab 3 mg/kg Q4W dosing regimen exceeded the MTD.

- FDA agrees with Applicant's position on durvalumab dose selection based on the following:
    - Study 06 showed that a complete sPD-L1 suppression was maintained in all patients who received durvalumab 20 mg/kg Q4W.
    - Cmax and Ctrough values of durvalumab following dosing with 20 mg/kg Q4W and fixed 1500 mg dose Q3W were similar in the PK stimulation.
    - Current dose selection of durvalumab in combination with tremelimumab is in agreement with the previous approved dosage of durvalumab monotherapy in Stage III NSCLC, which is a weight-based dosing of 10 mg/kg Q2W or a fixed regimen 1500 mg Q4W.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:
See section 0 PPK analysis for tremelimimab and durvalumab.

The Applicant's Position:
No dose adjustment is necessary based on body weight (> 30 kg) or other intrinsic or extrinsic factors based on covariate analysis in the tremelimumab or durvalumab PPK modeling.

The FDA's Assessment:
The Applicant's statement above should be corrected to state that "no dose adjustment is necessary based on body weight (**≥ 30 kg**) or other intrinsic or extrinsic factors based on covariate analysis in the

tremelimumab or durvalumab PPK modeling," as the flat dose regimen applies to patients whose weight is equal to 30 kg.

FDA agrees with Applicant's proposed body weight (BW) based dose regimen for patients < 30 kg to receive equivalent of tremelimumab 1 mg/kg and durvalumab 20 mg/kg Q4W in combination with platinum chemotherapy based on the following rationales:

- No patients <30 kg included in study 06 and POSEIDON. The safety profile of the fixed dose regimen in patients with extremely low body weight (less than 30 kg) is unknown. Body weight-based dosing is an acceptable approach to prevent over-exposure in these patients.
- The approved durvalumab dosing regimen has a body weight cutoff at 30 kg as BW-based dosing for BW< 30 kg and flat dosing for BW≥ 30 kg.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
No food-drug or drug-drug interaction studies have been conducted for tremelimumab or durvalumab. They are both administered through IV infusion, and as immunoglobulins eliminated by intracellular lysosomal proteolytic degradation, thus not anticipated to be affected by food or small molecule drugs via CYP450 inhibition/induction or transporter modulation.

The Applicant's Position:
There are no clinically relevant food-drug or drug-drug interactions with durvalumab in combination with tremelimumab and chemo in patients with metastatic NSCLC.

The FDA's Assessment:
FDA agrees with Applicant's position.

X X

Primary Reviewer	Team Leader
Yue, Xiang	Hong, Zhao
Ye, Yuan	Liang, Li

Sources of Clinical Data

Table of Clinical Studies

Data:

An overview of the clinical studies supporting the efficacy and safety of tremelimumab is presented below in Table 20.

The clinical efficacy data discussed in the application package are listed in Table 18.

Table 18 Clinical efficacy data

Pivotal	Supportive
Evidence supporting the efficacy claims in the proposed indication is based on the final analysis of the **POSEIDON** study.	Two studies from the Applicant's clinical program – MYSTIC and NEPTUNE – were conducted in a patient population that was relevant to POSEIDON.
Pivotal efficacy dataset: 338 patients randomized to the T + D + SoC arm compared with 337 patients randomized to the SoC alone arm.	**Summary of efficacy:** 372 patients randomized to the T + D arm in the MYSTIC study (vs. 372 patients randomized to SoC), and 410 patients randomized to T + D arm in the NEPTUNE study (vs. 413 patients randomized to SoC).

The clinical safety data discussed in the application package are listed in Table 19.

Table 19 Clinical safety data

Pivotal	Supportive
Evidence supporting the safety claims in the proposed indication is based on the final analysis of the **POSEIDON** study.	**Tremelimumab + Durvalumab + Chemotherapy Pool (T + D + Chemo Pool):** The T + D + SoC safety data from the POSEIDON study was pooled with the T + D + SoC safety data from the CASPIAN study (N=596 patients; Table 20). At the time of this application, these are the 2 completed studies in the Applicant's clinical program that evaluated immunotherapies in combination with chemotherapy.
Pivotal safety dataset: 330 patients in the T + D + SoC arm who received at least 1 dose of the study treatment compared with 333 patients in the SoC arm who received at least 1 dose of the study treatment.	**Tremelimumab + Durvalumab Pan-Tumor Pool (T + D Pan-Tumor Pool):** The supportive T + D Pan-Tumor Pool comprises safety and tolerability data from 9 studies in the clinical program (N=2280 patients; Table 20). These studies evaluated the safety of tremelimumab + durvalumab across various tumor types and stages of disease and provide a robust reference of the overall tremelimumab + durvalumab safety and tolerability profile.

Table 20 Listing of Clinical Trials Relevant to the BLA for tremelimumab

Study name Status[a] DCO/ NCT no.	Phase Design	Patient population	Key outcome measures	No. of patients randomized
Pivotal Phase III study				
POSEIDON NCT03164616 Complete (24 Jul 2019[b]; 12 Mar 2021[c])	Phase III Randomized, open-label, comparative, multicenter	Patients with metastatic NSCLC who have not received prior 1L treatment, and who do not have *EGFR* or *ALK* target mutations	OS, PFS, ORR Safety: AEs, laboratory evaluations, physical examinations, and vital signs	T + D + SoC: 338 D + SoC: 338 SoC: 337
Supportive Phase I-II studies				
Study 1108 NCT01693562 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 NCT01938612 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 NCT02000947 Complete 19 Nov 2019	Phase I open-label, dose-escalation, dose-expansion	Patients with advanced NSCLC	MTD, OR (Dose expansion) Safety: AEs, laboratory evaluations, physical examinations, vital signs	Escalation – T + D: 102 Expansion – T + D: 355
Study 10 NCT02261220 Complete 11 Apr 2018	Phase I open-label, multicenter	Patients with advanced solid tumors	OR (PD-L1 negative UC) Safety: AEs, laboratory evaluations, physical examinations, vital signs	Exploration and Expansion – T + D: 379
ATLANTIC NCT02087423 Complete 03 Jun 2016	Phase II Non-comparative, open-label, multicenter	Patients with locally advanced or metastatic NSCLC (Stage IIIB – IV) who have received at least 2 prior systemic treatment regimens	ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	D: 444

Study name Status[a] DCO/ NCT no.	Phase Design	Patient population	Key outcome measures	No. of patients randomized
CONDOR NCT02319044 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 NCT01843374 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 NCT02527434 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 NCT02519348 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 NCT02352948 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 NCT02125461 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

Study name Status[a] DCO/ NCT no.	Phase Design	Patient population	Key outcome measures	No. of patients randomized
MYSTIC NCT02453282 Complete 01 Jun 2017[b] 04 Oct 2018[c]	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 NCT03043872 Complete 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 NCT02542293 Complete 24 June 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 NCT02369874 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

[a] Status pertains to the status of the clinical study report (CSR). Follow-up data may be collected for individual studies; [b] Interim; [c] Final.
BICR Blinded Independent Central Review; D Durvalumab; FTIH First Time in Human; EP Etoposide and platinum (cisplatin or carboplatin); HNSCC Head and neck squamous cell carcinoma; MTD Maximum tolerated dose; NSCLC Non-small cell lung cancer; OBD Optimal biological dose; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; SoC Standard-of-care; T Tremelimumab; UC Urothelial carcinoma.

The Applicant's Position:

The primary evidence supporting the efficacy and safety claims in the proposed indication is based on the final analysis of the POSEIDON study.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding POSEIDON providing the primary evidence supporting the efficacy and safety of T + D + SoC for the proposed indication.

FDA requested that the Applicant pool safety data from patients with ES-SCLC who received a similar regimen (T + D + platinum-based chemotherapy) on the CASPIAN study (n=266; pooled safety population n=596) to support the Warnings and Precautions section of product labeling. Patients on the tremelimumab-containing arm on the CASPIAN study received platinum-based chemotherapy consisting of investigator's choice of carboplatin area under the curve (AUC) 5-6 mg/mL/min or cisplatin 75-80 mg/m^2 once every 3 weeks (Q3W) and etoposide 80-100 mg/m^2 on days 1-3 of each 3-week cycle for up to 6 cycles, durvalumab 1500 mg Q3W for 4 cycles followed by durvalumab 1500 mg Q4W, and tremelimumab 75 mg Q3W for 4 cycles followed by up to one additional dose. Although this regimen is not an FDA-approved regimen for the treatment of patients with ES-SCLC, it is the most similar regimen to tremelimumab-containing study therapy in POSEIDON given that in the remainder of the supportive studies described by the Applicant in Table 20, durvalumab and tremelimumab are administered without platinum-based chemotherapy.

Statistical and Clinical Evaluation

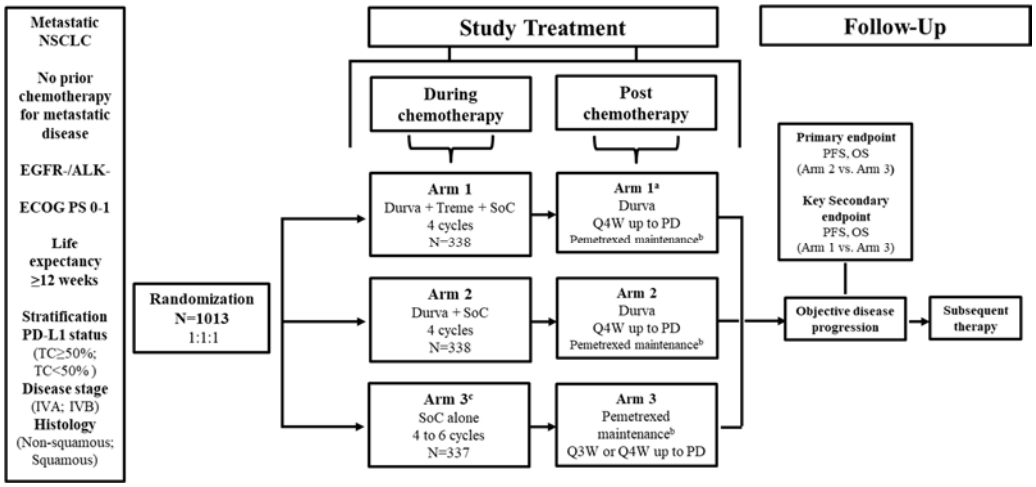
Review of Relevant Individual Trials Used to Support Efficacy

Pivotal POSEIDON study [D419MC00004]

Trial Design

The Applicant's Description:
The POSEIDON study design is illustrated in Figure 12.

Figure 12 Study design – POSEIDON



a One additional cycle of durvalumab + tremelimumab combination therapy was given at Week 16 (ie, in the post chemotherapy phase). Patients who completed 5 cycles of the durvalumab + tremelimumab combination, but subsequently have clinical progression or radiological progressive disease during the durvalumab monotherapy part of the combination regimen, could start retreatment with durvalumab + tremelimumab.

b Pemetrexed maintenance therapy from Week 12 to clinical progression or radiological progression for non squamous NSCLC patients who initially received treatment with pemetrexed and carboplatin/cisplatin, unless contraindicated per the Investigator.

c SoC chemotherapy was given Q3W for 4 cycles; additional 2 cycles could be given (ie, total 6 cycles) as clinically indicated and per Investigator's discretion. SoC chemotherapies were histology-based and included a combination of abraxane and carboplatin (non-squamous and squamous), pemetrexed and carboplatin (non squamous), and gemcitabine and cisplatin (squamous).

Study design and treatments:

POSEIDON (NCT03164616; EudraCT Number 2017-000920-81) was a Phase III, randomized, open label, comparative, multicenter, global study in patients with metastatic NSCLC. It was designed to compare the efficacy and safety of durvalumab in combination with standard of care chemotherapy ("D + SoC") with that of chemotherapy alone ("SoC") as 1L treatment in metastatic NSCLC.

Additionally, as a key secondary objective, the study also compared the efficacy and safety of tremelimumab in combination with durvalumab and standard of care chemotherapy ("T + D + SoC") with that of chemotherapy alone ("SoC") in the same patient population.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study design.

Patient population:

Adult patients (aged ≥18 years) with 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 2016). Patients had to have tumors that lacked activating EGFR mutations and ALK fusions. Patients with suspected brain metastases required IV contrast enhanced magnetic resonance imaging /computed tomography of the brain prior to study entry and were eligible provided they were stable 4 weeks after the imaging, had returned neurologically to baseline, and were off steroids at least

5 days prior to randomization.

The FDA's Assessment:

Stratification, randomization, treatments, and duration: Stratification factors for randomization were PD-L1 tumor expression status (TC≥50% vs. TC<50%), disease stage (Stage IVA vs. Stage IVB), and histology (non-squamous vs. squamous). Patients were randomized 1:1:1 to one of the following treatment arms:

- **Arm 1:** During chemotherapy, patients received tremelimumab 75 mg IV Q3W, durvalumab 1500 mg IV Q3W, and platinum-based chemotherapy Q3W for 4 cycles. A fifth dose of tremelimumab 75 mg was given at Week 16 in combination with durvalumab dose 6. After completion of 4 cycles of chemotherapy, durvalumab 1500 mg IV Q4W was given with or without pemetrexed according to the patient's tumor histology until unacceptable toxicity or disease progression. For patients with progressive disease during the durvalumab single agent portion of treatment, retreatment with durvalumab and tremelimumab could be administered if the patient would have potential clinical benefit from resuming combination therapy in the opinion of the investigator.
- **Arm 2:** During chemotherapy, durvalumab 1500 mg IV Q3W and chemotherapy Q3W were administered for 4 cycles. After completion of 4 cycles of chemotherapy, durvalumab 1500 mg IV Q4W was given with or without pemetrexed according to the patient's tumor histology until unacceptable toxicity or disease progression.
- **Arm 3:** Platinum-based chemotherapy was administered Q3W for 4 cycles. Patients could receive an additional 2 cycles (a total of 6 cycles post-randomization) as clinically indicated at the investigator's discretion. Patients with non-squamous NSCLC continued pemetrexed therapy from week 12 until disease progression or intolerable toxicity.

Treatment through progression and retreatment was permitted under specific conditions for the T + D + SoC chemotherapy and D + SoC chemotherapy arms, but not for patients in the SoC chemotherapy arm.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoints were overall survival (OS) and progression free survival (PFS; BICR, RECIST 1.1) compared between the D + SoC vs. SoC alone groups (Arm 2 vs. Arm 3; Figure 12). The study design included dual primary endpoints, such that for the study to be declared positive a statistically significant benefit in either PFS or OS for the D + SoC vs. SoC comparison needed to be demonstrated. Key secondary efficacy endpoints were OS and PFS (BICR, RECIST 1.1) compared between the T + D + SoC vs. SoC alone groups (Arm 1 vs. Arm 3; Figure 12).

Other secondary efficacy endpoints were objective response rate (ORR; BICR, RECIST 1.1), OS/PFS/ORR by PD L1 expression status and blood tumor mutational burden (bTMB), and patient reported outcomes

(PROs). Further secondary endpoints include Duration of Response (DoR), Best Objective Response (BoR), PFS landmarks, and second progression free survival (PFS2).

The safety and tolerability of the 3 treatment arms were assessed based on adverse events (AEs; CTCAE Version 4.03) and clinical laboratory findings reported while on treatment period and up to 90 days following the last dose of the treatment.

The FDA's Assessment:
In general, FDA agrees with the Applicant's description of the primary endpoints of PFS and OS comparing D + SoC and SoC and key secondary endpoints of PFS and OS comparing T + D + SoC and SoC. The comparison of OS for patients in the T + D + SoC arm vs. the SoC arm in the tumor mutation burden (TMB) high subpopulations were other secondary endpoints that were planned to be tested formally if the primary comparisons of PFS and OS between the D + SoC and SoC arms and the T + D + SoC and SoC arms were statistically significant. FDA considers efficacy results for endpoints that were not included as part of a formal testing plan to be descriptive only.

FDA agrees with the Applicant's description of safety and tolerability assessments.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The study was sized for the dual primary endpoints evaluating the OS and PFS benefits between D + SoC vs. SoC alone in the Intent to treat (ITT) Population. For the study to be positive, a statistically significant benefit for either PFS or OS needed.

The key secondary objective was to assess the efficacy of T + D + SoC compared with SoC alone in terms of PFS and OS. Sample size and power calculations for the dual primary and the key secondary endpoints of OS and PFS in the T + D + SoC vs SoC alone groups are presented in the study Statistical Analysis Plan.

Interim analyses: One interim analysis of PFS was planned when approximately 80% of the target PFS events (approximately 497) had occurred across the combined D + SoC and SoC alone arms (397 out of 497 events). The final analysis of PFS was conducted after 511 PFS events were reported across the combined D + SoC and SoC alone groups (75.7% maturity).

Three interim analyses of OS were performed, the first at the time of the interim PFS analysis (approximately 45% of the target OS events [approximately 532] in the combined D + SoC and SoC alone arms; 243 out of 532 events), the second at the time of the primary PFS analysis (approximately 61% of the target OS events in the D + SoC and SoC alone arms; 328 out of 532 events) and the third when approximately 84% of the target OS events have occurred in the D + SoC and SoC alone arms (328 out of 532 events). The final analysis of OS was conducted after 549 OS events were reported across the combined D + SoC and SoC alone groups (81.3% maturity).

The Lan DeMets spending function that approximates an O'Brien Fleming approach was used to account for multiplicity introduced by including interim analyses for superiority (Lan and DeMets 1983). The

boundaries for the treatment comparison were derived based upon the exact number of events at the time of analyses

The study used an external IDMC assess ongoing safety analyses as well as the interim efficacy analysis. Following each meeting, the IDMC report to the Sponsor and are able to recommend changes in the conduct of the study.

Multiple testing procedure (MTP)

Hypotheses were tested using MTP with an alpha exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses were tested in a pre defined order. According to alpha (test mass) splitting and alpha recycling, if the higher level hypothesis in the MTP was to be rejected for superiority, the next lower level hypothesis was then tested. The test mass that became available after each rejected hypothesis was recycled to lower-level hypotheses not yet rejected. This testing procedure stopped when the entire test mass was allocated to non rejected hypotheses. Implementation of this pre defined ordered testing procedure, including recycling, strongly controlled Type I error at 5% (2 sided), among all the dual primary endpoints and the key secondary endpoints included in MTP. For additional details, see SAP, Appendix 16.1.9, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the statistical analysis plan, including the sample size justifications for the primary and key secondary endpoints. The final OS analysis was planned after 532 OS events and was performed after 549 OS events. Additionally, the third interim analysis of OS was planned after 449 OS events, not 328 OS events as described above by the Applicant.

Protocol Amendments

The Applicant's Description:

Important amendments to the original study protocol, including those amendments that came into effect with respect to the recruitment of patients, and other significant changes to study conduct are summarised in Table 21. None of the modifications to the protocol had any impact on the integrity of the trial or interpretations of the results.

Table 21 Protocol amendments and other significant changes to study conduct

Amendment number/ date	Key details of 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	Modify inclusion and exclusion criteria; update schedule of assessment for pemetrexed; PD-L1 TC<25% analysis set was removed from the objectives and relevant sections of the CSP.
Amendment 2 Protocol version 3.0 16 March 2018	Increase sample size from 800 to 1000 subjects and update OS final analysis maturity; update collection of patient samples for stratification by PD L1; additions to SoC, overall risks and risks sections based on the MHRA recommendations.

Amendment number/ date	Key details of amendment
Amendment 3 Protocol version 4.0 25 September 2018	Updated primary and key secondary objectives and endpoints; reinstated the PD-L1 TC<25% analysis set; Secondary objectives added to assess the association of TMB with the efficacy of D + SoC compared with SoC y alone, T + D + SoC compared with SoC alone, and D + SoC compared with T + D + SoC; MTP was updated. One additional OS interim analysis was added at the timepoint of PFS interim analysis.
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; Updated language based on the revised CSP template Appendix Hy's Law v3

Data is derived from the source table; for further details refer to the source below
Source: Section 9.9.1, POSEIDON CSR, Module 5.3.5.1

Changes to planned analyses
All major changes to the planned analyses were made prior to the date of database lock for the PFS interim analysis (15 March 2019) and reflect changes made in protocol amendments.

The following changes of analysis from the protocol were based on CSP version 5.0, dated 20 April 2020.

- The SAP was revised to indicate that the following exploratory objective may not be produced, after an AstraZeneca imaging expert indicated that AstraZeneca did not 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 (DoR) was not a required analysis, so was not included for DoR endpoints in the SAP. This was consistent with other durvalumab studies.
  - The analysis of comparison of APF12 between treatment arms was removed to be consistent with other durvalumab studies.

Additional changes not included in SAP version 5.0 inlcuded:

- 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 analyzed using logistic regression, using Proc Logistic instead of Proc Genmod

The FDA's Assessment:

FDA agrees with the Applicant's descriptions of the protocol amendments.

Study Results

Compliance with Good Clinical Practices

Data:
Not applicable.
The Applicant's Position:
The Sponsor's procedures, internal quality control measures and audit program provide reassurance that the tremelimumab clinical development program is being conducted in accordance with good clinical practice (GCP), as documented by the International Conference on Harmonisation (ICH).

The FDA's Assessment:
FDA agrees with the Applicant's position.

Financial Disclosure

Data:
Financial disclosures for the POSEIDON are addressed in Section 0 of this assessment aid.

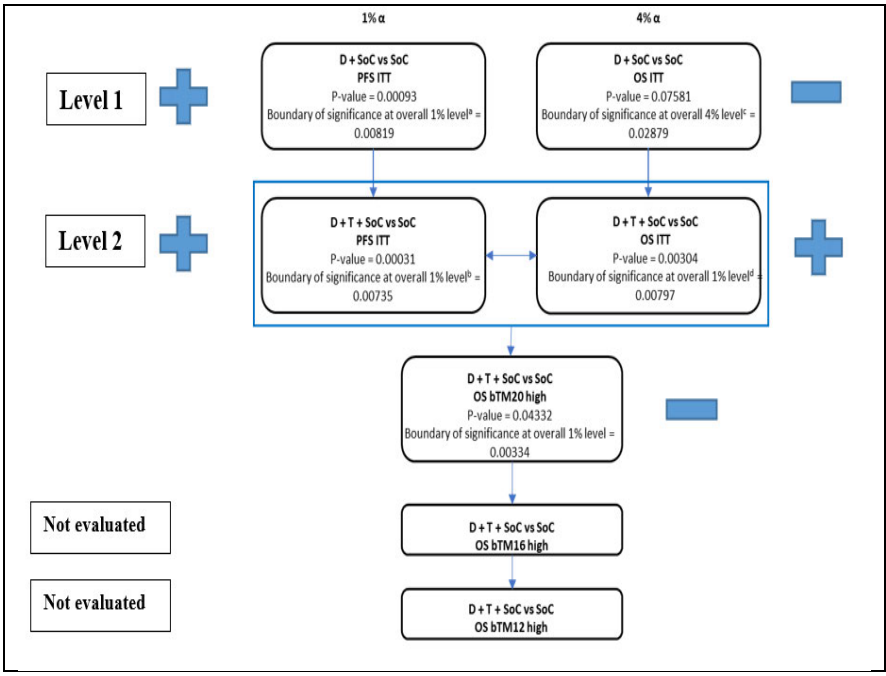
The Applicant's Position:
The integrity of POSEIDON data was not affected by the financial interest of the investigators.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Outcome of the MTP

The outcomes of the MTP are summarised in Figure 13.

Figure 13 Outcomes of the Multiple testing procedure (MTP)



[a,b,c,d] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.
bTMB20 Blood tumor mutational burden≥20 mut/Mb; bTMB16 Blood tumor mutational burden≥16 mut/Mb; bTMB12 Blood tumor mutational burden≥12 mut/Mb;
CTx Chemotherapy; D durvalumab;
IA2 Interim analysis 2; ITT Intent-to-treat; OS Overall survival;
PFS Progression-free survival;
SoC Standard-of-care chemotherapy;
T Tremelimumab.

In the MTP, the overall 5% Type 1 error (2 sided) was first split between the dual primary endpoints of PFS and OS for the D + SoC vs. SoC comparison: an alpha of 1% was allocated to the primary PFS analysis and an alpha of 4% was allocated to the primary OS analysis (Arm 2 vs. Arm 3; Figure 12).

- The final analyses of PFS (DCO: 24 July 2019) were conducted after 511 PFS events were reported across the combined D + SoC and SoC alone groups (75.7% maturity). The PFS HR favored the D + SoC treatment and was statistically significant at the 1% alpha level (Level 1; Figure 13). Therefore, per MTP, the 1% alpha was recycled to test PFS for the T + D + SoC vs. SoC alone comparison (key secondary endpoint). The PFS HR favored the T + D + SoC treatment and was statistically significantly at the 1% alpha level (Level 2; Figure 13).
- The final analyses of OS (DCO: 12 March 2021) were conducted after 549 OS events were reported across the combined D + SoC and SoC alone groups (81.3% maturity). While the OS HR numerically favored the D + SoC treatment, it did not cross the prespecified statistical threshold at the 4% alpha level (Level 1; Figure 13).
- Therefore, per the MTP, the 1% alpha level from the PFS for T + D + SoC vs. SoC was recycled to test OS for the T + D + SoC vs SoC comparison. The OS HR favored the T + D + SoC treatment and was statistically significant at the 1% alpha level (Level 2; Figure 13).
- Finally, the OS in the bTMB20 Population for the T + D + SoC vs. SoC comparison was tested at the 1% alpha recycled from Level 2 of the MTP. The OS HR favored the T + D + SoC treatment compared with SoC alone; however, it did not cross the prespecified threshold of statistical significance. Therefore, the bTMB16 and bTMB12 populations were not formally tested for significance (Figure 13).

The FDA's Assessment:

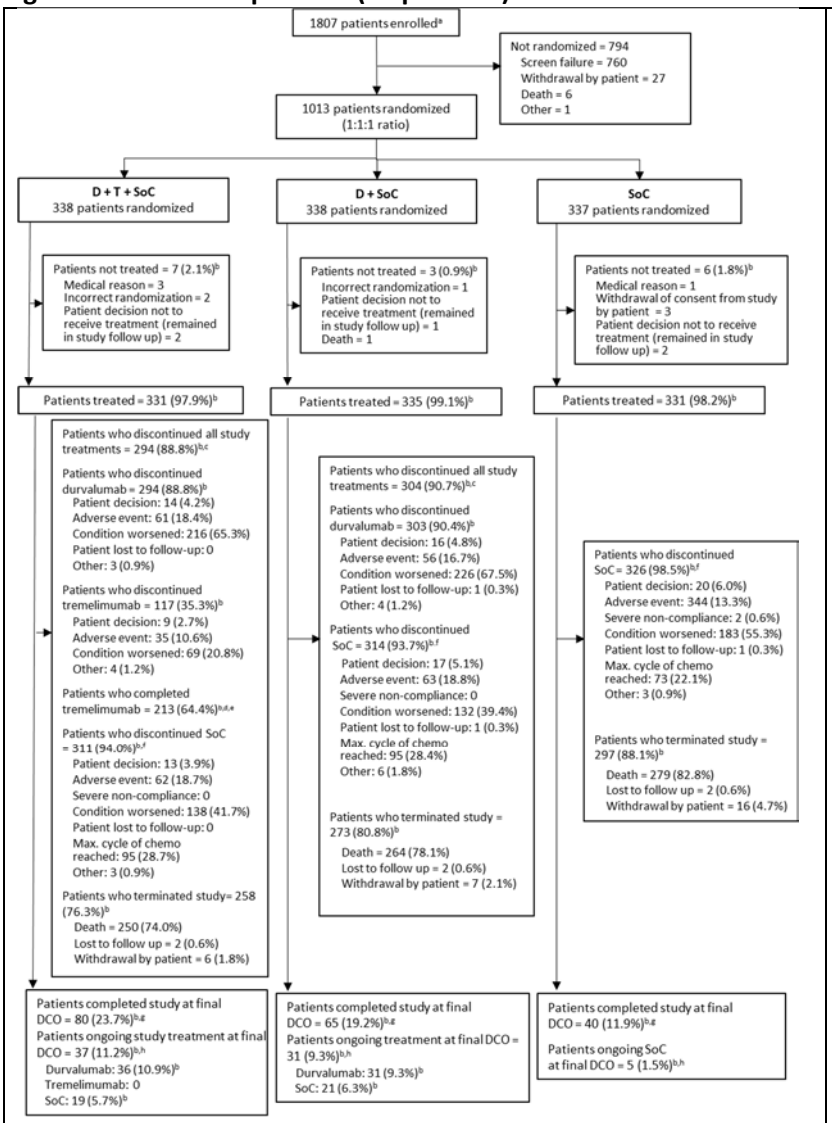
In general, FDA agrees with the Applicant's presentation of the multiple testing plan for formal testing of multiple endpoints and interim analyses. The interim analysis of the primary endpoint of BICR-assessed PFS was planned at 80% information fraction (397 PFS events) and was performed at approximately 87% observed information fraction (433 PFS events). Three interim analyses of the primary endpoint of OS were planned at 45% (243 OS events), 61% (328 OS events), and 84% (449 OS events) information fractions and were performed at approximately 52% (278 OS events), 75% (397 OS events), and 91% (483 OS events) observed information fractions (based on planned number of OS events of 532 at the time of final analysis), respectively. The information regarding the observed information fractions for each interim analysis was submitted to the FDA by the Applicant.

Patient Disposition

Data:

A total of 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 centers across 18 countries in North and Latin America, Europe, Asia Pacific, and Africa. The disposition of patients in the global cohort is summarized in Figure 14.

Figure 14 Patient disposition (all patients)



[g] Informed consent received.
[h] Percentages were calculated from number of patients in the FAS.
[i] A patient was considered as having discontinued treatment when the patient had discontinued all study treatments. Treatment included D, T, SoC and T retreatment where applicable.
[j] Percentages were calculated from number of patients who received treatment.
[k] Patients who completed T had 'maximum cycle of immunotherapy reached' reported for T on the eCRF. Patients who completed SoC had 'maximum cycle of chemotherapy reached' reported for any SoC molecule on the eCRF.
[l] A patient was considered as having discontinued SoC when all agents were discontinued. If different reasons for discontinuation were collected for each agent, the last discontinuation reason by date was selected. Patients who received a pemetrexed doublet, and who after the maximum 4 cycles of platinum-based doublet chemotherapy went onto maintenance pemetrexed, then the reason for discontinuation of SoC in the disposition table was the discontinuation reason for the last agent in the regimen (ie the pemetrexed in the maintenance phase after the 4 maximum cycles of platinum-based doublet were completed in the combination phase).
[m] Patients who completed study includes patients who were alive and remained in the study at final DCO. One patient received D and T but no SoC. One patient randomized to T + D + SoC treatment arm received SoC but no D and T and one patient randomized to D +SoC treatment arm received SoC but no D.
[n] A patient was considered to be ongoing treatment when receiving at least one study treatment at the DCO. Treatment includes D, T, SoC, and T retreatment where applicable.

One patient randomized to the T + D + SoC treatment arm received T + D but did not receive SoC. One patient randomized to the T + D + SoC treatment arm received SoC but did not receive T + D, and 1 patient randomized to the D + SoC treatment arm received SoC but did not receive D.; Data cut-off date: 12MAR2021; Source: Table 14.1.1, POSEIDON CSR, Module 5.3.5.1

The Applicant's Position:

The FAS included all randomized patients and followed the principles of intent-to-treat (patients were included based on randomized study treatment).

The FDA's Assessment:
FDA agrees with the Applicant's position.

Protocol Violations/Deviations

Data:

Table 22 Important protocol deviations in the POSEIDON study (full analysis set)

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

Data is derived from the source table; for further details refer to the source below.
Source: Table 14.1.2, POSEIDON CSR, Module 5.3.5.1.

The Applicant's Position:

The overall incidence of important protocol deviations was low (<3%) and their nature did not suggest an impact on the overall conduct of the study or the interpretation of its results, or with respect to the safety profile observed within the patient population described.

The FDA's Assessment:

FDA agrees with the Applicant's description of important protocol deviations and with the Applicant's position that the reported protocol deviations to not impact the interpretability of study results.

Demographic characteristics

Data:

The demographic and key baseline disease characteristics of all patients in the full analysis set are reported in Table 23.

At study entry the median age was 64 years of age (range: 27 to 87 years), with 47.1% of patients aged 65 years and above. The majority of patients were Male (76.0%) and 24.0% were Female; a lower percentage of patients were Female in the T + D + SoC arm (20.4%) compared with the D + SoC arm (25.1%) and SoC alone arm (26.4%).

Approximately half of the patients were White (55.9%), and 34.6% were Asian; a lower percentage of patients were Asian in the T + D + SoC arm (29.3%) compared with the D + SoC arm (36.4%) and SoC alone arm (38.0%).

The majority of patients were former (56.9%) or current smokers (21.1%), and 21.9% were never smokers; a lower percentage of patients were never smokers in the T + D + SoC arm (17.5%) compared with the D + SoC arm (24.9%) and SoC alone arm (23.4%).

Table 23 Key demographic and baseline characteristics of the POSEIDON study (Full Analysis Set)

	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)
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)
Smoking status n (%)				

	Number (%) of patients			
	T+D+SoC (N=338)	**D+SoC (N=338)**	**SoC (N=337)**	**Total (N=1013)**
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)
ECOG performance status[b]				
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)
Non-Squamous	214 (63.3)	209 (61.8)	214 (63.5)	637 (62.9)
Other	0	1 (0.3)	0	1 (0.1)
Missing	0	0	1 (0.3)	1 (0.1)
PD-L1 status[c]				
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]Age at randomization
[b]ECOG performance status at baseline, where baseline is defined as the last evaluable assessment prior to randomization.
[c]Stratification factor recorded on eCRF. PD-L1 tumor expression status is summarized based on laboratory data outside of the eCRF.
Percentages are calculated from number of patients in the full analysis set in that treatment group.
Data cut-off date: 12MAR2019; Source: Tables 14.1.4, 14.1.5, 14.1.16, 14.1.12 and 14.1.6.2, POSEIDON CSR, Module 5.3.5.1

The Applicant's Position:

Overall, the demographics and baseline disease characteristics of the patient population were generally representative of treatment-naïve patients with metastatic NSCLC who are eligible to receive frontline treatment.

The FDA's Assessment:
FDA agrees with the Applicant's description of the distribution of demographic characteristics in the intent-to-treat population in POSEIDON. The demographic characteristics of the study population are generally reflective of patients with metastatic NSCLC in the U.S., with the exception of the limited racial and ethnic diversity of patients enrolled on POSEIDON. In particular, only 2% of patients enrolled on the study were Black or African American. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) data, African American males have the highest rate of lung cancer diagnosis at 71.6 cases per 100,000 persons (NCI SEER, 2022).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Important baseline disease characteristics for the FAS are summarized in Table 23.

The Applicant's Position:
Overall, the baseline disease characteristics of the patient population were generally representative of treatment-naïve patients with metastatic NSCLC who are eligible to receive frontline treatment.

The FDA's Assessment:
FDA agrees with the Applicant's assessment that the distribution of disease characteristics in the intent-to-treat population in POSEIDON is representative of patients with metastatic NSCLC.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

The administration of all study drugs (including study treatment) was recorded in the appropriate sections of the eCRF.

There were 4 patients in the T + D + SoC arm and 4 patients in the D + SoC arm who used disallowed concomitant medication; these were all cases of corticosteroids that were prohibited for the T + D + SoC and D + SoC arms per the study protocol (Table 8 in the CSP, Appendix 16.1.1, POSEIDON CSR, Module 5.3.5.1). A total of 1001 (98.8%) patients received allowed concomitant medications during the study treatment. All allowed concomitant medications during study treatment were generally balanced between all 3 treatment arms.

Of the allowed concomitant medications during study treatment received by ≥20% of patients in any treatment arm, the most commonly received medications were serotonin (5HT3) antagonists (81.0%) and glucocorticoids (74.5%); concomitant medications with a ≥5% difference between at least 2 treatment arms in the T + D + SoC, D + SoC, and SoC alone arms, respectively were serotonin antagonists (78.1% vs 78.7% vs 86.4%), anilides (42.6% vs 35.5% vs 30.3%), combinations of penicillin, including beta-lactamase inhibitors (22.2% vs 18.9% vs 15.7%), colony stimulating factors (22.2% vs 18.3% vs 16.3%), propionic acid derivatives (20.4% vs 13.6% vs 18.1%), other opioids (17.8% vs 21.0% vs 13.4%), and other blood products (16.6% vs 14.2% vs 20.5%).

The Applicant's Position:
Treatment compliance was assured by reconciliation of site drug accountability logs.

Concomitant medications received by patients during this study were as expected for a population with advanced NSCLC receiving immune-oncology in combination with chemotherapy.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
The efficacy analyses were conducted using the ITT principle based on the treatment group to which the patients were randomized.

- The OS results are based on the DCO of 12 March 2021; and
- The PFS, ORR, and DoR results are based on the DCO of 24 July 2019.

POSEIDON was a positive study and met one of its primary efficacy objectives for success.

D + SoC demonstrated a statistically significant improvement in PFS compared with SoC (HR: 0.74; 95% CI: 0.620, 0.885; p=0.00093).

- D + SoC demonstrated a numerical improvement in OS compared with SoC; however, this comparison did not cross the prespecified threshold of statistical significance (HR: 0.86; 95% CI: 0.724, 1.016; p=0.07581; threshold p=0.02879). While D + SoC did not demonstrate statistical positivity for OS, the data indicate that a higher percentage of patients derive long-term survival benefit with D + SoC vs SoC with numerically higher estimates at OS 24 months (OS24: 29.6% vs 22.1%, respectively) and 36 months (OS36: 20.3% vs 13.3%, respectively).

The primary and secondary efficacy endpoints for the D + SoC vs. SoC comparison are discussed in detail in Section 11 of the POSEIDON CSR, Module 5.3.5.1.

The Applicant's Position:
POSEIDON was a positive study and met one of the 2 primary efficacy objectives prespecified for success.

The FDA's Assessment:
In general, FDA agrees with the Applicant's presentation of the efficacy results for the primary endpoints of PFS and OS in the D + SoC arm vs. the SoC arm from the final analysis of PFS (DCO: July 24, 2019) and the final analysis of OS (DCO: March 12, 2021).

Although a statistically significant PFS benefit was observed in patients treated with durvalumab in combination with chemotherapy when compared to patients treated with chemotherapy alone, a statistically significant OS benefit was not observed in patients treated with durvalumab in combination with chemotherapy. However, the magnitude of the OS hazard ratio was less than 1.0 for the

comparison of durvalumab in combination with chemotherapy compared to chemotherapy alone, and the landmark OS rates at 24 and 36 months, while descriptive, were numerically higher in the durvalumab in combination with chemotherapy treatment arm.

Data Quality and Integrity

The Applicant's Position:
For full details of the study data quality assurance see Section 9.6 of the POSEIDON CSR, Module 5.3.5.1
No such issues were identified for POSEIDON.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Efficacy Results – Secondary and other relevant endpoints

Data:
The Applicant's submission is based on the statistically significant and clinically meaningful benefits of T + D + SoC vs. SoC comparison which are the key secondary efficacy endpoints of the POSEIDON study. They are discussed in detail in the below section.

Table 24 Overview of efficacy results supporting the proposed indication – Full Analysis Set

Efficacy parameter	Tremelimumab + Durvalumab + SoC Chemotherapy (N=338)	SoC Chemotherapy (N=337)
Overall survival (OS)		
Events (%)	251 (74.3)	285 (84.6)
Median[a] (months); (95% CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
Hazard ratio[b] (95% CI)	0.77 (0.650, 0.916)	
Stratified log-rank p-value[c]	0.00304	
OS rate at 12 months (%); 95% CI[a]	54.8 (49.3, 60.0)	49.1 (43.6, 54.4)
OS rate at 18 months (%); 95% CI[a]	41.3 (36.0, 46.5)	34.1 (29.0, 39.2)
OS rate at 24 months (%); 95% CI[a]	32.9 (27.9, 37.9)	22.1 (17.8, 26.8)
OS rate at 36 months (%); 95% CI[a]	25.3 (20.8, 30.2)	13.3 (9.8, 17.4)
Progression-free survival (BICR; RECIST 1.1)		
Events (%)	238 (70.4)	258 (76.6)
Median[a] (months) (95% CI)[a]	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
Hazard ratio[b] (95% CI)	0.72 (0.600, 0.860)	
Stratified log-rank p-value[d]	0.00031	
PFS rate at 12 months (%); 95% CI[a]	26.6 (21.7, 31.7)	13.1 (9.3, 17.6)
Objective response rate (BICR; RECIST 1.1)[e]		
Number (%) with response	155/335 (46.3)	111/332 (33.4)
Odds ratio (95% CI)	1.72 (1.260, 2.367)	
Nominal p-value	<0.001	

Efficacy parameter	Tremelimumab + Durvalumab + SoC Chemotherapy (N=338)	SoC Chemotherapy (N=337)
Duration of response (BICR; RECIST 1.1)[e]		
Median[a] (months)	7.4	4.2
Percentage remaining in response at 12 months[a]	42.5	16.4

The OS results are based on the DCO of 12 March 2021; and the PFS, ORR, and DoR results are based on the DCO of 24 July 2019.

[a] Calculated using the Kaplan Meier technique.

[b] Based on a stratified Cox proportional hazard model.

[c] Boundary of declaring statistical significance at final OS analysis at 1% α level: 0.00797.

[d] Boundary of declaring statistical significance at final PFS analysis at 1% α level: 0.00735.

[e] Based on the number of patients who had measurable disease at baseline. ORR analysis was conducted using logistic regression adjusting for stratification factors. Per RECIST 1.1, the responses are unconfirmed. An ad hoc analysis for confirmed responses was conducted and is reported in the document.

Data source: Tables 14.2.2.1.1, Table 14.2.1.1.1; 14.2.3.1.1, 14.2.4.1.1, POSEIDON CSR, Module 5.3.5.1.

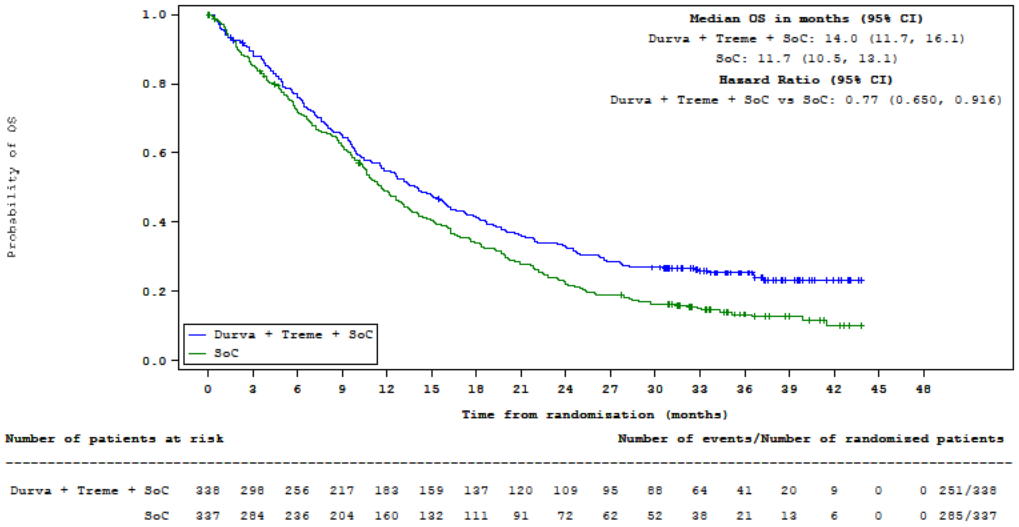
Overview of survival benefits

At final analysis (DCO: 12 March 2021), 536 out of 675 patients between the T + D + SoC and SoC arms had died (79.4% maturity). The median duration of follow up in all censored patients was 34.9 months (range: 0.0 to 44.5).

The combination of tremelimumab, durvalumab, and SoC achieved a statistically significant OS benefit compared with SoC alone (HR: 0.77; 95% CI: 0.650, 0.916; p=0.00304; Table 24). Compared with SoC alone, treatment with T + D + SoC reduced the overall risk of death by an average of 23%. The Kaplan Meier estimate of median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC arm, achieving a 2.3 month longer survival benefit.

Consistent with the mechanistic understanding of CTLA-4 and PD-L1 inhibition, a delayed separation of survival curves was observed between T + D + SoC and SoC alone and the proportional-hazards assumption was not met (p=0.039). The OS HR, therefore, provides an average estimate of benefit and is most appropriately interpreted in the context of the shape of the curves, which is characterized by transient initial survival benefit with chemotherapy, followed by long-term benefit with tremelimumab and durvalumab (Figure 15). The separation was sustained over the treatment period and was supported by the estimates of the 24 month and 36 month OS rates, with the T + D + SoC treatment demonstrating >10% higher OS rates at 24 month (OS24: 32.9% vs. 22.1%, respectively) and 36-month landmarks (OS36: 25.3% vs. 13.3%, respectively, representing a near doubling of survival rate in this long-term measure; Table 24).

Figure 15 Overall survival, Kaplan-Meier plot, T + D + SoC vs. SoC – Full Analysis Set



DCO: 12 March 2021.Data source: Figure 14.2.2.1.1.1, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the results of the two secondary endpoints of PFS per RECIST 1.1 according to BICR and OS comparing tremelimumab and durvalumab in combination with chemotherapy to chemotherapy. These key secondary endpoints were included in the formal testing plan controlling for overall Type I error rate. Efficacy results for other secondary endpoints presented in this section, such as ORR and DOR, are considered descriptive only as they were not included in the formal testing plan.

FDA agrees with the Applicant's position that a statistically significant OS benefit was observed in patients treated with tremelimumab and durvalumab in combination with chemotherapy as compared to patients who were treated with chemotherapy alone. From visual inspection of the Kaplan-Meier plots of OS it appears that there may be concerns regarding non-proportional hazards in the survival curves across two treatment arms. However, landmark OS rates were supportive of the overall survival benefit in patients treated with tremelimumab and durvalumab in combination with chemotherapy over time.

Sensitivity analyses of overall survival (full analysis set)

A sensitivity analysis was conducted for OS adjusting for the eCRF-derived stratification variables of disease stage (Stage IVA vs Stage IVB), histology (non-squamous vs squamous), and PD L1 status (TC ≥50% vs TC <50%). The results were consistent with the primary analysis with a HR estimate of 0.79 (95% CI: 0.667, 0.940; p=0.008) (see Table 14.2.2.3, POSEIDON CSR, Module 5.3.5.1).

Two multivariate Cox models were used: Model 1 adjusting for treatment and the stratification factors only, and Model 2 adjusting for treatment, the stratification factors and additional prespecified covariates (age at randomization [< 65 vs ≥ 65], sex [male vs female], smoking status [current smoker, former smoker, never smoker] and race [Asian vs non Asian]). The results were generally consistent with

the primary analysis (Model 1 HR = 0.78 [95% CI: 0.658, 0.925] and Model 2 HR = 0.76 [95% CI: 0.635, 0.903]; see Table 14.2.2.4, POSEIDON CSR, Module 5.3.5.1).

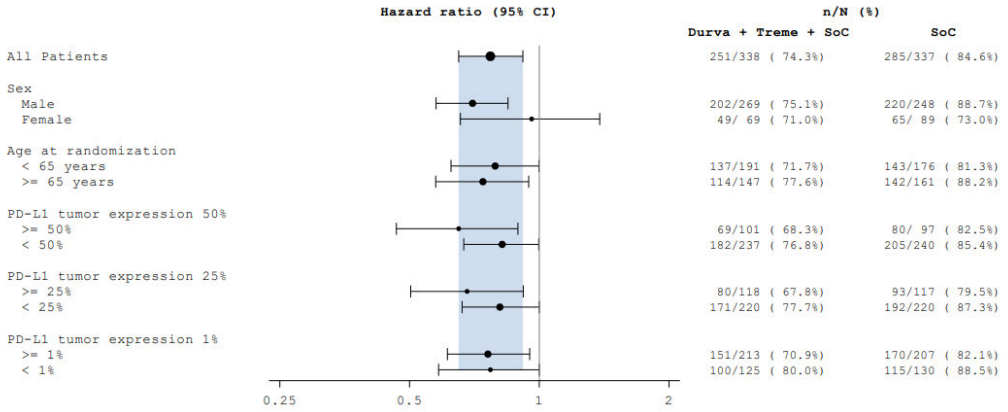
In order to assess the impact of non-proportional hazards a sensitivity analysis using a 3 component, stratified max-combo test with the same stratification factors as the primary analysis was conducted; in addition, an RMST of an area under-the curve approach was performed (Fleming and Harrington 1991, Karrison 2016). These analyses were generally consistent with the primary analyses (see Table 14.2.2.7.1 and Table 14.2.2.7.2, respectively, POSEIDON CSR, Module 5.3.5.1).

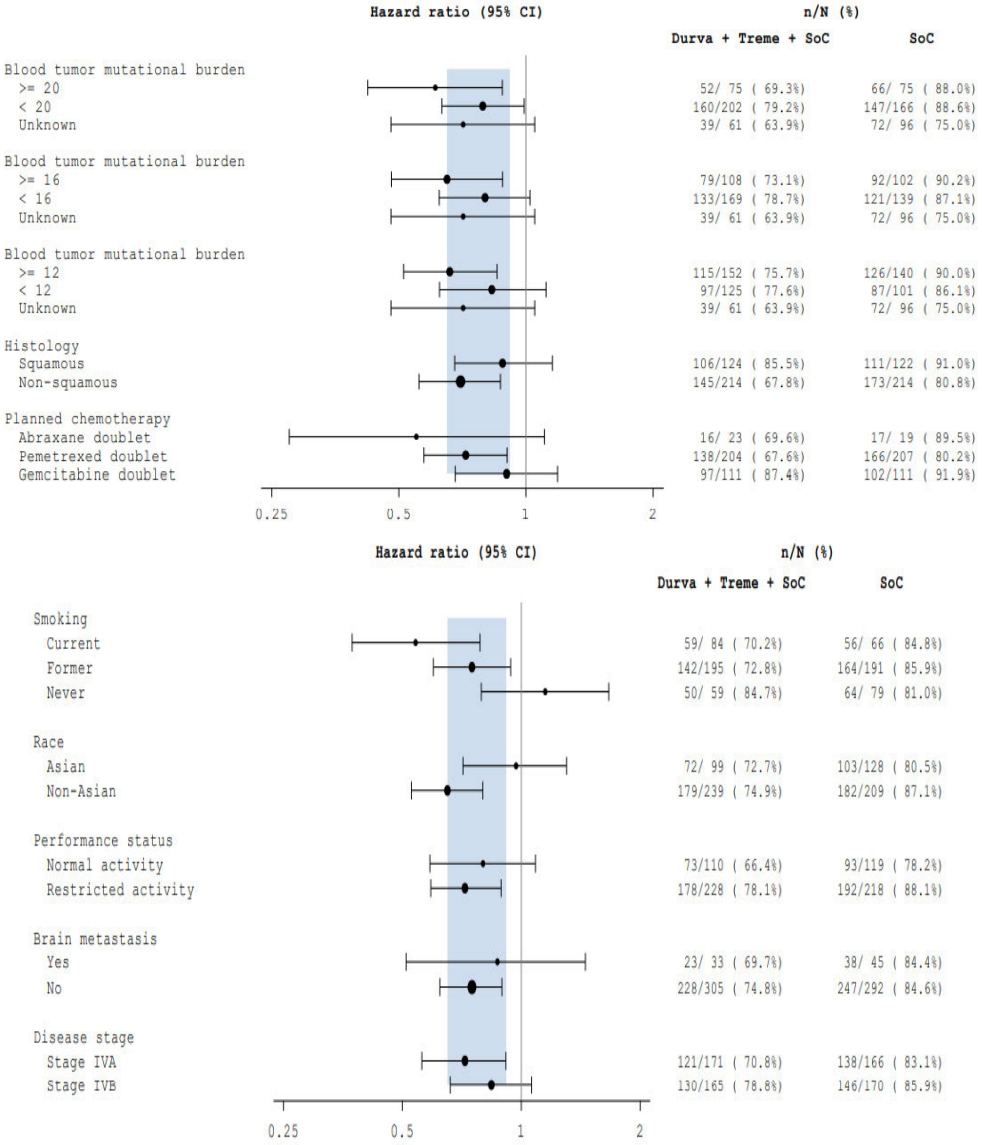
The FDA's Assessment:
In general, FDA agrees with the Applicant's presentation of the efficacy results from the sensitivity analyses of OS in this section. FDA considers these results to be supportive only.

Subgroup analyses of overall survival (full analysis set)

The OS analyses by prespecified subgroups were consistent with those of the primary analysis (Figure 16). An exception, though, was noted in the never smoker subgroup; however, results should be interpreted with caution due to low number of patients in this subgroup and wide CI that included 1. Given that PD L1 expression is a key established immune biomarker (NCCN Clinical Practice Guidelines in Oncology Version 2.2021), the prespecified subgroups also included PD-L1 TC 50%, PD-L1 TC 25%, and PD-L1 TC 1% expression levels. The OS results in all PD L1 TC expression subgroups were consistent with those of the primary analysis.

Figure 16 Overall survival, Forest plot of subgroup, full analysis set, T + D + SoC vs SoC



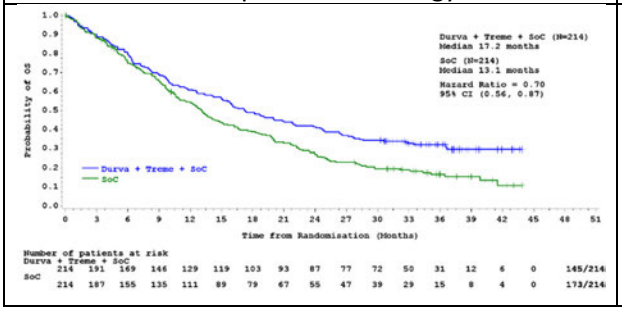
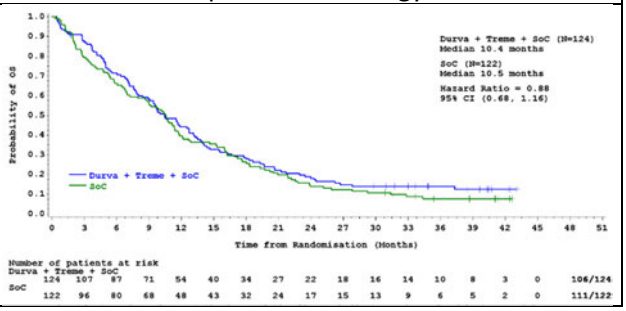


All patients: same model as in the main analysis while the hazard ratio and 95% CI for each subgroup level are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties.
The grey band represents the 95% confidence interval for the primary analysis hazard ratio.
Data cutoff: 12MAR2021; Source: Figure 14.2.2.5.1, POSEIDON CSR, Module 5.3.5.1.

Patients were stratified based on histology, PD-L1 tumor cell expression, and disease stage. No significant interaction (p=0.500) was found for the stratification factors of histology (non squamous vs squamous), PD L1 status (TC ≥50% vs TC <50%), and disease stage (Stage IVA vs Stage IVB) which were prespecified in the SAP and tested formally for any qualitative interaction with treatment (see Table 14.2.2.6.1, POSEIDON CSR, Module 5.3.5.1).

At the time the POSEIDON study was designed, several comparable studies were ongoing in this treatment setting that enrolled patients based on histology (eg, KEYNOTE-189 [non-squamous]; KEYNOTE-407 [squamous]). POSEIDON, in contrast, enrolled patients regardless of histology (similar to CHECKMATE-227; CHECKMATE-9LA). Analysis of histology subgroups indicated that the OS HRs for non-squamous and squamous patients were both <1, though it is noted that the survival benefits were more pronounced in patients with non-squamous histology (HR: 0.70; 95% CI: 0.558, 0.870) compared with those with squamous histology (HR: 0.88; 95% CI: 0.678, 1.155; Figure 17).

Figure 17 Overall survival, Kaplan-Meier curve by histology, full analysis set, T + D + SoC vs SoC

Non-squamous histology	Squamous histology
	

+ indicates a censored observation. The hazard ratio and CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and with the Efron method to control for ties, and the CI calculated using a profile likelihood approach; Data cutoff: 12 March 2021. Source: Data on file.

Post discontinuation anti cancer treatments were received by 40.8% of patients on T + D + SoC arm and 60.2% of patients on SoC arm. The majority of subsequent treatments were systemic therapies (36.4% of patients on T + D + SoC vs. 57.6% on SoC alone). A notably higher proportion of SoC patients received subsequent immunotherapies compared with those on T + D + SoC (33.2% of patients vs. 6.5%, respectively).

The FDA's Assessment:

In general, FDA agrees with the Applicant's presentation of the OS efficacy results in the pre-specified subgroups of patients presented in this section. However, analyses of subgroup results should be interpreted with caution as there was not adequate power to detect a treatment difference across these subgroups and formal testing was not planned for these analyses.

Progression-free survival (BICR, RECIST 1.1)

The combination of tremelimumab, durvalumab, and SoC achieved a statistically significant PFS benefit compared with SoC alone (HR: 0.72; 95% CI: 0.600, 0.860; p=0.00031; Table 24). Compared with SoC, treatment with T + D + SoC reduced the overall risk of progression or death by an average of 28%. The Kaplan Meier estimate of median PFS was 6.2 months on the T + D + SoC arm and 4.8 months on the SoC arm.

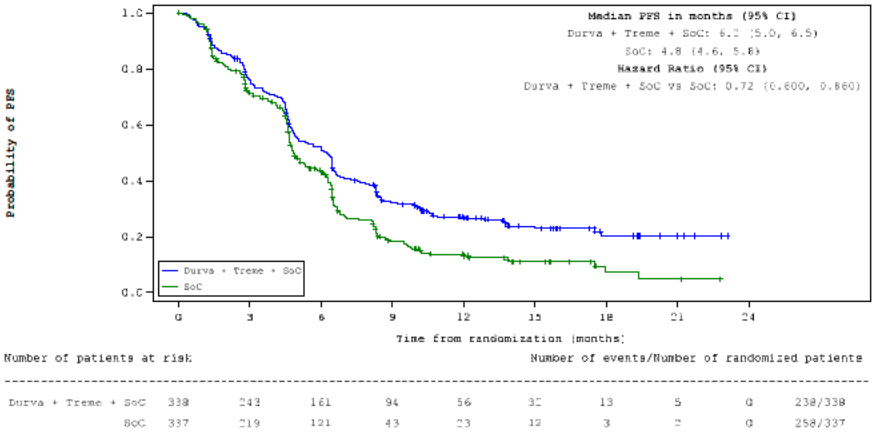
The separation of PFS curves in favor of T + D + SoC vs. SoC appeared approximately 2 months after randomization (Figure 18). The separation was sustained over the treatment period and was supported by the estimates of the 12-month PFS rate, with the T + D + SoC treatment demonstrating >10% higher

PFS rate compared with SoC alone (26.6% vs. 13.1%, respectively; representing a near doubling of PFS rate in this long-term measure Table 24).

Sensitivity analyses were conducted to assess robustness of the PFS effect to the potential source of bias in PFS measurement, including the possibility of evaluation-time bias, attrition bias, ascertainment bias, and using eCRF-derived variables. Results of the sensitivity analyses of PFS were generally consistent with those of the primary PFS analysis demonstrating the robustness of the PFS treatment effect estimate (HRs range for sensitivity analyses: 0.66 to 0.74).

The PFS benefit favoring T + D + SoC vs. SoC alone was observed across all prespecified subgroups demonstrating consistency with the primary PFS analysis (point estimate HRs for prespecified subgroups all <1).

Figure 18 Progression-free survival, Kaplan-Meier plot, T + D + SoC vs. SoC – Full analysis set



DCO: 24 July 2019.
Data source: Figure 14.2.1.1.1.1, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:

In general, FDA agrees with the Applicant's presentation of the BICR-assessed PFS results in this section. A statistically significant PFS benefit was observed in patients treated with tremelimumab and durvalumab in combination with chemotherapy as compared to patients who were treated with chemotherapy alone. Upon visual inspection of K-M plot as well as the log-negative log plot of survivor functions for each arm there may be concerns for non-proportional hazards for this analysis; however, there is a separation of the PFS curves for the two arms after approximately 2 months. The exploratory analyses of landmark rates at 3, 6, 9, and 12 months according to FDA's calculation (76% vs. 71%, 51% vs. 43%, 32% vs. 18%, 27% vs. 13%) provide some descriptions of the differences in PFS rates over time to complement the estimates of the median PFS and hazard ratio. Estimates of the PFS hazard ratios from the sensitivity analyses were supportive of the treatment benefit observed in the primary analysis of PFS. The PFS hazard ratios in the pre-specified subgroups were less than 1.0. However, the results of subgroup analyses should be interpreted with caution. The BICR-assessed PFS results in some selected subgroups are provided in Table 25.

Table 25: Progression-free survival (PFS) according to blinded independent central review (BICR) - subgroup analyses in the intent-to-treat (ITT) population[1] (FDA review)

Subgroups	PFS HR (95% CI)[2]
Age, in years	
< 65 (n=367)	0.71 (0.56, 0.90)
≥ 65 (n=308)	0.70 (0.54, 0.92)
Sex	
Male (n=517)	0.67 (0.55, 0.82)
Female (n=158)	0.77 (0.52, 1.13)
Race	
White (n=384)	0.64 (0.51, 0.81)
Asian (n=227)	0.88 (0.64, 1.19)
Black (n=16)	0.71 (0.21, 2.51)
Other (n=48)	0.54 (0.26, 1.11)
Region	
North America (n=84)	0.83 (0.50, 1.38)
Europe (n=274)	0.55 (0.41, 0.72)
Asia (n=220)	0.86 (0.62, 1.18)
Rest of World (n=97)	0.68 (0.42, 1.09)

[1]Comparing treatment arms tremelimumab and durvalumab in combination with SOC chemotherapy vs. SOC chemotherapy alone
[2]From unstratified Cox proportional hazards model
Source: Reviewer generated results from the Applicant submitted data adtte.xpt

Objective response rate/Duration of response

ORR and DoR were based on patients who had measurable disease at baseline. The results of ORR and DoR are based on the DCO of 24 July 2019 (Table 24).

Patients on T + D + SoC achieved higher ORR (unconfirmed, BICR; RECIST 1.1) with more than 10% incremental improvement compared with SoC alone (46.3% vs. 33.4%, respectively; OR: 1.72; 95% CI: 1.260, 2.367; nominal p<0.001). A post hoc analysis was conducted to determine the confirmed objective response, defined as the number (%) of patients with at least one visit response of CR or PR and a confirmatory scan no sooner than 4 weeks after the initial CR/PR. The confirmed ORR also demonstrated 14.4% incremental improvement favoring T + D + SoC over SoC (38.8% vs. 24.4%, respectively, OR: 2.00; 95% CI: 1.428, 2.807; nominal p<0.001).

Patients on T + D + SoC experienced durable responses (unconfirmed, BICR, RECIST 1.1), with a median duration of response of 7.4 months compared with 4.2 months on SoC alone. Based on the Kaplan-Meier estimates, 42.5% of patients on T + D + SoC compared with 16.4% of patients on SoC alone remained in response at 12 months after onset of response. A post hoc analysis, based on patients with

a confirmed ORR, also demonstrated durable responses on T + D + SoC compared to SoC alone (median DoR: 9.5 months vs. 5.1 months respectively). In patients who had a confirmed ORR, 49.7% on T + D + SoC remained in response at 12 months after onset of response compared with 21.4% on SoC alone.

For additional details on secondary efficacy endpoints, see Section 11.2, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:

In general, FDA agrees with the efficacy results for ORR and DOR presented in this section. ORR was not included under a formal testing plan controlling for the overall Type I error rate and FDA considers these results exploratory only. The ORR and DOR results in the ITT population are provided below.

Table 26: Overall Response Rate (Confirmed) and Duration of Response in Trial POSEIDON – ITT Population (FDA review)

	Tremelimumab + Durvalumab + Chemotherapy (n=338)	Chemotherapy alone (n=337)
Overall response rate (ORR), n(%)	130 (38)	81 (24)
95% CI[1]	(33, 44)	(20, 29)
Duration of response (DOR), in months[2]		
Median (95% CI)	9.5 (7.2. NR)	5.1 (4.4, 6.0)
DOR ≥ 6 months	67%	40%

[1] Clopper-Pearson method; [2] Kaplan-Meier method.
Note. Data cut-off date (DCO): July 24, 2019.
Source: Reviewer generated results from Applicant submitted data adeff.xpt.

The Applicant's Position:

Based on the MTP, the key secondary efficacy objectives of comparing T + D + SoC vs SoC were tested using recycled alpha through the statistically significant PFS outcome of the primary efficacy objective.

The combination of tremelimumab, durvalumab and SoC chemotherapy demonstrated statistically significant and clinically meaningful OS and PFS benefits over SoC despite being tested at a 1% significance level (adjusted for interim analyses to maintain strong control of the alpha at 1% [2-sided]). Compared with SoC alone, treatment with T + D + SoC reduced the overall risk of death by an average of 23%. Consistent with the mechanistic understanding of the CTLA-4 and PD-L1 inhibition, a delayed separation of survival curves was observed between T + D + SoC and SoC and the proportional hazards assumption was not met (p=0.039). The OS HR, therefore, provides an overall estimate of benefit and is to be interpreted in the context of the shape of the curves, which is characterized by transient initial survival benefit with chemotherapy, followed by long term benefit with tremelimumab and durvalumab. The survival benefits with T + D + SoC were sustained long term with a higher proportion of patients alive at the 24-month (32.9% vs. 22.1%, respectively) and 36-month (25.3% vs. 13.3%, respectively) landmarks. OS favored T + D + SoC compared with SoC chemotherapy (HR <1) across the PD-L1 analysis sets.

The FDA's Assessment:

FDA agrees with the Applicant's description of the testing strategy of the key secondary endpoints of BICR-assessed PFS and OS comparing treatment arms tremelimumab and durvalumab in combination with chemotherapy and chemotherapy alone. A statistically significant PFS and OS benefit was observed in patients treated with tremelimumab and durvalumab in combination with chemotherapy as compared to patients who were treated with chemotherapy alone. Upon visual inspection of K-M plot as well as the log-negative log plot of survivor functions for OS in each arm there may be concern for non-proportional hazards for these analyses. However, the exploratory analyses of landmark OS rates complement the estimates of the median OS and hazard ratio.

Dose/Dose Response

Data:
See Section 0.

The Applicant's Position:

No clinically meaningful exposure-efficacy relationships were identified for this dose regimen, indicating that no dose optimization for NSCLC is necessary. No dose adjustment is necessary based on body weight (>30 kg) or other intrinsic or extrinsic factors based on covariate analysis in the PPK modelling. No apparent relationship between body weight and efficacy was observed, suggesting that the fixed dosing regimen used in the study was appropriate. For additional details, see Section 6.

The FDA's Assessment:
See FDA assessment in Section 0.

Durability of Response

Data:
DOR is presented as a secondary endpoint.

The Applicant's Position:
See secondary endpoint: DOR.

The FDA's Assessment:
FDA agrees.

Persistence of Effect

Data:

The primary endpoints of OS and PFS are based on time-to-event analysis; thus, persistence of efficacy is inherent in the chosen efficacy measures. See secondary efficacy endpoints: ORR and DoR.

The Applicant's Position:

The combination of tremelimumab, durvalumab, and SoC chemotherapy demonstrated survival benefits that were sustained over the long term. In patients who had a confirmed ORR, the percentage of responders with an estimated DoR of 12 months or longer was 49.7% in the T + D + SoC arm compared with 21.4% in the SoC chemotherapy arm. The OS curve separation was sustained over the treatment period and was supported by the estimates of the 24 month and 36 month OS rates, with the T + D + SoC treatment demonstrating >10% higher OS rates at 24-months (32.9% vs 22.1%, respectively) and 36-month landmarks (25.3% vs 13.3%, respectively), representing a near doubling of survival rate in this long-term measure.

The FDA's Assessment:

Persistence of effect is a term better suited for continuous variables (hypertension, biomarker, monitoring, etc.) than to characterize or compare effect of treatment on the selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The combination of tremelimumab, durvalumab, and SoC chemotherapy demonstrated a significant improvement in OS while delaying the deterioration in health-related quality of life. Longer time to deterioration (TTD) was observed for patient-reported global health status/QoL, and all functioning and symptom scales in favor of T + D + SoC compared to SoC alone. Greater improvement rates in the T + D + SoC versus SoC alone were observed for patient-reported global health status/QoL and all functioning and symptom scales.

For additional details on secondary efficacy endpoints, see Section 11.2, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:

FDA acknowledges the Applicant's presentation of the results of COA (PRO) endpoints in this section. Given the lack of control for Type I error rate for these analyses, FDA considers these results to be exploratory and did not independently verify the results presented in this section.

Efficacy Results – Contribution of Components

Contributions of chemotherapy, durvalumab, and tremelimumab to the treatment effect of the T + D + SoC combination)

In a combination treatment regimen, the US FDA guidance recommends establishing the contribution of each component to the overall treatment effect. The 3 arm additive design of the pivotal POSEIDON study supports a clear evaluation of the contribution of each component of the proposed regimen – chemotherapy, durvalumab, and tremelimumab – within the pivotal study supporting the submission. They are discussed in this section.

Contributions of chemotherapy to the overall T + D + SoC treatment effect

In the proposed treatment regimen, the rationale of combining chemotherapy with immunotherapy is

to derive benefit of the early disease control provided by chemotherapies. In keeping with global treatment guidelines, the POSEIDON study allowed flexibility in the choice of chemotherapies, selected based on histology and Investigator's preference. Patients on the T + D + SoC arm were allowed up to 4 cycles of chemotherapy, while patients on the SoC arm were permitted to receive up to 6 cycles of chemotherapy (ie, additional 2 cycles as clinically indicated and based on Investigator's preference).

The contributions of chemotherapy to the overall T + D + SoC treatment effect were characterized based on the clinical benefits observed in the SoC arm in the POSEIDON study. The magnitude of key efficacy parameters on the SoC arm was consistent with that reported in the reported clinical literature (Gandhi et al [KEYNOTE-189] 2018; Hellman et al [CheckMate-227] 2019; Paz-Ares et al [Checkmate 9LA] 2021). The KM estimates of median OS and median PFS were 11.7 months (95% CI: 10.5, 13.1) and 4.8 months (95% CI: 4.6, 5.8), respectively, the confirmed ORR was 24.4%, the median DoR in patients with a confirmed response was 5.1 months, and the percentage of patients with a DoR of 12 months or longer was 21.4% (Table 27). The SoC arm in the supportive MYSTIC study also performed in a similar manner (see Section 7, MYSTIC CSR, Module 5.3.5.1).

Table 27 Contribution of chemotherapy, durvalumab, and tremelimumab to the overall T + D + SoC treatment effect in the POSEIDON study

	Treatment arm		
Efficacy measure	**T + D + SoC**	**D + SoC**	**SoC**
Overall survival			
T + D + SoC vs SoC: HR, (95% CI); 2-sided p-value	0.77 (0.650, 0.916); 0.00304		
D + SoC vs SoC: HR, (95% CI); 2-sided p-value		0.86 (0.724, 1.016); 0.07581	
T + D + SoC vs D + SoC: HR, (95% CI); 2-sided p-value	0.92 (0.776, 1.100); 0.373		
Median OS (months) (95% CI)	14.0 (11.7, 16.1)	13.3 (11.4, 14.7)	11.7 (10.5, 13.1)
OS rate (%) at 24 months (95% CI)	32.9 (27.9, 37.9)	29.6 (24.8, 34.6)	22.1 (17.8, 26.8)
OS rate (%) at 36 months (95% CI)	25.3 (20.8, 30.2)	20.3 (16.1, 25.0)	13.3 (9.8, 17.4)
Progression-free survival			
T + D + SoC vs SoC: HR, (95% CI); 2-sided p-value	0.72 (0.600, 0.860); 0.00031		
D + SoC vs SoC: HR, (95% CI); 2-sided p-value		0.74 (0.620, 0.885); 0.00093	
T + D + SoC vs D + SoC: HR, (95% CI); 2-sided p-value	0.97 (0.815, 1.166); 0.796		
Median (months) (95% CI)	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 5.8)
PFS rate (%) at 12 months (95% CI)	26.6 (21.7, 31.7)	24.4 (19.7, 29.5)	13.1 (9.3, 17.6)
Objective response rate			
T + D + SoC vs SoC: Odds ratio, (95% CI); 2-sided p-value	2.00 (1.428, 2.807); <0.001		
D + SoC vs SoC: Odds ratio, (95% CI); 2-sided p-value		2.26 (1.611, 3.185); <0.001	
D + T + SoC vs D + SoC: Odds ratio, (95% CI); 2-sided p-value	0.89 (0.646, 1.218); 0.461		
Duration of response (confirmed; from the onset of response [months])			
Median duration (25th, 75th percentiles)	9.5 (5.0, NR)	7.0 (3.9, NR)	5.1 (3.7, 7.5)
Percentage remaining in response [g]			
At 12 months	49.7	38.9	21.4
At 18 months	40.7	29.6	NR

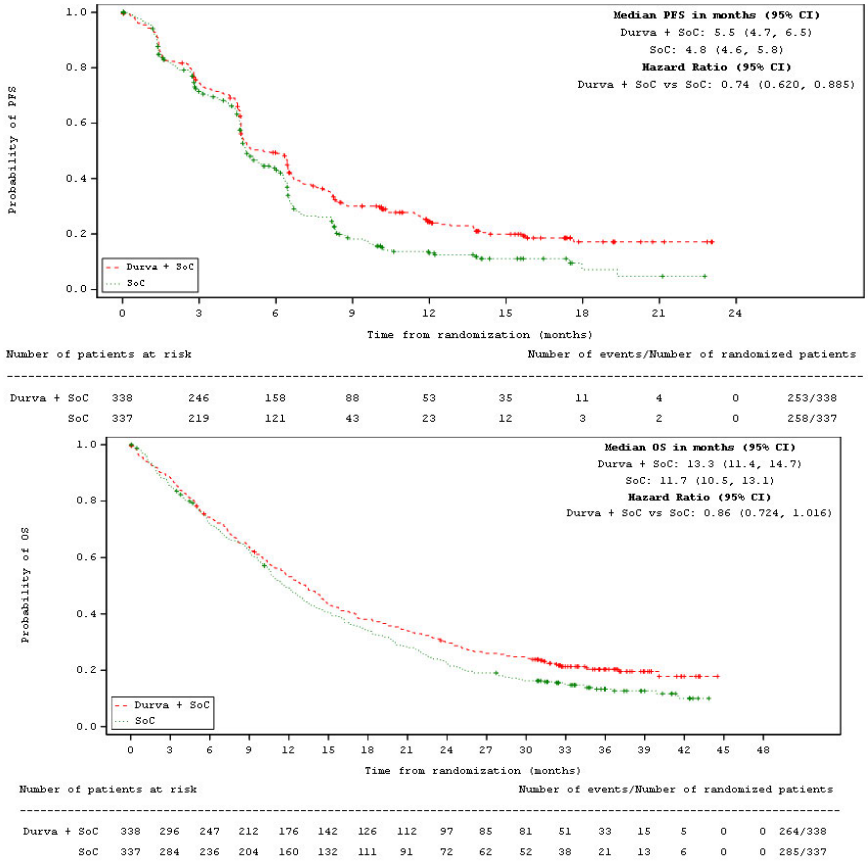
Data derived from Tables 14.2.1.1.1, 14.2.2.1.1, 14.2.3.1.8, 14.2.4.1.8, POSEIDON CSR, Module 5.3.5.1

In summary, in the proposed immunotherapy/chemotherapy combination, chemotherapy provides early disease control. The addition of chemotherapy plausibly prevents the initial crossing of survival curves which is commonly observed in immunotherapy-alone studies (Hellman et al [CheckMate-227] 2019) as reported in similar immunotherapy/chemotherapy combination studies (Paz-Ares et al [Checkmate 9LA] 2021). However, and as anticipated, the long term, durable responses remained limited with SoC chemotherapy alone, with only 21.4% of patients with confirmed ORR remaining having a response of 12 months or longer compared to 49.7% of patients in the T + D + SoC arm (Table 24).

Contributions of durvalumab to the overall T + D + SoC treatment effect

In the proposed treatment regimen, the rationale of combining durvalumab with tremelimumab is to derive benefit of the distinct yet synergistic mechanisms of blocking PD-L1 and CTLA-4 mediated immune resistance pathways. The contributions of durvalumab to the overall T + D + SoC treatment effect were characterized based on the clinical benefits observed between D + SoC vs. SoC arms in the POSEIDON study (Table 27).

Figure 19 Progression-free survival (top) and overall survival (bottom), Kaplan-Meier Plot, D + SoC vs. SoC



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Data source: Figures 14.2.1.1.1.2 and 14.2.2.1.1.2, POSEIDON CSR, Module 5.3.5.1

PFS: The addition of durvalumab to SoC chemotherapy demonstrated a statistically significant PFS benefit compared with SoC chemotherapy alone (HR: 0.74; 95% CI: 0.620, 0.885; p=0.00093), representing a 26% reduction in the risk of progression or death. The PFS benefit with D + SoC over SoC chemotherapy was sustained long-term with numerically higher PFS rate at the PFS12 landmark (24.4% vs 13.1%, respectively) (Table 27; Figure 19).

ORR: In the D + SoC arm, the confirmed ORR was >15% higher vs. SoC chemotherapy (41.5% vs. 24.4%, respectively). More durable responses were reported on D + SoC arm vs SoC chemotherapy (median DoR: 7.0 vs. 5.1 months, respectively), with a higher percentage of patients remaining in response at 12 months after onset of response in the D + SoC arm vs SoC arm (38.9% vs 21.4%, respectively) (based on patients with confirmed response).

OS: The addition of durvalumab to SoC chemotherapy numerically improved OS compared with SoC chemotherapy (HR: 0.86; 95% CI: 0.724, 1.016; p=0.07581). While the treatment comparison did not cross the prespecified threshold of statistical significance, the addition of durvalumab to SoC reduced the average risk of death by 14%. The separation of OS KM curves in favor of D + SoC appeared around 11 months and remained separated from SoC throughout the treatment period in favor of D + SoC. The treatment effects with D + SoC vs. SoC were sustained long-term, with numerically higher OS rates at 24 months (29.6% vs 22.1%, respectively) and 36 months (20.3% vs 13.3%, respectively) (Table 27; Figure 19).

Given that PD-L1 expression is a key established immune biomarker (NCCN Clinical Practice Guidelines in Oncology Version 2.2021), the prespecified OS subgroups included subgroups based on PD-L1 TC50%, PD-L1 TC25%, and PD-L1 TC1% expression levels. Numerically, in terms of HR, the maximum OS improvement was noted in the PD-L1 subgroup with the highest expression (PD-L1 TC≥50% HR: 0.63; 95% CI: 0.453, 0.879), with numerical improvements observed in subgroups with low PD-L1 expressions (PD-L1 TC<25% HR: 0.90; 95% CI: 0.734, 1.102; and PD-L1 TC<1% HR: 0.99; 95% CI: 0.756, 1.296). Acknowledging the caveats around subgroup analysis, and while no detriments in terms of the OS HR were observed, the contribution of durvalumab to SoC in these analysis sets was most apparent in those patients with higher levels of PD-L1 expression.

In the PD-L1 subgroups of the supportive MYSTIC study, a similar observation was noted. The most improvement in OS with durvalumab vs. SoC was observed in the PD-L1 TC≥25% subgroup (HR: 0.76; 97.54% CI: 0.564, 1.019; 2-sided p-value of 0.036). In patients with PD-L1 TC<1%, durvalumab did not show an improvement in OS compared to SoC chemotherapy (HR: 1.18; 95% CI: 0.856, 1.618) (see Section 7.2.1.1, MYSTIC CSR, Module 5.3.5.1).

<u>Contributions of tremelimumab to the overall T + D + SoC treatment effect</u>

In the proposed treatment regimen, the primary objective of combining tremelimumab with durvalumab was to derive benefit of the distinct yet synergistic mechanisms of blocking CTLA-4 and PD-L1 mediated immune resistance pathways. The contribution of tremelimumab to the overall treatment benefits of T + D + SoC regimen was characterized in 3 parts:

Based on the overall survival benefits observed with combining the T + D + SoC vs. SoC alone in the POSEIDON study (FAS and PD-L1 TC<1% analysis sets)

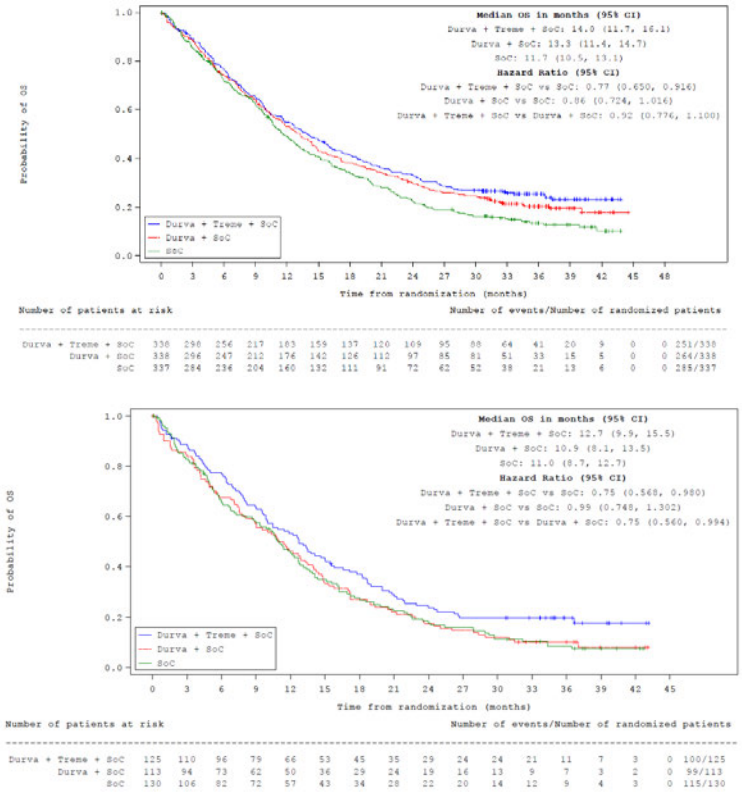
The combination of tremelimumab, durvalumab and SoC chemotherapy demonstrated statistically significant and clinically meaningful OS and PFS benefits over SoC despite being tested at a 1% significance level (adjusted for interim analyses to maintain strong control of the alpha at 1% [2-sided]). Compared with SoC alone, treatment with T + D + SoC reduced the overall risk of death by an average of 23%. Consistent with the mechanistic understanding of the CTLA-4 and PD-L1 inhibition, a delayed separation of survival curves was observed between T + D + SoC and SoC and the proportional hazards assumption was not met (p=0.039). The OS HR, therefore, provides an overall estimate of benefit and is to be interpreted in the context of the shape of the curves (Figure 15), which is characterized by transient initial survival benefit with chemotherapy, followed by long term benefit with tremelimumab and durvalumab. The survival benefits with T + D + SoC were sustained long term with a higher proportion of patients alive at the 24-month (32.9% vs 22.1%, respectively) and 36-month (25.3% vs 13.3%, respectively) landmarks. OS favored T + D + SoC compared with SoC chemotherapy (HR <1) across the PD-L1 analysis sets, with the most marked numerical improvement observed in the PD-L1 TC <1% analysis set (HR: 0.75; 95% CI: 0.568, 0.980; p = 0.035).

Based on the clinical benefits observed between T + D + SoC vs. D + SoC chemotherapy in the POSEIDON study (FAS and PD-L1 TC<1% analysis sets)

The prespecified MTP did not include an alpha-controlled comparison between T + D + SoC and D + SoC arms (Figure 12). Therefore, the two treatment arms were compared based on descriptive statistics.

The addition of tremelimumab to D + SoC demonstrated an incremental improvement in OS over that observed with D + SoC (HR: 0.92; 95% CI: 0.776, 1.100) in the full analysis set (Table 27). This improvement was observed throughout the OS KM separation curve and was particularly pronounced in the long term, with numerically higher OS rates observed at 24 months (32.9% vs 29.6% on D + SoC, respectively) and 36 months (25.3% vs 20.3%, respectively) (Table 27; and Figure 20). Due to the delayed separation of the KM curves, the totality of the clinical benefit of the T + D + SoC treatment regimen is most appropriately described based on the OS HR in combination with the clinical benefits observed at long-term survival landmarks and durable responses.
Patients on T + D + SoC experienced more durable responses compared with those on D + SoC (median DoR: 9.5 vs 7.0 months, respectively). In patients who had a confirmed ORR, 49.7% on T + D + SoC remained in response at 12 months after the onset of response compared with 38.9% on D + SoC; 40.7% vs. 29.6% remained in response at 18 months after the onset of response, respectively (Table 27).

Figure 20 Overall survival in the full analysis set (top) and PD-L1 TC<1% analysis set (bottom), Kaplan-Meier curves



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Data source: Figures Figure 14.2.2.1.1 and 14.2.2.1.3, POSEIDON CSR, Module 5.3.5.1

Furthermore, the improvement in OS with T + D + SoC vs. D + SoC was observed across the PD-L1 TC <50%, PD-L1 TC <25%, and PD-L1 TC <1% expression levels (HR range: 0.75 to 0.92) (see Tables 14.2.2.1.2, 14.2.2.1.3 and 14.2.2.1.4, POSEIDON CSR, Module 5.3.5.1). Based on the magnitude of OS HR, the contributions of adding tremelimumab to D + SoC vs. D + SoC was most notable in patients with PD-L1 TC <1% expression levels (Figure 20; OS HR: 0.75; 95% CI: 0.560, 0.994) and the OS36 landmark 19.8% vs 10.2%, respectively [see Table 14.2.2.1.3, POSEIDON CSR, Module 5.3.5.1]). This observation supports the understanding that, in patients with lower levels of PD-L1 expression for whom durvalumab may provide limited additive efficacy, combination with tremelimumab serves to enhance the efficacy of the regimen.

Based on the clinical benefits observed between T + D vs. D in the supportive MYSTIC study (PD-L1 TC ≥25% and PD-L1 TC <1% analysis sets).

The combination of tremelimumab and durvalumab vs. durvalumab demonstrated an improvement in OS in patients with PD-L1 TC<1% (HR: 0.62; 95% CI: 0.442, 0.876) but not in patients with PD-L1 TC ≥25% (HR: 1.09; 95% CI: 0.836, 1.421) (see Section 7.2.3.4, MYSTIC CSR, Module 5.3.5.1). These observations were supported by numerically higher ORR on T + D compared with D alone in the PD-L1 TC <1% analysis set (22.4% vs 9.5%) (see Table 11.2.6.1.6, MYSTIC CSR, Module 5.3.5.1).

The Applicant's Position:

The POSEIDON study was designed to evaluate the hypothesis that a limited early course of tremelimumab primes the immune response, and, when combined with a full course of durvalumab, sustained and long-term benefit would be observed. Furthermore, the addition of upfront chemotherapy might enable rapid disease control in a higher percentage of patients, thereby avoiding the early mortality observed with immunotherapy-only treatments immunotherapies in certain clinical trials, which manifests as an initial crossing of the survival curve (tremelimumab + durvalumab combination, see MYSTIC CSR, Module 5.3.5.1).

Results of the POSEIDON study corroborated the above hypotheses. A short course of tremelimumab, a CTLA-4 antibody and a potential new medicine, in combination with durvalumab and SoC chemotherapy improved PFS by 28% and OS by 23% compared with SoC chemotherapy alone. The benefit of adding tremelimumab to the combination of durvalumab + SoC was demonstrated by the separation of OS KM curve and this separation was particularly pronounced in the long-term. A consistent higher OS rate for T + D + SoC compared to both D + SoC and SoC chemotherapy was noted throughout the entire KM curves providing reassurance that the overall treatment effect is robust.

The 3-arm additive design of POSEIDON allowed for a clear evaluation of the contribution of chemotherapy, durvalumab, and tremelimumab within the pivotal study supporting the submission. Consistent with the understanding of the mechanism of action of PD-L1 and CTLA-4 inhibitions, the improvement in OS was observed across all PD-L1 expression levels, with the most notable numerical improvement with D + T + SoC vs. D + SoC observed in the PD-L1 TC <1% level.

Results of the POSEIDON study support the observation that in patients with lower levels of PD L1 expression for whom durvalumab monotherapy alone may provide limited additive efficacy, combination with tremelimumab serves to enhance the efficacy of the regimen. This is consistent with the understanding of the known mechanism of action of PD-L1 and CTLA-4 inhibitors. Tumors with low PD-L1 expression tend to be poorly infiltrated by T-cells. Tremelimumab-mediated CTLA-4 inhibition may prime T cell responses leading to enhanced tumor infiltration. Continuous PD-L1 blockade with durvalumab may further enhance T-cell function and support a sustained anti-tumor response. The concurrent addition to tremelimumab to chemotherapy which causes tumor cell death and the release of neoantigens may further enhance immune priming facilitating improved outcomes. Observations in POSEIDON are supported by the results of the MYSTIC study that also indicate larger clinical benefit with durvalumab at higher levels of PD-L1 expression and show greater benefit of T + D vs D alone in patients with low PD-L1 expression. The contribution of tremelimumab to the regimen's efficacy is most notable in these patients.

The FDA's Assessment:

FDA acknowledges the Applicant's position regarding the contribution of each component in the combination treatment regimen in POSEIDON. In assessing the contribution of components, FDA considered data from the D + SoC arm in POSEIDON as well as additional supportive data from external studies. Although a formal comparison of the T + D + SoC and D + SoC arms was not included in the statistical analysis plan, the three-arm study design allowed for contemporaneous descriptive comparisons between the two regimens which supports the assessment of the contribution of

components.

Regarding the contribution of durvalumab to the overall regimen:

- Within the POSEIDON study, the PFS comparison of D + SoC vs. SoC was statistically significant and favored the D + SoC arm. Although the OS comparison did not meet the prespecified threshold of statistical significance (HR: 0.86; 95% CI: 0.72, 1.02; p=0.07581), there were numerically higher OS rates observed in the D + SoC arm compared to the SoC arm at 24 months (30% vs 22%, respectively) and 36 months (20% vs 13%, respectively).

Regarding the contribution of tremelimumab to the overall regimen:

- Within the POSEIDON study, although a statistically significant benefit in PFS and OS was observed in patients treated with T + D + SoC as compared with those treated with SoC, the descriptive analyses of the PFS and OS results comparing the T + D + SoC and D + SoC treatment regimens demonstrate numerically similar median PFS and OS results. Due to the lack of formal comparisons between the PFS and OS results in the two experimental arms, a statistically significant difference between arms cannot be demonstrated. However, separation of the OS Kaplan-Meier curves during the trial follow-up period was observed when comparing the T + D + SoC and D + SoC arms, supporting the Applicant's position of an incremental benefit that increases over time with the addition of tremelimumab.

- Cognizant of caveats of cross-trial comparisons, such as variability of performance between trials, FDA also considered the Applicant's retrospective assessments of the MYSTIC study, in which durvalumab with or without tremelimumab was compared to platinum-based chemotherapy in patients with previously untreated, metastatic NSCLC, to support the addition of tremelimumab to the overall regimen. The primary analysis population in MYSTIC was comprised of the subgroup of patients with a PD-L1 tumor composite score (TC) of ≥ 25%, whereas the POSEIDON study evaluated a PD-L1 unselected population. Based upon a retrospective subgroup assessment of the results of MYSTIC, the Applicant hypothesizes that patients with low/negative PD-L1 expression may derive the greatest benefit from CTLA-4 inhibition; this pattern of benefit is also noted in the subgroup analysis of patients with PD-L1 expression <1% in POSEIDON in which a OS HR of 0.75 (95% CI: 0.56, 0.99) and an OS landmark rate of 20% vs 10% at 36 months was observed favoring T + D + SoC over D + SoC.
  FDA did not independently verify results from the MYSTIC study but acknowledges the Applicant's position regarding the retrospective, exploratory analyses of MYSTIC.

Regarding the mechanistic plausibility of dual immune checkpoint blockade for the treatment of NSCLC, results of two studies of nivolumab and ipilimumab with or without platinum-based chemotherapy provide supportive evidence for the additive benefit of CTLA-4 blockade to the longstanding paradigm of the use of anti-PD-(L)1 therapies for the treatment of patients with metastatic NSCLC:

- Nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy is an approved regimen for the treatment of patients with metastatic NSCLC based on the results of CHECKMATE-9LA in which the combination regimen demonstrated a statistically significant improved median OS of 14.1 months (95% CI 13.2, 16.2) over the 10.7 month (95% CI 9.5, 12.5)

median OS observed with chemotherapy (OPDIVO USPI).

- Nivolumab in combination with ipilimumab is an approved regimen for the treatment of patients with metastatic NSCLC with PD-L1 tumor expression ≥ 1% based on the results of CHECKMATE-227 in which the combination regimen demonstrated a statistically significant improvement in median OS of 17.1 months (95% CI 15, 20.1) over platinum-doublet chemotherapy (mOS 14.9 months [95% CI 12.7, 16.7]) (OPDIVO USPI).

Additionally, FDA has granted approval of dual immune checkpoint blockade regimens for the treatment of patients with esophageal cancer, hepatocellular carcinoma, malignant pleural mesothelioma, melanoma, and renal cell carcinoma, providing supportive evidence for their efficacy in solid tumors.

In summary, the contribution of components of T + D + SoC in POSEIDON was assessed descriptively primarily through in-trial comparisons to the D + SoC arm. The benefit of adding tremelimumab to the combination was demonstrated by small improvements in PFS and OS observed in the T + D + SoC arm compared to the D + SoC arm which increased in magnitude and were sustained over time. In addition, external results from studies supporting the approvals of nivolumab in combination with ipilimumab with or without two cycles of platinum-based chemotherapy provide mechanistic plausibility for the efficacy of dual immune checkpoint blockade for the treatment of patients with metastatic NSCLC.

Additional Analyses Conducted on the Individual Trial

Data:

In order to aid interpretation, a post-hoc analysis was conducted to determine the confirmed ORR, defined as the number (%) of patients with at least one visit, response of CR or PR and a confirmatory scan no sooner than 4 weeks after the initial CR/PR.

The Applicant's Position:
A post-hoc analysis of confirmed ORR demonstrated 14.4% incremental improvement favoring T + D + SoC vs SoC (38.8% vs 24.4%, respectively; odds ratio: 2.00; 95% CI: 1.428, 2.807; nominal p<0.001). A post-hoc analysis, based on patients with a confirmed ORR, showed durable responses with T + D + SoC compared with SoC alone (median DoR: 9.5 months vs 5.1 months, respectively). For patients who had a confirmed ORR, the percentage of responders with an estimated DoR of 12 months or longer was 49.7% in the T + D + SoC arm compared with 21.4% in the SoC chemotherapy arm.

The FDA's Assessment:
FDA acknowledges the Applicant's presentation of ORR and DOR results in this section. FDA considers these results from post-hoc analyses are exploratory only.

Integrated Review of Effectiveness

The FDA's Assessment:

See FDA's comment under "Efficacy Results – Contribution of Components."

Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Two studies from the Applicant's clinical program – MYSTIC and NEPTUNE – provide supportive evidence of clinical activity of the tremelimumab and durvalumab (T + D) combination in 1L metastatic NSCLC patients. Key similarities and differences between the pivotal POSEIDON and supportive MYSTIC and NEPTUNE studies are summarized in Table 28.

Table 28 Key similarities and differences between POSEIDON, MYSTIC, and NEPTUNE studies

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

1L First-line; NSCLC Non-small cell lung cancer; TC Tumor cell; PD-L1 Programmed cell death ligand-1; SoC Standard-of-care chemotherapy; T + D Tremelimumab in combination with durvalumab; bTMB Blood tumor mutational burden.

MYSTIC

MYSTIC was a Phase III, randomized, open label study in patients with metastatic NSCLC (Table 3). It was designed to compare the efficacy and safety of durvalumab with or without tremelimumab (D; T + D) vs. that of SoC alone as 1L treatment in metastatic NSCLC. The 3 primary efficacy objectives were to assess the efficacy of durvalumab vs. SoC in terms of OS, and, separately, durvalumab + tremelimumab vs. SoC in terms of OS and PFS in patients with high PD L1 expression (ie, PD L1 TC ≥25%).

D vs. SoC: Treatment with durvalumab demonstrated a clinically meaningful improvement in OS compared to SoC alone (HR: 0.76; 97.54% CI: 0.564, 1.019; p=0.036). However, the comparison did not reach the threshold of statistical significance according to the MTP, with the alpha level split across 3 primary endpoints and an alpha of 0.0246 applied for this endpoint to mark the significance boundary. Despite crossing Kaplan Meier curves indicative of non proportional hazards, which has also been seen with other PD-1/PD-L1 monotherapies in comparison to SoC chemotherapy, the observed HR of 0.76 revealed an improvement favoring durvalumab monotherapy versus SoC chemotherapy that was

additionally substantiated by higher OS rates in landmark timepoint analyses beyond 12 months. The Kaplan Meier estimate of median OS was 16.3 months (95% CI: 12.2, 20.8) for the durvalumab arm vs. 12.9 months (95% CI: 10.5, 15.0) for the SoC arm. The estimated survival rates at 18 and 24 months were higher on durvalumab vs. SoC (18 months: 47.8% vs. 33.6%; 24 months: 38.3% vs. 22.7%), indicating improved longer term treatment benefit over SoC. The near miss of statistical significance in the primary analysis may have also been influenced by the markedly higher proportion of SoC patients (39.5%) who received subsequent immunotherapy after discontinuation of initial study treatment compared to those on durvalumab (39.5% vs. 6.1%, respectively).

T + D vs. SoC**:** While treatment with tremelimumab + durvalumab (T + D) did not significantly improve OS or PFS vs. SoC (OS HR: 0.85 [98.77% CI: 0.611, 1.173]; p=0.202; PFS HR: 1.05 [99.5% CI: 0.722, 1.534]; p=0.705), a favorable trend for OS was observed. The alpha was split across 3 primary endpoints and an alpha of 0.0123 was applied for the OS endpoint to mark the significance boundary. Despite crossing Kaplan Meier curves indicative of non-proportional hazards, the observed HR of 0.85 revealed a trend favoring tremelimumab + durvalumab versus SoC chemotherapy that was also supported by higher OS rates in landmark timepoint analyses beyond 12 months. The proportion of patients alive was higher on durvalumab + tremelimumab arm vs. SoC arm at 18 and 24 months (OS18: 42.4% vs. 33.6%, and OS24: 35.4% vs. 22.7%, respectively) as was the proportion of patients alive or progression free at 12 months (PFS12: 25.8% vs. 14.3%), supporting prolonged benefit with tremelimumab + durvalumab over SoC. An imbalance in subsequent immunotherapy and systemic therapy between the tremelimumab + durvalumab and SoC chemotherapy may have also confounded results of the OS analyses (11.1% vs. 39.5%, respectively).

NEPTUNE

NEPTUNE was a Phase III, randomized, open label study in patients with metastatic NSCLC. It was designed to compare the efficacy and safety of durvalumab + tremelimumab vs. that of SoC alone as 1L treatment in metastatic NSCLC. 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.

In the bTMB ≥20 mut/Mb analysis set (n=129), a clinically meaningful improvement in OS was observed for durvalumab + tremelimumab vs. SoC, with the durvalumab + tremelimumab treatment demonstrating a reduction in the risk of death by 29% compared with SoC. However, with only 62% of the Full Analysis Set evaluable for bTMB, the treatment comparison did not reach the threshold of statistical significance (HR: 0.71; 95% CI: 0.485, 1.045; p=0.0808), based on the power provided by 69 and 60 patients with bTMB ≥20 mut/Mb in the T + D and SoC treatment groups, respectively.

The Applicant's Position:

MYSTIC and NEPTUNE studies were conducted in a patient population that was relevant to POSIEDON. The key similaries and differences between POSEIDON and MYSTIC/NEPTUNE are summarized in Table 28. The results of both MYSTIC and NEPTUNE indicated that, as 1L treatment for metastatic NSCLC, the combination of tremelimumab and durvalumab provided a favorable OS trend compared with SoC chemotherapies. While the treatment comparison between T + D vs. SoC did not cross the prespecified

statistical threshold, OS trends favoring the T + D combination were observed compared with SoC alone. Kaplan Meier estimates of survival landmarks in both studies indicated that treatment effects with tremelimumab + durvalumab were sustained over long term. For additional details on the MYSTIC and NEPTUNE efficacy results, see Module 2.7.3 and MYSTIC and NEPTUNE CSRs, Module 5.3.5.1.

The FDA's Assessment:

FDA acknowledges the Applicant's presentation of results from MYSTIC and NEPTUNE to provide supportive data demonstrating the clinical activity of tremelimumab and durvalumab combination therapy in patients with metastatic NSCLC. The results presented in this section were not independently verified by the FDA.

Secondary and Other Endpoints

Data:
Not applicable.

The Applicant's Position:
Both MYSTIC and NEPTUNE studies provide supportive evidence of clinical activity of the tremelimumab and durvalumab (T + D) combination in 1L metastatic NSCLC. For brevity, the evidence focused on the primary efficacy endpoints of the 2 studies. For secondary and other efficacy endpoints, refer the respective CSRs in Module 5.3.5.1.

The FDA's Assessment:
FDA acknowledges the Applicant's statement regarding results from MYSTIC and NEPTUNE.

Subpopulations

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees.

Additional Efficacy Considerations

The FDA's Assessment:

None.

Integrated Assessment of Effectiveness

Data:

- The combination of tremelimumab, durvalumab, and chemotherapy demonstrated a statistically significant and clinically meaningful PFS (HR: 0.72; 95% CI: 0.600, 0.860; p=0.00031) and OS (HR:

0.77; 95% CI: 0.650, 0.916; p=0.00304) benefits compared with chemotherapy alone. The short course of tremelimumab, a CTLA-4 antibody and a potential new medicine, in combination with durvalumab and SoC chemotherapy improved PFS by 28% and OS by 23% compared with chemotherapy alone. The survival benefits with T + D + SoC were supported by numerically higher response rates and durable responses.

- The survival benefits favoring T + D + SoC over SoC were consistent across all prespecified subgroups with all point estimate OS HRs<1, except for non-smokers where results should be interpreted with caution, given the small sample size and wide confidence interval. The survival benefits were more pronounced in patients with non-squamous histology compared with those with squamous histology.

- The survival benefits with T + D + SoC vs. SoC alone were sustained over long-term (OS24: 32.9% vs. 22.1%, respectively; OS36: 25.3% vs. 13.3%, respectively).

- The individual components of the T + D + SoC regimen provided distinct contributions to the treatment effect: (1) chemotherapy provided initial disease control, and (2) tremelimumab and durvalumab complement each other to provide long-term benefits.

The Applicant's Position:
POSEIDON was a positive study and met one of its primary efficacy objectives for success.

POSEIDON study demonstrated that, as first-line treatment in patients with metastatic NSCLC, the combination of tremelimumab, durvalumab, and SoC chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS and PFS compared with SoC chemotherapy alone.

The FDA's Assessment:
FDA's independent analyses of the efficacy results for POSEIDON, in general, are consistent with the Applicant's position and presentation on the efficacy results for the key secondary endpoints of BICR-assessed PFS and OS comparing T + D + SoC and SoC.

POSEIDON met one of its primary endpoints of BICR-assessed PFS comparing D + SoC and SoC and key secondary endpoints of BICR-assessed PFS and OS comparing T + D + SoC and SoC in the intent-to-treat population of adult patients with metastatic non-small cell lung cancer (NSCLC), with results that were statistically significant and clinically meaningful. T + D + SoC yields a net favorable benefit-risk profile compared to SoC in the intended population.

Due to limitations in the design of POSEIDON with respect to PRO assessment and analysis, FDA was not able to conclude that the treatment regimen resulted in a clinically meaningful improvements on PROs.

Subgroup analyses results should be interpretated with caution due to the nature of these analyses. Regarding contribution of components of individual drugs to the combination, please refer to FDA's comments under "Efficacy Results – Contribution of Components" section above.

Review of Safety

Data:
The evidence supporting the safety and tolerability claims in the proposed indication is based on the results of the pivotal POSEIDON study, a Phase III, randomized, multi-center, open-label, comparative global study, and this study is the primary source of safety data in this application.

In addition, this application package includes Supportive Safety Data that comprises 2 safety pools: Tremelimumab + Durvalumab + Chemotherapy Pool (ie, T + D + Chemo Pool; N=596) and Tremelimumab + Durvalumab Pan Tumor Pool (ie, T + D Pan Tumor Pool; N=2280). Data supporting safety and tolerability claims are presented in the below sections.

The Applicant's Position:

Overall, the safety data across the POSEIDON T + D + SoC arm, T + D + Chemo pool and T + D pan-tumor pool demonstrated that the combination of tremelimumab, durvalumab and SoC chemotherapy had a manageable and tolerable safety profile.

The AEs reported in the T + D + SoC arm were consistent with the known safety and tolerability profiles of tremelimumab and durvalumab combination, and in line with the established safety profiles of individual chemotherapies. The addition of tremelimumab and durvalumab to chemotherapy did not compromise the ability to administer the proposed combination therapy of T + D + SoC in POSEIDON. No new safety concerns were identified.

The FDA's Assessment:
The primary safety population is comprised of the 330 patients who received T + D + SoC in POSEIDON. To further support the safety analysis, FDA evaluated a pooled safety population of 596 patients with lung cancer who were treated with tremelimumab 75 mg with durvalumab 1500 mg and platinum-based chemotherapy enrolled in POSEIDON (n=330) and CASPIAN (n=266). Patients enrolled in CASPIAN had ES-SCLC. FDA generally agrees with the Applicant that the AEs reported in the T + D + SoC arm were consistent with the known safety profiles of immune checkpoint inhibitors and the individual chemotherapies.

As patients in the Applicant's T + D Pan-Tumor Pool received variable dosing regimens of tremelimumab and durvalumab, data from this pooled population were not independently analyzed in FDA's review of the safety of the study regimen.

Safety Review Approach

The Applicant's Position:

The Applicant has in place robust and rigorous safety reporting procedures that are designed to meet regulatory requirements worldwide. Safety surveillance activities for tremelimumab and durvalumab are conducted on an ongoing basis and involve scheduled reviews of the global drug safety database, clinical study data, and published literature.

The safety data from the pivotal POSEIDON study and the 2 supportive safety pools are adequate to evaluate the safety and tolerability profile of T + D + SoC.

The evidence supporting the safety claims in the proposed indication is based on the final analysis of the POSEIDON study.

The assessment of safety, tolerability, and immunogenicity is supported by safety assessments in 2 pooled datasets. Durvalumab + Tremelimumab + Chemotherapy Pool (T + D + Chemo Pool) and Tremelimumab + Durvalumab Pan-Tumor Pool (T + D Pan-Tumor Pool) (Table 19). This pool provides a large dataset to detect and characterize uncommon AEs and support evaluation of the overall T + D safety profile, AESIs, and imAEs.

The FDA's Assessment:
FDA agrees with the Applicant's description of the safety review approach.

Review of the Safety Database

Overall Exposure

Data:
The exposure to tremelimumab and durvalumab immunotherapies is summarized by their overall exposure. The exposure to chemotherapies is summarized by that in the combination stage ("During Chemotherapy"; Figure 12) and maintenance stage ("Post Chemotherapy"; Figure 12).

- T + D + SoC arm: The median exposure to tremelimumab was 20 weeks (range: 1.1 to 38.3). Patients received a median of 5 cycles of tremelimumab (range: 1 to 9); the planned 5 cycles of tremelimumab were completed by 66.1% of patients. Overall, the median exposure to durvalumab was 29.79 weeks (range: 1.1 to 189.6). Patients received a median of 8 cycles of durvalumab (range: 1 to 49). Per study design, patients continued on durvalumab until disease progression; with 41.8% of patients receiving at least 10 cycles of durvalumab treatment.
- The median exposure to chemotherapy in the combination stage was 12.14 weeks (range: 1.1 to 50.9). A total of 78.5% of patients received 4 cycles of chemotherapy in the combination stage. In the maintenance stage, the median exposure to chemotherapy was 32 weeks (range: 2.9 to 177.3), driven by the pemetrexed maintenance allowed.
- SoC alone arm: In the combination stage, the median exposure to chemotherapy was 12.3 weeks (range: 0.7 to 24.3). Per study design, after the initial 4 cycles, patients could receive additional 2 cycles of chemotherapy (a total of 6 cycles), as clinically indicated and per Investigator's discretion. A total of 74.2% of patients received ≥4 cycles, 27.3% of patients received ≥5 cycles, and 23.1% of patients received 6 cycles of chemotherapy. In the maintenance stage, the median exposure to chemotherapy was 19 weeks (range: 0.1 to 172.3), driven by the pemetrexed maintenance allowed.

In both T + D + SoC and SoC arms, patients were administered histology specific, platinum based chemotherapies per local treatment guidelines. Chemotherapies were balanced between the T + D + SoC and SoC arms, including abraxane doublet (7.3% vs. 5.1%, respectively), gemcitabine doublet (32.5% vs. 33.6%), and pemetrexed doublet (60.2% vs. 61.3%). Per study design, patients who received

pemetrexed as part of their chemotherapy were permitted to continue with it as maintenance. Of the 198 patients in the T + D + SoC arm who had received pemetrexed doublet, 149 (75.3%) continued with pemetrexed maintenance, and of the 204 patients in the SoC arm who had received a pemetrexed doublet, 131 (64.2%) continued with pemetrexed maintenance.

The Applicant's Position:
Overall, the extent of exposure to T + D + SoC and SoC was in line with the planned study design and was adequate to assess the safety and tolerability of tremelimumab, durvalumab, and the administered chemotherapies. The addition of tremelimumab and durvalumab did not compromise the ability to administer the planned chemotherapy.

The FDA's Assessment:
FDA agrees that the extent of patients' exposure to T + D + chemo was adequate to assess the safety and tolerability of tremelimumab and durvalumab in combination with standard first-line chemotherapies. The majority of patients in the safety population (66%) received all five doses of tremelimumab, while 79% of patients received at least four doses.

Relevant characteristics of the safety population:

Data:

For the analyses of the demographic and baseline disease characteristics, see Section 0 and Table 2.7.4.1.2A and Table 2.7.4.1.2B, Module 5.3.5.3.

The Applicant's Position:

POSEIDON: Overall, the demographics and baseline disease characteristics of the patient population in POSEIDON study were generally representative of treatment-naïve patients with metastatic NSCLC who are eligible to receive frontline treatment.

POSEIDON vs T + D + Chemo pool and T + D Pan-tumor pool: Demographics and baseline characteristics in the T + D + SoC arm of POSEIDON were consistent with the T + D + Chemo pool. Compared with the T + D pan-tumor pool, there were more male patients (80.0% vs 69.5%) and more smokers (82.7% vs 71.2%), and fewer white patients (60.9% vs 68.7%) in the T + D + SoC arm of POSEIDON.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the demographics and baseline characteristics of the POSEIDON study population as presented in Table 23. The majority of patients in the primary safety population and T + D + chemo pooled safety population were male (80% and 78% respectively). The median age of patients in the primary and pooled safety populations was 63 years old, with 33% of patients from each population ≥ 65 years old. The majority of patients in the primary and pooled safety populations were White (61% and 70% respectively). A total of 21 patients (6.4%) in POSEIDON were enrolled in the U.S. Most patients enrolled in the primary and pooled safety population were current or former smokers (83% and 88% respectively).

FDA agrees that the demographics and baseline characteristics of the primary safety population for the

T + D + SoC arm of POSEIDON are generally reflective of the U.S. patient population with treatment-naïve, metastatic NSCLC. While a minority of patients enrolled in POSEIDON were from the U.S., the clinical trial was conducted globally, in multiple regions, enrolling patients from Asia, Europe, South America, and Russia. However, Black patients were underrepresented accounting for only 2.0% of randomized patients in the trial. Additionally, the median age of patients in the trial was 63 years old while patients diagnosed with NSCLC in the U.S. are older with a median age at diagnosis of approximately 70 years old (Howlader, SEER Cancer Statistics Review, 1975-2017).

Adequacy of the safety database:

Data:

The evidence supporting the safety and tolerability claims in the proposed indication is based on the results of the pivotal POSEIDON study. It includes 330 patients in the T + D + SoC arm who received at least 1 dose of the study treatment compared with 333 patients in the SoC arm who received at least 1 dose of the study treatment. In addition, this application package includes Supportive Safety Data that comprises 2 safety pools: Tremelimumab + Durvalumab + Chemotherapy Pool (ie, T + D + Chemo Pool; N=596) and Tremelimumab + Durvalumab Pan-Tumor Pool (ie, T + D Pan-Tumor Pool; N=2280).

The Applicant's Position:

The size of the safety database for POSEIDON, supported by the pool of studies in T + D + Chemo Pool and T + D Pan Tumor Pool are considered adequate to support the safety and tolerability assessment for the use of tremelimumab in combination with durvalumab and platinum based chemotherapy in the intended patient population.

The FDA's Assessment:

FDA agrees with the Applicant's position that the safety data from POSEIDON and the supportive pooled safety population of 596 patients enrolled in POSEIDON and CASPIAN and treated with T + D + platinum-based chemotherapy permit adequate assessment of the safety profile of durvalumab and tremelimumab in combination with chemotherapy.

FDA did not independently verify the safety data from the T + D Pan Tumor Pool given that these patients received variable doses of tremelimumab in combination with durvalumab and did not receive chemotherapy as part of the regimen.

Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
No issues relating to data integrity or quality were identified for the POSEIDON study.

The Applicant's Position:
The submission contains all required components of the eCTD. The overall quality and integrity of the application is adequate for substantive review to be completed. No meaningful concerns affecting a complete review of safety have been reported.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Categorization of Adverse Event

Data:
N/A, please see The Applicant's position.

The Applicant's Position:

The evaluation of safety and tolerability was based on the overall incidence of AEs, Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) Grade 3 or 4 AEs, serious adverse events (SAEs), AEs resulting in death, AEs resulting in permanent discontinuation of durvalumab or tremelimumab, AEs resulting in dose delays or infusion interruptions, adverse events of special interest (AESIs), adverse events of possible interest (AEPIs), and immune mediated adverse events (imAEs), and on data pertaining to clinical laboratory results (clinical chemistry, hematology, and urinalysis), vital signs ECGs, and physical examination findings.

The relationship between the study treatment and AEs was also assessed by the investigator. Given that the POSEIDON study is an open label study with an active comparative group, and the subjective nature of causality assessments, the safety results discussed in this document focus on overall safety profile, regardless of causality.

The integrated analysis of AEs for the safety pools was based on all treatment-emergent adverse events (TEAEs) as defined in each individual study. There are some minor differences in data conventions. These differences are minor and they do not have a significant impact on the ability to pool data from these studies.

Medical Dictionary for Regulatory Activities (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.

Adverse events of special interest (AESIs), Adverse events of possible interest (AEPIs) and immune-mediated adverse events (imAEs) are defined in the sponsors clinical development program and are described in the CSR (see Section 12.2.3, POSEIDON CSR, Module 5.3.5.1). The algorithm for determining

the imAEs is described in full in the latest version of the AstraZeneca imAE Charter (Appendix 16.1.9, POSEIDON CSR, Module 5.3.5.1).

The FDA's Assessment:
FDA agrees with the Applicant's position on the categorization of adverse events for POSEIDON. AEs were coded using MedDRA version 23.1 and were graded according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0). The safety assessment focused on the frequency and severity of all treatment-emergent AEs (TEAEs) from POSEIDON, which were defined as AEs occurring after the first dose of study treatment to within 30 days after the last dose of study therapy. Additional analyses included assessment of TEAEs leading to death, serious adverse events (SAEs), and TEAEs leading to dose reduction, interruption, or permanent discontinuation of T + D + SoC. The FDA review was completed using MedDRA preferred terms (PTs) and CTCAE grade as well as custom grouped terms (GTs) when performing independent analyses of immune-related AEs (imAEs).

During the course of the POSEIDON study, the Applicant redefined the process for identifying immune-mediated AEs (imAEs) with additional revision to the criteria for defining adverse events of special interests (AESIs) and adverse events of potential interest (AEPIs). These were consistent modifications across the durvalumab development program and were developed with input from the FDA. The Applicant's description of the revised process is provided below.

AESIs are defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy.

AEPIs are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes.

AESI and AEPI event categories for durvalumab include diarrhea/colitis and intestinal perforation, pneumonitis/ILD, hepatitis/transaminase increases, endocrinopathies (adrenal insufficiency, hyperthyroidism, hypothyroidism, hypophysitis/hypopituitarism, and Type I diabetes mellitus), nephritis/blood creatinine increases, rash/dermatitis, pancreatitis/serum lipase and amylase increases, myocarditis, myositis/polymyositis, and neuropathy/neuromuscular toxicity (e.g., Guillain-Barre and myasthenia gravis). Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology are AESI and AEPI event categories as well and include pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematologic and rheumatologic events, and infusion-related/hypersensitivity/anaphylactic reactions.

The imAEs were determined by a programmatic algorithm that requires specific treatment for AESIs to be considered imAEs such as systemic corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (e.g., therapies for hyperthyroidism including beta blockers, calcium channel blockers, methimazole, propylthiouracil, and sodium perchlorate). Guidance for identifying,

evaluating, and treating imAEs was provided to the investigators at the initiation of the study.

The same specific treatment is also required for AEPIs, however, this requirement in the programmatic algorithm was applied only to AEPIs that were retained for further treatment consideration after identifying those that have been assessed by the investigator as causally related to any study treatment and/or as an imAE.

Routine Clinical Tests

Data:
N/A, please see The Applicant's Position.

The Applicant's Position:

The pooled laboratory analyses are based on the data collected during the treatment period, which is defined as up to 90 days after the last dose of study treatment or date of initiation of subsequent systemic anticancer therapy excluding palliative radiotherapy (whichever occurred first). Clinical chemistry and hematology laboratory parameters were evaluated at 1 month, 2 months, and 3 months after the last dose of study treatment, depending on the study, for all patients who discontinued study treatment. Thyroid laboratory parameters were evaluated up to at least 1 month after study drug discontinuation.

All laboratory values are graded according to CTCAE version 4.03 and the reference ranges used in the individual studies.

The FDA's Assessment:
FDA agrees with the Applicant's position. The safety monitoring plan was adequate and consistent with standard of care. Routine laboratory assessments were required within 28 days of randomization, then on days 1 and 8 of the first four cycles of therapy, and then at the start of cycle 5 and each cycle thereafter until disease progression.

Safety Results

Deaths

Data:

Table 29 Adverse Events with Outcome of Death by Preferred Term in POSEIDON and the two safety pools (Incidence ≥ 2 patients in any Treatment Group) (Safety Analysis Set)

	Number (%) of patients [a]				
	POSEIDON		T + D + Chemo pool	Chemo pool	T + D Pan-tumor pool
Preferred term	T + D + SoC (N = 330)	SoC (N = 333)	(N = 596)	(N = 599)	(N = 2280)
Patients with any AE with outcome of death	**41 (12.4)**	**30 (9.0)**	**68 (11.4)**	**45 (7.5)**	**153 (6.7)**
Pneumonia	7 (2.1)	7 (2.1)	12 (2.0)	8 (1.3)	14 (0.6)

Preferred term	Number (%) of patients [a]				
	POSEIDON		T + D + Chemo pool (N = 596)	Chemo pool (N = 599)	T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)			
Sepsis	3 (0.9)	1 (0.3)	3 (0.5)	1 (0.2)	7 (0.3)
Septic shock	0	0	0	0	6 (0.3)
Febrile neutropenia	1 (0.3)	2 (0.6)	3 (0.5)	2 (0.3)	0
Pancytopenia	0	1 (0.3)	0	2 (0.3)	0
Cerebrovascular accident	2 (0.6)	1 (0.3)	2 (0.3)	2 (0.3)	3 (0.1)
Depressed level of consciousness	0	0	0	0	2 (< 0.1)
Ischaemic stroke	1 (0.3)	0	1 (0.2)	0	2 (<0.1)
Acute coronary syndrome	1 (0.3)		1 (0.2)	0	3 (0.1)
Cardiac arrest	0	0	1 (0.2)	1 (0.2)	4 (0.2)
Cardiac failure	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.2)	5 (0.2)
Cardiopulmonary failure	2 (0.6)	1 (0.3)	2 (0.3)	2 (0.3)	0
Acute respiratory failure	0	0	1 (0.2)	0	4 (0.2)
Asphyxia	0	0	0	0	2 (< 0.1)
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	2 (<0.1)
Dyspnoea	1 (0.3)	0	1 (0.2)	0	3 (0.1)
Interstitial lung disease	0	0	0	0	2 (< 0.1)
Pneumonia aspiration	0	0	0	0	4 (0.2)
Pneumonitis	1 (0.3)	0	3 (0.5)	2 (0.3)	7 (0.3)
Pulmonary embolism	1 (0.3)	5 (1.5)	3 (0.5)	5 (0.8)	10 (0.4)
Pulmonary haemorrhage	0	2 (0.6)	1 (0.2)	2 (0.3)	2 (<0.1)
Respiratory failure	0	0	1 (0.2)	0	3 (0.1)
Acute kidney injury	2 (0.6)	0	2 (0.3)	0	3 (0.1)
Death	3 (0.9)	1 (0.3)	7 (1.2)	3 (0.5)	10 (0.4)
Multiple organ dysfunction syndrome	0	0	1 (0.2)	0	3 (0.1)
Sudden cardiac death	0	0	0	1 (0.2)	3 (0.1)
Sudden death	0	0	3 (0.5)	1 (0.2)	5 (0.2)

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 the POSEIDON and Study 22.
MedDRA version 23.1; Source: see Table 2.7.4.3.1A and Table 2.7.4.3.1B, Module 5.3.5.3

In the POSEIDON study, full safety narratives were prepared for patients who an AE with an outcome of death. Safety narratives are also prepared for patients who died due to disease progression on study

treatment and within 30 days of the last dose. For brevity, this document does not summarise the narratives. They are submitted in the POSEIDON CSR, Section 14.4, Module 5.3.5.1. For narratives of deaths for all studies in the safety pool, refer to the respective CSRs.

The Applicant's Position:
As of the final analysis DCO, 251 (74.3%) patients died in the T + D + SoC arm, 265 (78.4%) patients died in the D + SoC arm, and 285 (84.6%) patients died in the SoC alone arm.

In POSEIDON and the safety pools, the majority of deaths were related to disease under investigation only. The AEs with an outcome of death in POSEIDON and the safety pools are provided below.

POSEIDON**:** The incidence of AEs with an outcome of death was numerically higher in the T + D + SoC arm than the SoC alone arm (12.4% vs 9.0%; Table 11). There is no particular pattern in the type of AEs that led to death and may reflect the longer exposure in this arm and the underlying co morbidities of the study population. The most common PT in both treatment arms was pneumonia, which was reported for 7 patients (2.1%) in each arm.
POSEIDON vs T + D + Chemo Pool**:** The incidence of AEs with an outcome of death in the T + D + Chemo pool was similar to that in the T + D + SoC arm of POSEIDON (12.4% vs 11.4%). Pneumonia was the most common PT (2.0%), with other AEs dispersed across a number of PTs with no obvious trend (Table 11).
POSEIDON vs T + D Pan-Tumor Pool**:** The incidence of AEs with an outcome of death was higher in POSEIDON compared with T + D pan-tumor pool (12.4% vs. 6.7%); however, no particular pattern was observed, and PTs were dispersed across system organ class; the most common PT was pneumonia (0.6%) (Table 11). It should be noted that in the D+T pool the indication and characteristics of studies diverse from the POSEIDON study, associated with the fact that chemotherapy wasn't used, may account for some of the differences observed.

The FDA's Assessment:
FDA reviewed all fatal adverse events that occurred within the primary safety population of POSEIDON as of the data cutoff of November 11, 2021. FDA agrees with the Applicant's assessment that there appears to be no pattern to the type of AEs leading to death between the T + D + SoC and SoC arms.

A total of 41 patients (12%) on the T + D + SoC arm had an AE leading to death; of these, the Applicant considered 11 patients (3.3%) to have had an AE leading to death that was at least possibly related to any part of study therapy. FDA reviewed the narratives of all fatal adverse events that occurred in the POSEIDON study and identified one patient (patient ID (b) (6)) on the T + D + SoC arm with a fatal adverse event of respiratory tract infection, one patient with a fatal event of COPD (patient ID (b) (6)), one patient with a fatal event of pneumonia (patient ID (b) (6)), one patient with a fatal event of dyspnea (patient ID (b) (6)), two patients with a fatal event of death (patient IDs (b) (6)), and one patient with a fatal event of sudden death (patient ID (b) (6)) for which the contribution of study therapy cannot be excluded,. In addition, one patient with a fatal event of sudden death identified by the investigator as related to study therapy more likely died of sudden cardiac death unrelated to study therapy, one patient with a fatal event of COVID-19 identified by the investigator as related to study therapy more likely died of COVID-19-related pneumonia and respiratory failure, and one patient with a fatal event of gastric ulcer perforation identified by the investigator as related to study therapy was considered unrelated by FDA's review (patient IDs (b) (6)

(b) (6)). Overall, according to FDA's assessment, a total of 14 patients (4.2%) had a fatal AE at least possibly related to study therapy. Table 30 provides a summary of all fatal adverse events not related to disease progression in POSEIDON.

Table 30: Summary of fatal TEAEs in POSEIDON (FDA review)

	T + D + SoC N=330	D + SoC N=334	SoC N=333
Total patient deaths due to AE	41 (12%)	34 (10%)	30 (9%)
Acute kidney injury, renal failure[a]	2	1	0
Acute myocardial infarction[b]	3	2	2
Autoimmune hepatitis	1	0	0
Autoimmune myocarditis	1	0	0
Autoimmune nephritis	1	0	0
Autoimmune pancreatitis	1	0	0
Cardiopulmonary failure	2	0	1
Cardiac arrest[c]	0	2	0
Cardiac failure[d]	2	1	1
Cellulitis	1	0	0
Cerebral infarction[e]	3	0	1
Chronic obstructive pulmonary disease	1	0	1
Suicide[f]	1	1	0
COVID-19[g]	2	0	1
Death[h]	4	9	1
Dehydration	1	0	0
Embolism	0	2	1
Febrile neutropenia	1	1	2
Gastric ulcer perforation	1	0	0
Hemophagocytic lymphohistiocytosis	0	1	0
Hemorrhage[i]	2	1	4
Nosocomial infection	1	0	0
Pancreatitis	0	0	1
Pancytopenia	0	0	1
Pneumonia[j]	7	9	8
Pneumonitis	1	0	0
Pulmonary embolism	1	3	5
Road traffic accident	0	1	0
Sepsis	3	1	1
Shock	1	0	0
Ventricular fibrillation	0	0	1

Source: ADAE (Adverse Events Analysis Dataset)_Overall Survival. Variables used: ACTARM, AEDECOD, AESDTH, USUBJID.
[a]Includes acute kidney Injury, renal failure
[b]Includes acute myocardial infarction, myocardial infarction, coronary artery disease, acute coronary syndrome

[c]Includes cardiac arrest, cardiac death
[d]Includes cardiac failure acute, cardiac failure
[e]Includes cerebral infarction, cerebrovascular accident, ischemic stroke
[f]Includes completed suicide, suicide attempt
[g]IncludesCOVID-19, COVID-19 pneumonia
[h]Includes death, sudden death
[i]Includes hemorrhagic stroke, gastric ulcer hemorrhage, pulmonary hemorrhage, shock hemorrhagic, subdural hemorrhage
[j]Includes pneumonia, pneumonia aspiration, pneumocystis jirovecii pneumonia, lower respiratory tract infection

Table 31 describes the fatal AEs that were individually reviewed and provides FDA's determination of death causality in greater detail.

Table 31: FDA Assessment of Causality for Fatal Adverse Events Not Clearly Attributable to Disease Progression or Well-Defined Alternative Etiology (FDA review)

Patient ID	Documented Cause of Death	Brief Narrative	FDA's Assessment of Causality	Included in USPI
(b) (6)	Pneumonia	65 year old male who was treated with T + D + SoC was hospitalized for Grade 3 pneumonia on study day 141, 76 days after his last dose of study therapy (D + T) and 69 days after his last dose of chemotherapy (gemcitabine). The patient died 10 days after the onset of Grade 3 pneumonia; details about his hospitalization were not available. The investigator attributed the death to pneumonia unrelated to D + T + SoC.	**Likely due to infectious pneumonia; unable to rule out contribution of T + D + SoC**	Yes
	Pneumonia	65 year old male who was found to have disease progression on study day 605, 57 days after receiving his last dose of D + T, in the setting of fever and positive blood cultures. The patient was hospitalized, diagnosed with hospital acquired pneumonia and disease progression, and treated with IV antibiotics. The patient died of pneumonia on study day 666.	**Due to infectious pneumonia and disease progression**	No
	Death	60 year old male with a history of ischemic cardiac disease, with an ECOG PS of 0 died on study day 20, 19 days after receiving the last infusion of durvalumab, tremelimumab, carboplatin, and 12 days after the last dose of gemcitabine. The patient lived alone and his brother found him deceased at home.	**Sudden death, unlikely due to study therapy** Given the patient's history of ischemic heart disease and	No

			sudden death, the cause of death was likely due to a sudden cardiac event and less likely due to study therapy	
(b) (6)	Pneumonia	75 year old male who developed fever, acute kidney injury, and pneumonia on study day 61. A CT scan also confirmed disease progression. The patient was hospitalized and treated with IV antibiotics and died of respiratory failure.	**Due to infectious pneumonia and disease progression**	No
	Respiratory tract infection	65 year old male who developed hypoxia on study day 103. A CT angiogram was negative for pulmonary emboli, but showed bibasilar interstitial lung changes which may have been inflammatory per the radiologist's interpretation. He was treated with oral steroids, broad spectrum antibiotics, and infliximab, and died on study day 113, 42 days after his last doses of D + T + SoC and 21 days after his last dose of durvalumab.	**Possibly due to immune-mediated pneumonitis** Given the CT findings and treatment with steroids and infliximab, immune-mediated pneumonitis cannot be excluded.	Yes
	Chronic obstructive pulmonary disease	81 year old male with a history of chronic obstructive pulmonary disease (COPD). On study day 172, 8 days after last D + T + SoC, the patient reportedly developed a COPD exacerbation and died at home.	**COPD; cannot rule out contribution of T + D + SoC** Patient had a history of two prior COPD exacerbations while on study but additional details about this event are not available.	Yes

(b) (6)	Pneumonia	54 year old female who developed sudden respiratory distress and was found to have bilateral diffuse lung infiltrates on study day 84, 30 days after last dose of D + T + Soc and 16 days after last dose of abraxane. Laboratory studies revealed leukocytosis with left shift; the patient was treated with IV antibiotics and died on study day 85.	**Likely due to infectious pneumonia** Given the sudden onset, leukocytosis, and treatment with IV antibiotics, this event was likely due to infectious pneumonia and less likely related to study therapy.	No
	Death	84 year old male who fell at home on study day 5 and had a traumatic femur fracture. On study day 151, the patient died, 36 days after last dose of tremelimumab and 8 days after last dose of durvalumab and pemetrexed. The study investigator suspected pneumonia. The reporting Investigator did not consider the death to be related to the disease under study. The primary cause of death was unknown, and the patient's guardian declined to share the patient's death certificate.	**Sudden death, cannot rule out contribution of T + D + SoC**	Yes
	Suicide attempt	79 year old male hung himself on a shed next to his house. He was resuscitated by emergency medical services , but subsequently had unstable hemodynamics. The patient died on study day 171.	**Completed suicide not due to study therapy**	No
	Pneumonia	84 year old male who was hospitalized for neck pain on study day 5, 4 days after the first dose of T + D + SoC, and developed fever on study day 6. On study day 8, a CT scan showed subpleural ground glass opacities in bilateral upper lobes and right lower lobe dependent portions. The patient was treated with broad-spectrum antibiotics and died on study day 14.	**Infectious pneumonia, unlikely due to study therapy**	No
	Pneumonia	77 year old male was found to have pneumonia via CT scan on study day 177. Influenza testing was positive. The patient died on study day 180.	**Infectious pneumonia unlikely due to study therapy**	No

(b) (6)				
	Death	51 year old male who died at home of unknown causes on study day 455, 13 days after his last dose of durvalumab and pemetrexed. No additional information was available.	**Death; cannot rule out contribution of T + D + SoC**	Yes
	Sudden death	67 year old male who collapsed and died at home on study day 46, 16 days after last dose of D + T + SoC and 9 days after last dose of gemcitabine. On study day 45, the patient complained of fatigue, dyspnea, and poor appetite.	**Sudden death; cannot rule out contribution of T + D + SoC**	Yes
	Dyspnea	67 year old male who developed grade 3 dyspnea on study day 844. The patient did not undergo any medical evaluation for the dyspnea. The patient died on study day 846, 10 days after receiving a dose of durvalumab.	**Sudden death with dyspnea; cannot rule out contribution of T + D + SoC**	Yes
	Pneumonia	69 year old male who had ECOG PS of 1 and widespread metastases at time of study entry received one cycle of T + D + SoC. On study day 3, the patient was hospitalized with pneumonia and grade 4 thrombocytopenia. The patient was treated with broad-spectrum antibiotics and vasopressors. On study day 14, the patient developed acute renal failure. The patient died on study day 16.	**Infectious pneumonia unlikely due to study therapy** Given the short onset after receipt of study therapy and treatment with IV antibiotics, this is not likely an event of immune-mediated pneumonitis.	No
	Pneumonia	61 year old female whose last dose of study treatment with T + D + SoC was on study day 22 after which study treatment was permanently discontinued because of the worsening of the patient's condition. On study day 44, the patient began second-line therapy with paclitaxel. The patient received 2 cycles of paclitaxel with the last infusion given on study day 6. On study day 77, a serious adverse event of renal failure was reported and progression of lung cancer was identified. The patient died on study day 91.	**Disease progression unlikely due to study therapy**	No

Source: D419MC00004 CSR Section 14.4 Narratives, Applicant response to FDA-issued IR.

Table 32 provides a summary of fatal adverse reactions included in the prescribing information for tremelimumab and durvalumab.

Table 32: Fatal adverse reactions in patients receiving T + D + SoC in POSEIDON (FDA review)

Patient ID	Adverse reaction
(b) (6)	Febrile neutropenia
	Renal failure
	Sepsis
	Acute kidney injury
	Autoimmune hepatitis
	Autoimmune myocarditis
	Autoimmune nephritis
	Autoimmune pancreatitis
	Ischemic stroke
	Pneumonitis
	Pneumonitis
	Sepsis
	COPD
	Dyspnea
	Death
	Death
	Sudden death

Serious Adverse Events

Data:

Table 33 Most Common SAEs in POSEIDON and the two safety pools (Incidence ≥ 1.0% in any treatment group) (Safety Analysis Set)

	Number (%) of patients				
	POSEIDON				
Preferred term	T + D + SoC (N = 330)	SoC (N = 333)	T + D + Chemo pool (N = 596)	Chemo pool (N = 599)	T + D Pan-tumor pool (N = 2280)
Any SAE	**146 (44.2)**	**117 (35.1)**	**267 (44.8)**	**214 (35.7)**	**1020 (44.7)**
Pneumonia	36 (10.9)	16 (4.8)	52 (8.7)	27 (4.5)	132 (5.8)
Anaemia	18 (5.5)	21 (6.3)	27 (4.5)	33 (5.5)	22 (1.0)
Diarrhoea	8 (2.4)	2 (0.6)	15 (2.5)	6 (1.0)	56 (2.5)
Pyrexia	8 (2.4)	1 (0.3)	8 (1.3)	3 (0.5)	42 (1.8)
Thrombocytopenia	8 (2.4)	3 (0.9)	14 (2.3)	12 (2.0)	4 (0.2)
Febrile neutropenia	7 (2.1)	4 (1.2)	18 (3.0)	16 (2.7)	0
Acute kidney injury	6 (1.8)	1 (0.3)	6 (1.0)	3 (0.5)	18 (0.8)
Pneumonitis	6 (1.8)	1 (0.3)	11 (1.8)	4 (0.7)	45 (2.0)
Colitis	5 (1.5)	0	10 (1.7)	0	39 (1.7)
Pulmonary embolism	5 (1.5)	9 (2.7)	12 (2.0)	9 (1.5)	34 (1.5)
Sepsis	5 (1.5)	2 (0.6)	5 (0.8)	3 (0.5)	21 (0.9)
Cerebrovascular accident	4 (1.2)	1 (0.3)	4 (0.7)	4 (0.7)	8 (0.4)
Neutropenia	4 (1.2)	3 (0.9)	9 (1.5)	10 (1.7)	2 (<0.1)
Death	3 (0.9)	1 (0.3)	7 (1.2)	3 (0.5)	10 (0.4)
Dyspnoea	3 (0.9)	2 (0.6)	5 (0.8)	5 (0.8)	42 (1.8)
Hyponatraemia	3 (0.9)	1 (0.3)	12 (2.0)	5 (0.8)	18 (0.8)
Dehydration	2 (0.6)	2 (0.6)	2 (0.3)	2 (0.3)	23 (1.0)
Enterocolitis	2 (0.6)	0	6 (1.0)	0	9 (0.4)
Vomiting	2 (0.6)	0	5 (0.8)	3 (0.5)	27 (1.2)
Pleural effusion	0	2 (0.6)	1 (0.2)	4 (0.7)	27 (1.2)
Abdominal pain	0	0	0	1 (0.2)	24 (1.1)
Back pain	0	0	0	1 (0.2)	24 (1.1)

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).
COVID-19 events only apply to POSEIDON and Study 22.
MedDRA version 23.1; Source: see Table 2.7.4.4.3A and Table 2.7.4.4.3B, Module 5.3.5.3.

The Applicant's Position:

POSEIDON**:** The incidence of SAEs was higher in the T + D + SoC arm compared with the SoC alone arm (44.2% vs 35.1%) (Table 33). The most common PT in each arm was pneumonia, which had a higher incidence in the T + D + SoC arm compared with the SoC alone arm (10.9% vs 4.8%). The only other ≥ 2% difference in incidence between treatment arms was for pyrexia; the events were generally of CTCAE Grade 1 or 2 severity. There were no actions taken regarding the study treatment for all SAEs of pyrexia..

POSEIDON vs T + D + Chemo Pool**:** The incidence of SAEs between the T + D + SoC arm of POSEIDON and the T + D + Chemo pool was similar.

POSEIDON vs T + D Pan-tumor Pool**:** The incidence of SAEs between the T + D + SoC arm of POSEIDON and the T + D pan-tumor pool was similar. Compared with the T + D pan tumor pool, the incidence of SAEs with PT pneumonia was higher in the T + D + SoC arm of POSEIDON. The lower incidence of pneumonia in the T + D Pan-tumor pool could be due to varied patient populations with non-thoracic malignancies. The incidence of anemia, thrombocytopenia, and febrile neutropenia was also higher in the POSEIDON T + D + SoC arm, which is possibly related to the chemotherapy component in POSEIDON.

The FDA's Assessment:
FDA agrees that the incidence of SAEs were higher in the T + D + SoC arm compared with the SoC arm (44% vs 37%). Grade ≥3 SAEs occurred at a rate of 33% and 27% in the T + D + SoC and SoC arms respectively. The most common SAE was pneumonia defined by a grouped term including Candida pneumonia, lower respiratory tract infection, Pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia klebsiella, which occurred in 11% of patients who received T + D + SoC and 6% of patients who received SoC. Common SAEs (≥2%) that occurred in patients who received T + D + SoC were pneumonia (11%), anemia (5), diarrhea (2.4%), pyrexia (2.4%), thrombocytopenia (2.4%), and febrile neutropenia (2.1%).

SAEs for which there was a ≥1% difference in incidence between treatment arms T + D + SoC and SoC are summarized in Table 34.

Table 34: SAEs with ≥1% difference in incidence rates of SAEs between treatment arms of T + D + SoC and SoC (FDA review)

SAE	T + D + Soc (n=330) %	SoC alone (n=333) %	D + SoC (n=334) %
Total SAE	44	37	43
Acute kidney injury[a]	1.8	0.3	1.2
Diarrhea	2.4	0.6	2.1
Pneumonia[b]	11	5.7	7.2
Pneumonitis[c]	1.8	0.6	0.6
Pyrexia	2.4	0.3	0.3

Source: ADSL (Subject-Level Analysis Dataset)_Overall Survival, ADAE (Adverse Events Analysis Dataset)_ Overall Survival.
Variables used: ACTARM, USUBJID, AEDECOD, AAE003FL.
Grouped Terms:
[a]Acute kidney injury: acute kidney injury, renal impairment
[b]Pneumonia: candida pneumonia, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella

[c]Pneumonitis: interstitial lung disease, pneumonitis

The addition of tremelimumab to the D + SoC treatment regimen did not appear to increase the incidence of SAEs that occurred in the D + SoC arm (44% vs. 43%). SAEs with a ≥1% higher incidence in the T + D + SoC arm compared to the D + SoC arm included pneumonia, pneumonitis, and pyrexia.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 35 Most common AEs Leading to Discontinuation of any Study Treatment in POSEIDON and the two safety pools (reported for ≥ 2 patients in the POSEIDON T + D + SoC arm) (Safety Analysis Set)

	Number (%) of patients				
	POSEIDON		T + D + Chemo Pool (N = 596)	Chemo Pool (N = 599)	T + D Pan-tumor pool (N = 2280)
Preferred term	T + D + SoC (N = 333)	SoC (N = 330)			
Any AE leading to discontinuation of any study treatment	**73 (22.1)**	**51 (15.3)**	**130 (21.8)**	**76 (12.7)**	**367 (16.1)**
Pneumonia	8 (2.4)	7 (2.1)	10 (1.7)	8 (1.3)	9 (0.4)
Anaemia	5 (1.5)	4 (1.2)	7 (1.2)	4 (0.7)	1 (<0.1)
Acute kidney injury	4 (1.2)	1 (0.3)	4 (0.7)	5 (0.8)	4 (0.2)
Blood creatinine increased	4 (1.2)	0	4 (0.7)	0	1 (<0.1)
Pneumonitis	3 (0.9)	1 (0.3)	5 (0.8)	1 (0.2)	35 (1.5)
Sepsis	3 (0.9)	0	3 (0.5)	0	6 (0.3)
Pulmonary embolism	2 (0.6)	4 (1.2)	4 (0.7)	4 (0.7)	6 (0.3)
Colitis	2 (0.6)	0	5 (0.8)	0	23 (1.0)
Diarrhoea	2 (0.6)	0	5 (0.8)	0	26 (1.1)
Nausea	2 (0.6)	1 (0.3)	4 (0.7)	1 (0.2)	2 (<0.1)
Drug-induced liver injury	2 (0.6)	0	2 (0.3)	0	5 (0.2)
Autoimmune nephritis	2 (0.6)	0	2 (0.3)	0	0
Fatigue	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.2)	5 (0.2)
Neutrophil count decreased	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.2)	0

Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
COVID-19 events only apply to POSEIDON and Study 22.
MedDRA version 23.1.
Source: see Table 2.7.4.5.1.1A and 2.7.4.5.1.1B, Module 5.3.5.3.

The Applicant's Position:

POSEIDON**:** The incidence of AEs leading to discontinuation of any study treatment was higher in the T +

D + SoC arm compared to the SoC alone arm (22.1% vs 15.3%) (Table 35). Pneumonia was the most common PT in both treatment arms. There was no clear trend in the type of events leading to discontinuation of any study treatment. See Section 14.4, POSEIDON CSR, Module 5.3.5.1 for narratives for all patients who had an AE that led to discontinuation of study treatment.

POSEIDON vs T + D + Chemo Pool**:** The incidence of AEs leading to discontinuation of study treatment was similar between the T + D + SoC arm of POSEIDON and the T + D + Chemo pool. The PTs of the individual AEs were also similar.

POSEIDON vs T + D Pan-tumor pool**:** The incidence of AEs leading to discontinuation of any study treatment was lower in the T + D pan tumor pool than in the POSEIDON T + D + SoC arm (16.1% vs 22.1%). This is possibly due to discontinuation of SoC chemotherapy, as there was less difference between the 2 groups in the incidence of AEs leading to discontinuation of tremelimumab or durvalumab (see Table 2.7.4.5.1.2B, Module 5.3.5.3).
Adverse events leading to discontinuation of durvalumab or tremelimumab were reported for a similar percentage of patients across the T + D + SoC arm of POSEIDON, T + D + Chemo pool, and T + D pan-tumor pool (see Table 2.7.4.5.1.2A and Table 2.7.4.5.1.2B, Module 5.3.5.3). There was no clear trend in the types of events leading to discontinuation of durvalumab or tremelimumab.

The FDA's Assessment:
In general, FDA agrees with the Applicant's position regarding AEs leading to treatment discontinuation and their incidences of 22% and 15% for the T + D + SoC and SoC arms, respectively. The addition of tremelimumab to D + SoC did not appear to increase the rate of AEs leading to treatment discontinuation, which occurred at a rate of 20% in the D + Soc arm.

A total of 17% of patients in the T + D + SoC arm of POSEIDON required discontinuation of either tremelimumab or durvalumab due to an AE; 13% of patients on the D + SoC arm had an AE requiring discontinuation of durvalumab.

The most common TEAE leading to treatment discontinuation in both the T + D + SoC and SoC arms was pneumonia (2.4% and 2.1% respectively). Additional TEAEs leading to treatment discontinuation in ≥1% of patients in the T + D + SoC arm included acute kidney injury (2.1%), diarrhea/colitis (1.5%), and anemia (1.5%). Minor variations in the incidences of AEs between the Applicant and the FDA's analyses are due to differences in preferred terms comprising each grouped term as described in Table 36.

Table 36: TEAEs leading to treatment discontinuation in ≥1% of patients in POSEIDON (FDA review)

	T + D + SoC (N=330) n (%)	Durva + SoC (N=334) n (%)	SoC (N=333) n (%)
Any TEAE	73 (22)	68 (20)	51 (15)
Pneumonia[a]	8 (2.4)	6 (1.8)	7 (2.1)
Acute kidney injury[b]	7 (2.1)	5 (1.5)	4 (1.2)
Diarrhea/colitis[c]	5 (1.5)	3 (0.9)	0 (0.0)

Anemia	5 (1.5)	6 (1.8)	4 (1.2)
Pulmonary embolism	2 (0.6)	3 (0.9)	4 (1.2)
Fatigue[d]	2 (0.6)	4 (1.2)	1 (0.3)

Sources: adsl.xpt, adae.xpt
a: Includes pneumonia, pneumonia aspiration
b: Includes acute kidney injury, creatinine renal clearance decreased, blood creatinine increased, renal failure, renal impairment
c: Includes colitis, diarrhea, enteritis, enterocolitis
d: Includes fatigue, asthenia

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

POSEIDON**:** The incidence of AEs leading to dose modification of any study treatment was higher in T + D + SoC arm than the SoC alone arm (62.4% vs 53.8%) (see Table 2.7.4.5.4A, Module 5.3.5.3). Events were most commonly in the Blood and Lymphatic Disorders system organ class. Events were reported for a wide range of PTs, with difference not ≥ 5% between treatment arms.

POSEIDON vs T + D + Chemo Pool**:** Compared to the T + D + Chemo pool, the incidence of AEs leading to dose modification of any study treatment was higher in the T + D + SoC arm of POSEIDON (62.4 vs 56.7%), but the type of events were similar (see Table 2.7.4.5.4A, Module 5.3.5.3). The incidence of AEs leading to dose modification of tremelimumab or durvalumab was similar between the T + D + SoC arm POSEIDON and the T + D + Chemo pool (52.7% vs 47.8%) (see Table 2.7.4.5.5A, Module 5.3.5.3).

POSEIDON vs T + D Pan-tumor pool**:** The incidence of AEs leading to dose modification of any study treatment was higher in the T + D + SoC arm of POSEIDON compared to that in the T + D pan-tumor pool (62.4% vs 27.3%) (see Table 2.7.4.5.4B, Module 5.3.5.3). Dose modification of the chemotherapy agents accounts for some of this difference but there still remained a higher incidence of dose modifications for tremelimumab or durvalumab in the T + D + SoC arm of POSEIDON compared to the T + D pan tumor pool (52.7% vs 27.3%). This may be due to the longer treatment duration in POSEIDON and management of toxicities by dose modifications. In the T + D pan-tumor pool, the most common SOCs were Investigations (6.1%), Infections and infestations (5.2%), and Gastrointestinal disorders (5.0%) (see Table 2.7.4.5.5B, Module 5.3.5.3).

The FDA's Assessment:
A total 59% of patients who received T + D + SoC had TEAEs leading to dose interruption of at least one of the agents in the combination regimen; this was similar to the incidence of TEAEs leading to dose interruption in the D + SoC arm (57%). Excluding laboratory abnormalities, the most common TEAEs (≥5%) leading to dose interruption were hepatitis and diarrhea/colitis.

Table 37: TEAEs leading to dose interruption of any drug in ≥ 2% of patients in POSEIDON (FDA review)

	T + D + SoC (N=330) n(%)	Durva + SoC (N=334) n(%)	SoC (N=333) n(%)
Any TEAE	196 (59)	189 (57)	169 (51)
Hepatitis[a]	20 (6)	12 (3.6)	12 (3.6)
Diarrhea/colitis[b]	19 (6)	7 (2)	3 (0.9)
Pneumonia[c]	14 (4.2)	13 (3.9)	10 (3)
Rash[d]	13 (3.9)	5 (1.5)	1 (0.3)
Fatigue[e]	10 (3.0)	16 (4.8)	7 (2.1)
Pancreatitis[f]	10 (3.0)	10 (3.0)	1 (0.3)
Pneumonitis[g]	10 (3.0)	5 (1.5)	0 (0)

Source: ADSL (Subject-Level Analysis Dataset)_Overall Survival, ADAE (Adverse Events Analysis Dataset)_Overall Survival.
Variables used: ACTARM, AEACN, AEDECOD, AETOXGRN, IPINTRPI, USUBJID.
a: Includes alanine aminotransferase increased, aspartate aminotransferase increased, drug-induced liver injury, hepatic failure, hepatitis
b: Includes colitis, diarrhea, enteritis, enterocolitis
c: Includes pneumonia, pneumonia aspiration, lower respiratory tract infection, pneumonia bacterial, pneumonia klebsiella
d: Includes dermatitis, drug eruption, eczema, erythema multiforme, rash maculo-papular, rash pruritic, mucosal inflammation, rash
e: Includes fatigue and asthenia
f: Includes amylase increased, pancreatitis
g: Includes immune-mediated pneumonitis, pneumonitis, interstitial lung disease

TEAEs leading to dose interruption or delay of tremelimumab or durvalumab occurred in 41% of patients on the T + D + SoC arm. Adverse reactions which required dosage interruption or delay of tremelimumab and durvalumab in >1% of patients included anemia, leukopenia, pneumonia, pneumonitis, colitis, diarrhea, hepatitis, rash, fatigue/asthenia, increased amylase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased lipase, neutropenia, thrombocytopenia, and leukopenia.

Significant Adverse Events

The Applicant's Position:
No AEs were classified as other significant AEs in POSEIDON study.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Immune-mediated adverse events (imAEs)

This section focuses on the programmatically determined imAEs in the POSEIDON study, T + D + Chemo pool and the T + D pan-tumor pool.

A total of 111 patients (33.6%) in the T + D + SoC arm and 17 patients (5.1%) in the SoC alone arm

reported AESIs/AEPIs that met the criteria to be imAEs. The majority of imAEs were of CTCAE Grade 1 or 2 severity; maximum CTCAE Grade 3 or 4 imAEs were reported in 10% of patients receiving T + D + SoC and 1.5% receiving SoC (Table 38).

The incidence of imAEs by grouped term across the T + D + SoC arm of POSEIDON and the safety pools is discussed in detail in this section.

A total of 208 patients (34.9%) in the T + D + Chemo pool and 665 patients (29.2%) in the T + D pan-tumor pool reported AESIs/AEPIs that met the criteria to be imAEs (Table 14). The incidence of imAEs across the POSEIDON T + D + SoC arm, T + D + Chemo pool and the T + D pan-tumor pool is generally comparable (33.6%, 34.9% and 29.2%, respectively) (Table 38).

The proportion of patients with imAEs who received interventions (systemic corticosteroids, high-dose steroids, endocrine therapy and immunosuppressants) across the T + D + SoC arm of POSEIDON, T + D + Chemo pool and the T + D pan-tumor pool are generally comparable (Table 38).

Table 38 Immune mediated Adverse Events in any Category (Safety Analysis Set)

	Number (%) of patients				
	POSEIDON		T + D + Chemo pool (N=596)	Chemo pool (N=599)	T + D Pan-tumor pool (N = 2280)
AE Category	T + D + SoC (N=330)	SoC (N=333)			
Any AE	111 (33.6)	17 (5.1)	208 (34.9)	26 (4.3)	665 (29.2)
Any AE of maximum CTCAE Grade 3 or 4	33 (10.0)	5 (1.5)	68 (11.4)	6 (1.0)	243 (10.7)
Any SAE (including events with outcome of death)	32 (9.7)	4 (1.2)	64 (10.7)	6 (1.0)	239 (10.5)
Any AE with outcome of death	2 (0.6)	0 (0.0)	5 (0.8)	1 (0.2)	9 (0.4)
Received systemic corticosteroids	87 (26.4)	13 (3.9)	153 (25.7)	20 (3.3)	488 (21.4)
Received high-dose steroids	66 (20.0)	6 (1.8)	123 (20.6)	9 (1.5)	374 (16.4)
Received endocrine therapy	39 (11.8)	4 (1.2)	82 (13.8)	6 (1.0)	262 (11.5)
Received other immunosuppressants	5 (1.5)	0 (0.0)	9 (1.5)	0 (0.0)	38 (1.7)
Any AE leading to discontinuation of study treatment	19 (5.8)	2 (0.6)	41 (6.9)	2 (0.3)	147 (6.4)
Event outcome resolved	58 (17.6)	12 (3.6)	106 (17.8)	14 (2.3)	334 (14.6)
Event outcome not resolved	51 (15.5)	5 (1.5)	97 (16.3)	11 (1.8)	322 (14.1)

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.

MedDRA version 23.1 was used; Source: see Table 2.7.4.9.1, POSEIDON CSR, Module 5.3.5.3

Pneumonitis

POSEIDON**:** Twelve patients (3.6%) in the T + D + SoC arm and 2 patients (0.6%) in the SoC alone arm had imAEs of pneumonitis (grouped term). CTCAE Grade 3 or 4 imAEs were reported in 3 patients (0.9%) in the T + D + SoC arm and in both the patients in the SoC alone arm. One patient had CTCAE Grade 5 imAE in the T +D + SoC arm, while there was no death in the SoC alone arm. See Table 2.7.4.9.2, Module 5.3.5.3, for more details. All patients in both the arms received high-dose corticosteroid treatment, and 1 patient in the T +D + SoC arm received immunosuppressants. Three (0.9%) patients in the T +D + SoC arm and both the patients in the SoC arm discontinued study drug. Resolution occurred in 9 patients (2.7%) in the T +D + SoC arm, and in both patients in the SoC alone arm, as of the DCO date.

The median time to onset for the imAE of pneumonitis was 191.5 days (range: 43 to 665 days) in the T +D + SoC arm and 76.5 days (range: 68 to 85 days) in the SoC arm. See Tables 2.7.4.9.37.1 and 2.7.4.14.37.3, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool: In total, 21 patients (3.5%) in the T + D + Chemo pool had imAEs of pneumonitis. CTCAE Grade 3 or 4 imAEs were reported in 6 patients (1.0%). Grade 5 imAEs were reported in 3 patients (0.5%). All patients in the T + D + Chemo pool received high-dose steroid treatment, and 1 patient received immunosuppressant. Seven patients (1.2%) discontinued study drug. Resolution occurred in 11 patients (1.8%) and the imAEs did not resolve in 7 patients (1.2%) as of the DCO date. See Table 2.7.4.9.2, Module 5.3.5.3, for more details.

The median time to onset for the imAE of pneumonitis in the T + D + Chemo pool was 140 days (range: 6 to 665 days). See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of pneumonitis in the POSEIDON T + D + SoC arm and the T + D + Chemo pool was similar (3.6% vs 3.5%).

POSEIDON vs T + D Pan-tumor pool**:** In total, 86 patients (3.8%) had imAEs of pneumonitis in the T + D pan-tumor pool. CTCAE Grade 3 or 4 imAEs were reported in 31 patients (1.4%). The majority of patients (79 patients, 3.5%) received high-dose steroids, and 7 patients (0.3%) received immunosuppressants. CTCAE Grade 5 events were reported in 7 patients (0.3%). Thirty-nine patients (1.7%) discontinued study drug. Resolution occurred in 51 patients (2.2%); 28 patients (1.2%) had unresolved imAEs as of the DCO date.

The median time to onset for the imAE of pneumonitis was 57.5 days (range: 8 to 912 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of pneumonitis in the POSEIDON T + D + SoC arm and the T + D pan-tumor pool was similar (3.6% vs 3.8%).

Hepatic events

POSEIDON**:** Twelve patients (3.6%) in the T + D + SoC arm had imAEs of hepatic events (grouped term). CTCAE Grade 3 or 4 imAEs were reported in 7 patients (2.1%). One patient had a CTCAE Grade 5 imAE. Eleven patients (3.3%) received high-dose steroids and 1 patient received immunosuppressants. Three patients (0.9%) discontinued study drug. Resolution occurred in 7 patients (2.1%) and the imAEs did not resolve in 4 patients (1.2%) as of the DCO date. No patients in the SoC alone arm had imAEs of hepatic events (grouped term). See Table 2.7.4.9.3, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of hepatic events was 102.5 days (range: 6 to 970 days). See Table 2.7.4.9.37.1, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** In total, 23 patients (3.9%) in the T + D + Chemo pool had imAEs of hepatic events. CTCAE Grade 3 or 4 imAEs were reported in 15 patients (2.5%). Two patients (0.3%) had CTCAE Grade 5 imAEs. Twenty-two patients (3.7%) received high-dose steroids, and 2 patients (0.3%) received immunosuppressants. Ten patients (1.7%) discontinued study drug. Resolution occurred in 12 patients (2.0%) and the imAEs did not resolve in 9 patients (1.5%) as of the DCO date. See Table 2.7.4.9.3, Module 5.3.5.3, for more details.

The median time to onset for the imAE of hepatic events was 42 days (range: 6 to 970 days) in the T + D + Chemo pool. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Overall, the incidence of hepatic events in the POSEIDON T + D + SoC arm and the T + D + Chemo pool was similar (3.6% vs 3.9%).

POSEIDON vs T + D Pan-Tumor Pool**:** In total, 80 patients (3.5%) had imAEs of hepatic events in the T + D pan-tumor pool. CTCAE Grade 3 or 4 imAEs were reported in 57 patients (2.5%). Sixty-eight patients (3.0%) received high-dose steroids, 8 patients (0.4%) received immunosuppressants. CTCAE Grade 5 imAEs were reported in 2 patients. Twenty-seven patients (1.2%) discontinued study drug. Resolution occurred in 47 patients (2.1%); 31 patients (1.4%) had unresolved events as of the DCO date.

The median time to onset for the imAE of hepatic events was 36 days (range: 1 to 533 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of hepatic events across the POSEIDON T + D + SoC arm and the T + D pan-tumor pool was similar (3.6% vs 3.5%).

Gastrointestinal events (Diarrhoea/Colitis and intestinal perforations)

Diarrhoea/Colitis

POSEIDON**:** In total, 17 patients (5.2%) in the T + D + SoC arm and 2 patients (0.6%) in the SoC alone arm had imAEs of diarrhoea/colitis. CTCAE Grade 3 or 4 imAEs were reported in 6 patients (1.8%) in the T + D + SoC arm. Both the patients in the SoC alone arm had CTCAE Grade 1 or 2 events. See Table 2.7.4.9.4, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of diarrhoea/colitis was 62 days (range: 13 to 476 days) in the T +D + SoC arm and 50.5 days (range: 30 to 71 days) in the SoC alone arm. See Tables 2.7.4.9.37.1 and 2.7.4.37.3, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** The incidence of imAEs of diarrhoea/colitis in the POSEIDON T + D + SoC arm and the T + D + Chemo Pool was similar (5.2% vs 6.5%). CTCAE Grade 3 or 4 imAEs were reported in 15 patients (2.5%) in the T + D + Chemo pool. One patient had a CTCAE Grade 5 imAE. See Table 2.7.4.9.4, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of diarrhoea/colitis was 62 days (range: 5 to 570 days) in the T + D + Chemo pool. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details. The median time to onset was comparable as that in the POSEIDON T + D + SoC arm.

POSEIDON vs T + D Pan-Tumor pool**:** Overall, the incidence of imAEs of diarrhoea/colitis in the POSEIDON T + D + SoC arm and the T + D pan-tumor pool was comparable (5.2% vs 7.3%). CTCAE Grade 3 or 4 imAEs were reported in 79 patients (3.5%) in the T + D pan-tumor pool. There were no deaths reported. See Table 2.7.4.9.4, Module 5.3.5.3, for more details.

The median time to onset for the imAE of diarrhoea/colitis was 57 days (range: 3 to 906 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details. The median time to onset of the imAEs in the T + D pan-tumor pool arm was comparable to that in the POSEIDON T +D + SoC arm (57 days vs 62 days).

Intestinal perforation

None of the patients in the POSEIDON T + D + SoC arm, T + D + Chemo pool or in the T + D pan-tumor pool had imAEs of intestinal perforation (grouped term). See Table 2.7.4.9.5, Module 5.3.5.3.

Endocrinopathies

Adrenal insufficiency

POSEIDON**:** In total, 8 patients (2.4%) in the T + D + SoC arm had imAEs of adrenal insufficiency (grouped term). CTCAE Grade 3 or 4 imAEs were reported in 2 patients (0.6%) in the T + D + SoC arm. There were no CTCAE Grade 5 events reported. Three patients (0.9%) received high-dose steroid treatment, and 1 patient received endocrine therapy. There were no discontinuations due to these imAEs. Resolution occurred in 1 patient (0.3%) in the T +D + SoC arm and the imAEs did not resolve in 7 patients (2.1%). No patients in the SoC alone arm had imAEs of adrenal insufficiency. See Table 2.7.4.9.6, Module 5.3.5.3, for more details.

The median time to onset for the imAE of adrenal insufficiency was 118 days (range: 42 to 189 days) in the T +D + SoC arm See Table 2.7.4.9.37.1, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** In total, 13 patients (2.2%) in the T + D + Chemo pool had imAEs of adrenal insufficiency; CTCAE Grade 3 or 4 imAEs were reported in 5 patients (0.8%). There were no

deaths reported. Seven patients (1.2%) received high-dose steroid treatment, and 1 patient received endocrine therapy. Resolution occurred in 2 (0.3%) patients and the imAEs were ongoing in 11 patients (1.8%). See Table 2.7.4.9.6, Module 5.3.5.3, for more details.

The median time to onset for the imAE of adrenal insufficiency was 122 days (range: 42 to 333 days) in the T + D + Chemo pool. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of with adrenal insufficiency in the POSEIDON T + D + SoC arm and the T + D + Chemo pool similar (2.4% vs 2.2%).

POSEIDON vs T + D Pan-Tumor Pool**:** In total, 33 patients (1.4%) had imAEs of adrenal insufficiency in the T + D pan-tumor pool. CTCAE Grade 3 or 4 imAEs were reported in 17 patients (0.7%). Eleven patients (0.5%) received high-dose steroids and 7 patients (0.3%) received endocrine therapy. One patient discontinued study treatment. There were no CTCAE Grade 5 imAEs reported; 11 patients (0.5%) had imAEs resolved and 22 patients (1.0%) had ongoing imAEs as of the DCO date.

The median time to onset in the POSEIDON T +D + SoC arm for imAEs of adrenal insufficiency was comparable to that in the T + D pan-tumor pool (105 days [range: 20 to 428 days]). See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of adrenal insufficiency in the POSEIDON T + D + SoC arm and the T + D pan-tumor pool was comparable (2.4% vs 1.4%).

Type I Diabetes mellitus

POSEIDON**:** One patient (0.3%) in the T + D + SoC arm (CTCAE Grade 3 or 4 in severity) and none of the patients in the SoC alone arm had imAE of Type I diabetes mellitus (grouped term). The patient received endocrine (insulin) therapy (see Table 2.7.4.9.7, Module 5.3.5.3). The time to onset of the event was 69 days (see Table 2.7.4.9.37.1, Module 5.3.5.3,).

POSEIDON vs T + D+ Chemo Pool**:** In total, 3 patients (0.5%) had imAEs in the T + D + Chemo pool; 2 of these imAEs were of CTCAE Grade 3 or 4 severity. There were no CTCAE Grade 5 imAEs reported. All 3 patients received endocrine therapy (see Table 2.7.4.9.7, Module 5.3.5.3). The median time to onset for the imAE of Type I diabetes mellitus was 85 days (range: 69 to 230 days). See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Overall, the incidence of Type I diabetes mellitus was comparable between the POSEIDON T + D + SoC arm and the T + D + Chemo pool (0.3% vs 0.5%).

POSEIDON vs T + D Pan-Tumor Pool**:** In total, 6 patients (0.3%) had imAEs of Type I diabetes mellitus in the T + D pan-tumor pool; half of these events were of CTCAE Grade 3 or 4 severity. All the patients required endocrine therapy. One event resolved as of the DCO date and 5 patients (0.2%) had ongoing events. The median time to onset for the imAEs of Type I diabetes mellitus was 58 days (range: 7 to 220 days) in the T + D pan-tumor pool and was comparable to that in the POSEIDON T +D + SoC arm. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of Type I diabetes mellitus in the POSEIDON T + D + SoC arm was the same as that in the T+ D pan-tumor pool (0.3%).

Hyperthyroid events

POSEIDON**:** In total, 9 patients (2.7%) in the T + D + SoC arm and 1 patient (0.3%) in the SoC alone arm had imAEs of hyperthyroid events (grouped term). None of these imAEs were of CTCAE Grade 3 or 4 severity. There were no deaths in either arm. All patients in both the arms received endocrine therapy. None of these imAEs led to discontinuation of study drug. Resolution occurred in 7 patients (2.1%) in the T +D + SoC arm, and the remaining events in both arms remained unresolved as of the DCO date. See Table 2.7.4.9.8, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of hyperthyroid events was 47 days (range: 22 to 147 days) in the T +D + SoC arm and 351 days for the event in SoC alone arm. See Tables 2.7.4.9.37.1 and 2.7.4.37.3, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** In total, 30 patients (5.0%) in the T + D + Chemo pool had imAEs of hyperthyroid events. One patient had an imAE of CTCAE Grade 3 or 4 severity. There were no Grade 5 imAEs reported. Twenty-eight patients (4.7%) in the T + D + Chemo pool received endocrine therapy and 5 patients (0.8%) received high-dose steroid treatment. One patient discontinued study drug. Resolution occurred in 21 patients (3.5%) and 9 patients (1.5%) had unresolved events as of the DCO date. See Table 2.7.4.9.8, Module 5.3.5.3, for more details. The median time to onset for the imAEs of hyperthyroid events was 50 days (range: 22 to 283 days) in the T + D + Chemo pool. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Compared to the T + D + SoC arm of POSEIDON, the incidence of imAEs in the T + D + chemo pool was comparable (2.7% vs 5.0%).

POSEIDON vs T + D Pan-Tumor pool**:** In total, 62 patients (2.7%) had imAEs of hyperthyroid events. CTCAE Grade 3 or 4 events were reported in 5 patients (0.2%). There were no CTCAE Grade 5 events reported in the T + D pan-tumor pool. Fifty-three patients (2.3%) received endocrine therapy and 11 patients (0.5%) received high-dose steroids. One patient discontinued study drug. Resolution occurred in 47 patients (2.1%) and the remaining 15 patients (0.7%) had unresolved events as of the DCO date.The median time to onset for the imAE of hyperthyroid events was 33.5 days (range: 4 to 176 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of hyperthyroid events in the POSEIDON T + D + SoC arm and the T+ D pan-tumor pool was the same (2.7%).

Hypophysitis

POSEIDON**:** In total, 5 patients (1.5%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of hypophysitis (grouped term). CTCAE Grade 3 or 4 imAEs were reported in 2 patients (0.6%). There were no CTCAE Grade 5 imAEs. Two patients (0.6%) received endocrine therapy and 1 patient (0.3%) received

high-dose steroids. None of these imAEs led to discontinuation of study drug. All imAEs were ongoing as of the DCO date. See Table 2.7.4.9.9, Module 5.3.5.3, for more details. The median time to onset of the imAEs of hypophysitis was 104 days (range: 84 to 189 days). See Table 2.7.4.9.37.1, Module 5.3.5.3, for more details.

POSEIDON vs T + D+ Chemo Pool: In total, 8 patients (1.3%) in the T + D + Chemo pool had imAE of hypophysitis. CTCAE Grade 3 or 4 severity imAEs were reported in 3 patients (0.5%). There were no CTCAE Grade 5 imAEs reported. Four patients (0.7%) in the T + D + Chemo pool received endocrine therapy and 2 patients (0.3%) received high-dose steroid. One patient discontinued study drug. All imAEs were ongoing as of the DCO date. See Table 2.7.4.9.9, Module 5.3.5.3, for more details. The median time to onset for the imAEs of hypophysitis was 98 days (range: 12 to 197 days) in the T + D + Chemo pool and was comparable to that in the POSEIDON T +D + SoC arm. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

Overall, the incidence of imAEs of hypophysitis in the POSEIDON T + D + SoC arm and the T + D + Chemo pool was comparable (1.3% vs 1.5%).

POSEIDON vs T + D Pan-Tumor pool**:** In total, 16 patients (0.7%) had imAEs of hypophysitis in the T + D pan-tumor pool; about half of these events were of CTCAE Grade 3 or 4 in severity. There were no CTCAE Grade 5 imAEs. Four patients (0.2%) received endocrine therapy and 8 patients (0.4%) received high-dose steroids. Two patients discontinued study treatment. Resolution occurred in 7 patients (0.3%) and the remaining 9 patients (0.4%) had ongoing imAEs as of the DCO date. The median time to onset for the imAE of hypophysitis was 123.5 days (range: 63 to 388 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Overall, the incidence of hypophysitis in the POSEIDON T + D + SoC arm and the T+ D pan-tumor pool was comparable (0.7% vs 1.5%). With the low incidence of imAEs of hypophysitis in POSEIDON and the T + D pan-tumor pool, no meaningful interpretation can be derived.

Hypothyroid events

POSEIDON**:** In total, 27 patients (8.2%) in the T + D + SoC arm and 3 patients (0.9%) in the SoC alone arm had imAEs of hypothyroid events. All events were of CTCAE Grade 1 or 2 severity in both the arms. See Table 2.7.4.9.10, Module 5.3.5.3, for more details. The median time to onset for the imAEs of hypothyroid events was 105 days (range: 8 to 596 days) in the T +D + SoC arm and 115 days (range: 1 to 195) in the SoC alone arm. See Tables 2.7.4.9.37.1 and 2.7.4.9.37.3, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** Results for the T + D + Chemo pool were generally similar to that of POSEIDON T + D + SoC arm. The majority of events were of CTCAE Grade 1 or 2 severity. There were no deaths or discontinuations reported in the T + D + Chemo pool. See Table 2.7.4.9.10, Module 5.3.5.3, for more details. The median time to onset for the imAEs of hypothyroid events was 104 days (range: 8 to 596 days) in the T + D + Chemo pool and was comparable to that in the POSEIDON T +D + SoC arm. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

POSEIDON vs T + D Pan-Tumor pool**:** Overall, the incidence of hypothyroid events across the POSEIDON T + D + SoC arm and the T + D pan-tumor pool was similar (8.2% vs 9.2%). CTCAE Grade 3 or 4 events were reported in 6 patients (0.3%) in the T + D pan-tumor pool. There were no CTCAE Grade 5 imAEs reported. The median time to onset for the imAEs of hypothyroid events was 85 days (range: 1 to 624 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Thyroiditis

POSEIDON**:** Four patients (1.2%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of thyroiditis (grouped term); all imAEs were classified as CTCAE Grade 1 or 2 severity. All 4 patients received endocrine therapy. There were no CTCAE Grade 5 imAEs reported. One patient discontinued study drug. Two (0.6%) of the imAEs resolved and the remaining 2 (0.6%) imAEs were ongoing at the DCO date. See Table 2.7.4.9.11 for more details. The median time to onset was 92 days (range: 42 days to 127 days) (see Table 2.7.4.9.37.1, Module 5.3.5.3).

POSEIDON vs T + D+ Chemo Pool**:** Three more patients had imAEs of thyroiditis in the T + D+ Chemo pool along with the 4 patients in POSEIDON. There were no CTCAE Grade 5 imAEs reported. There were no discontinuations reported other than the one in POSEIDON. All 7 patients received endocrine therapy. Resolution occurred in 2 of the 7 patients (0.3%) and the imAEs did not resolve in remaining 5 patients (0.8%) at the time of the DCO date. See Table 2.7.4.9.11, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of thyroiditis was 114 days (range: 35 to 305 days). See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

POSEIDON vs T + D Pan-Tumor pool**:** The incidence of thyroiditis between the POSEIDON T + D + SoC arm and the T+ D pan-tumor pool was comparable (1.2% vs 0.7%); the imAEs were generally of CTCAE Grade 1 or 2 severity in the T + D pan-tumor pool. Of the 15 patients with an imAE of thyroiditis, 13 patients (0.6%) received endocrine therapy and 2 patients received high-dose steroids. There were no CTCAE Grade 5 imAEs of thyroiditis reported. Resolution occurred in 5 patients (0.2%) as of the DCO date.

The median time to onset for the imAE of thyroiditis was 57 days (range: 22 to 141 days) in the T + D pan-tumor pool. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Renal Events

POSEIDON**:** In total, 4 patients (1.2%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of renal events (grouped term); the events were generally of CTCAE Grade 1 or 2 in severity. All 4 patients received high-dose steroids. One patient had a CTCAE Grade 5 event and 3 patients (0.9%) discontinued study drug. All 4 patients received high-dose steroids. Resolution occurred in 1 patient (0.3%) and the events did not resolve in the remaining 2 patients (0.6%) as of the DCO date. See Table 2.7.4.9.12 for more details. The median time to onset of these events was 260 days (range: 23 to 1072 days) (see Table 2.7.4.9.37.1, Module 5.3.5.3).

POSEIDON vs T + D + Chemo Pool**:** There were no patients in the T + D + Chemo arm of CASPIAN who had imAEs of renal events; all 4 were from the respective arm of POSEIDON. See Table 2.7.4.9.12, Module 5.3.5.3, for more details.

POSEIDON vs T + D Pan-Tumor pool**:** In total, 9 patients (0.4%) had imAEs of renal events in the T + D pan-tumor pool. One of these events was of CTCAE Grade 3 or 4 severity. Seven patients (0.3%) received high-dose steroids. Three patients discontinued study drug; there were no CTCAE Grade 5 imAEs reported. Resolution occurred in 5 patients (0.2%) and the events did not resolve in 4 patients (0.2%) as of the DCO date. See Table 2.7.4.9.12, Module 5.3.5.3, for more details.

The median time to onset for the imAEs of renal events was longer in the POSEIDON T +D + SoC arm compared to that in the T + D pan-tumor pool (260 days vs 79 days). Of the 4 imAEs of renal events in the T + D + Soc arm of POSEIDON, 2 were autoimmune nephritis and the other 2 were blood creatinine increased. The time to onset of the 2 events of autoimmune nephritis were 36 and 23 days, respectively. The time to onset for the 2 events of blood creatinine increased were 449 and 1072 days, respectively, indicating that the longer median time to onset (260 days) in the T + D + SoC arm of POSEIDON was driven by these 2 events. Additionally, with fewer imAEs reported in the T + D + SoC arm of POSEIDON and the T + D pan-tumor pool, no meaningful interpretation can be derived. See Table 2.7.4.9.37.6 and Listing 2.7.4.9.40, Module 5.3.5.3, for more details.

Overall, the incidence of renal events between the POSEIDON T + D + SoC arm and the T+ D pan-tumor pool was comparable (1.2% vs 0.4%).

Dermatitis/Rash

POSEIDON**:** In total, 24 patients (7.3%) in the T + D + SoC arm and 7 patients (2.1%) in the SoC alone arm had imAEs of dermatitis/rash and the majority of these imAEs were generally of CTCAE Grade 1 or 2 severity. There were no CTCAE Grade 5 imAEs reported. See Table 2.7.4.9.13 for more details. The median time to onset for the imAEs of dermatitis/rash was 64.5 days (range: 1 to 913 days) in the T +D + SoC arm and 7 days (range: 3 to 16 days) in the SoC alone arm. See Tables 2.7.4.9.37.1 and 2.7.4.37.3, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** Overall, the incidence of dermatitis/rash imAEs in the POSEIDON T + D + SoC arm and the T + D + Chemo pool was consistent (7.3% vs 7.2%). CTCAE Grade 3 or 4 imAEs were reported in 10 patients (1.7%). There were no CTCAE Grade 5 imAEs reported. The median time to onset of the imAEs was 51 days (range: 1 to 913 days). See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

POSEIDON vs T + D Pan-Tumor Pool**:** Overall, the incidence of imAEs of dermatitis/rash was higher in the POSEIDON T + D + SoC arm than that in the T + D pan-tumor pool (7.3% vs 4.9%); the apparent difference was likely driven in large extent by differences in pruritis (1.2% difference) possibly due to chemotherapy treatments in POSEIDON and the remainder may be explained by single events (erythema multiforme, pemphigoid, erythema, eczema [n = 2]) (see Tables 2.7.4.14.19 and 2.7.4.14.24, Module 5.3.5.3). CTCAE Grade 3 or 4 imAEs were reported in 17 patients (0.7%). There were no CTCAE

Grade 5 imAEs reported. The median time to onset of the imAEs was 35.5 (range: 1 to 778 days) days. See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Pancreatic events

POSEIDON**:** In total, 6 patients (1.8%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of pancreatic events (grouped term); 4 events CTCAE Grade 3 or 4 severity. There was one CTCAE Grade 5 event reported. Four patients (1.2%) received high-dose steroid treatment. Resolution occurred in 4 (1.2%) patients. See Table 2.7.4.9.14, Module 5.3.5.3, for more details.

The median time to onset for the imAE of pancreatic events was 40.5 days (range: 7 to 224 days). See Table 2.7.4.9.37.1, Module 5.3.5.3, for more details.

POSEIDON vs T + D + Chemo Pool**:** Overall, the incidence of imAEs of pancreatic events in the POSEIDON T + D + SoC arm and the T + D + Chemo Pool was similar (1.8% vs 1.3%).CTCAE Grade 3 or 4 events were reported in 5 patients (0.8%). One patient had a CTCAE Grade 5 event. Six patients (1.0%) received high-dose steroid treatment. Resolution occurred in 5 (0.8%) patients and events did not resolve in 2 patients (0.3%) as of the DCO date. See Table 2.7.4.9.14, Module 5.3.5.3, for more details.

The median time to onset for the imAE of pancreatic events was 67 days (range: 7 to 224 days) in the T + D + Chemo pool. See Table 2.7.4.9.37.4, Module 5.3.5.3, for more details.

POSEIDON vs T + D Pan-Tumor pool**:** Overall, the incidence of imAEs of pancreatic events was similar across the POSEIDON T + D + SoC arm and the T + D pan-tumor pool (1.8% vs 2.0%). CTCAE Grade 3 or 4 events were reported in 31 patients (1.4%) in the T + D pan-tumor pool. Thirty-seven patients (1.6%) received high-dose steroids and 1 patient received immunosuppressant. There were no Grade 5 events reported. Eight patients (0.4%) discontinued study treatment. Resolution occurred in 36 patients (1.6%); the imAEs did not resolve in 9 patients (0.4%). See Table 2.7.4.9.14, Module 5.3.5.3, for details.

The median time to onset of the imAEs of pancreatic events in the T + D pan-tumor pool was longer than in the POSEIDON T + D + SoC arm at 66 days (range: 2.0 to 408 days). See Table 2.7.4.9.37.6, Module 5.3.5.3, for more details.

Myocarditis

POSEIDON**:** One patient (0.3%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of myocarditis (grouped term). The event led to discontinuation of study drug and then death (see Table 2.7.4.9.15, Module 5.3.5.3). The time to onset of the imAE was 23 days (see Table 2.7.4.9.37.1, Module 5.3.5.3).

POSEIDON vs T + D + Chemo Pool**:** There was one more event of myocarditis reported in CASPIAN along with the above event from POSEIDON; the event in CASPIAN was of CTCAE Grade 3 or 4 severity. Both the events received high-dose steroids. The event from CASPIAN did not resolve as of the DCO date. The median time to onset of the imAE was 24 days (range: 23 to 25 days) (see Table 2.7.4.9.37.4, Module 5.3.5.3).

POSEIDON vs T + D Pan-Tumor pool**:** One patient had a CTCAE Grade 3 or 4 imAE of myocarditis in the T + D pan-tumor pool. The patient received high-dose steroids, and immunosuppressants and eventually discontinued study drug. The time to onset of this event was 236 days (see Table 2.7.4.9.37.6, Module 5.3.5.3). The incidence of myocarditis imAEs was low, hence, no meaningful comparisons can be made across the safety pools.

Myositis

POSEIDON**:** Two patients (0.6%) in the T + D + SoC arm and none in the SoC alone arm had imAEs of myositis (grouped term). Both imAEs were of CTCAE Grade 3 or 4 severity. One of the imAEs led to discontinuation of study drug; no Grade 5 imAEs were reported. Both patients received high-dose steroids. One of the imAEs resolved and the other did not resolve as of the DCO date (see Table 2.7.4.9.18, Module 5.3.5.3). The median time to onset was 34.5 days (range: 26 to 43 days). See Table 2.7.4.9.37.1, Module 5.3.5.3, for more details.

POSEIDON vs T + D+ Chemo Pool**:** There was one more imAE of myositis reported in CASPIAN along with the above 2 imAEs from POSEIDON. The patient discontinued study drug. The imAE event from CASPIAN resolved. The median time to onset was 43 days (range: 26 to 278 days) (see Table 2.7.4.9.37.4, Module 5.3.5.3).

POSEIDON vs T + D Pan-Tumor Pool**:** A total of 6 patients (0.3%) had CTCAE Grade 3 or 4 imAEs of myositis in the T + D pan-tumor pool. Five patients received high-dose steroids. Two patients discontinued study drug. Grade 5 imAEs were not reported. Four of the imAEs resolved and 2 did not resolve as of the DCO date. The median time to onset was 36.5 days (range: 22 to 46 days) (see Table 2.7.4.9.37.6, Module 5.3.5.3). The incidence of myositis imAEs was low, hence, no meaningful comparisons can be made across the different pools.

Guillain-Barre syndrome

One patient in the T + D pan-tumor pool had a Grade 3 or 4 imAE of Guillain-Barre syndrome (grouped term). The patient received high-dose steroid treatment. The patient discontinued study drug (see Table 2.7.4.9.17, Module 5.3.5.3). The imAE resolved. The time to onset of the imAE was 92 days (see Table 2.7.4.9.37.6, Module 5.3.5.3).

Myasthenia gravis

One patient in the T + D pan-tumor pool had a CTCAE Grade 1 or 2 imAE of myasthenia gravis (grouped term). The patient received high-dose steroids. The event was not resolved as of the DCO date (see Table 2.7.4.9.16, Module 5.3.5.3). The time to onset of the event was 78 days (see Table 2.7.4.9.37.6, Module 5.3.5.3).

Other/rare miscellaneous imAEs

For a summary of other/rare miscellaneous imAEs (grouped term) by PTs, see Tables 2.7.4.9.19, 2.7.4.9.22 and 2.7.4.9.24, Module 5.3.5.3. The most common PT (occurring in ≥ 5 patients in any group)

reported was arthralgia; 6 patients (1.8%), 7 patients (1.2%) and 15 patients (0.7%) in the POSEIDON T + D +SoC arm, T + D + Chemo pool and the T + D pan-tumor pool, respectively.

The Applicant's Position:
Overall, the incidence of imAEs reported was consistent with tremelimumab and durvalumab safety profile. The frequency of imAEs across the POSEIDON T + D + SoC arm, T + D + Chemo pool and the T + D pan-tumor pool is generally comparable. Consistent with the mechanism of action, the frequency of imAEs was higher in the POSEIDON T + D + SoC arm, T + D + Chemo Pool and the T + D pan-tumor pool than the SoC alone arm of POSEIDON and the Chemo pool. Overall, imAEs were manageable and resolved by treating with systemic corticosteroids, high-dose steroids, immunosuppressants and endocrine therapy, per the toxicity management guidelines

The FDA's Assessment:
The Applicant utilized a programmatic process to identify whether AESI and AEPI qualified as imAEs. ImAE frequencies were calculated based on rules and a treatment algogrithim that considered interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy. This method of adjudicating imAEs was discussed in prior meetings with the FDA, and FDA was in agreement with the proposed approach.

FDA independently verified the incidence of imAEs in all three treatment arms of POSEIDON and the pooled safety population using the ADIMAE dataset and the preferred grouped terms and flags established by the Applicant (the immune mediated AESI or AEPI flag). In the Warnings and Precautions section of the tremelimumab label, reported rates of imAEs are based upon those identified in the pooled safety populations (n=596); FDA agrees with the Applicant's analysis above on the incidence of imAEs being generally similar between the T + D + SoC arm in POSEIDON compared to the T + D + Chemo pool and the T + D Pan Tumor pool.

The addition of tremelimumab to the treatment regimen resulted in a higher incidence of imAEs in the T + D + SoC arm (34%) compared to the D + SoC (19%); a marginal increase in Grade 3-4 imAEs was observed in the T + D + SoC arm compared to the D + SoC arm (10% vs. 7%). ImAEs that occurred at an incidence of ≥ 2% or greater in the T + D + SoC arm as compared to the D + SoC arm were hypothyroidism and colitis. The incidence of pneumonitis was similar between the T + D + SoC and D + SoC arms.

Table 39: Immune-mediated adverse events observed in POSEIDON (FDA review)

	T + D + SoC (N=330)		**Durva + SoC (N=334)**		**SoC (N=333)**	
	Grade 1-5 n (%)	**Grade 3-4 n (%)**	**Grade 1-5 n (%)**	**Grade 3-4 n (%)**	**Grade 1-5 n (%)**	**Grade 3-4 n (%)**
Any imAE	111 (34)	33 (10)	64 (19)	23 (7)	17 (5)	5 (1.5)
Hypothyroid events						

Hypothyroidism	27 (8)	0 (0)	17 (5)	0 (0)	2 (0.6)	0 (0)
Blood thyroid stimulating hormone increased	0 (0)	0	2 (0.6)	0	1 (0.3)	0
Dermatitis/Rash						
Rash	10 (3)	2 (0.6)	5 (1.5)	2 (0.6)	3 (0.9)	0 (0.0)
Pruritus	9 (2.7)	0	3 (0.9)	0	1 (0.3)	0
Rash maculo-papular	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)
Eczema	2 (0.6)	0	0 (0.0)	0	0 (0)	0
Diarrhoea/Colitis						
Colitis	12 (3.6)	4 (1.2)	4 (1.2)	1 (0.3)	0 (0.0)	0 (0.0)
Diarrhea	4 (1.2)	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0 (0.0)
Enterocolitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic events						
ALT increased	4 (1.2)	2 (0.6)	7 (2.1)	6 (1.8)	0 (0)	0 (0.0)
AST increased	3 (0.9)	0 (0.0)	7 (2.1)	4 (1.2)	0 (0)	0 (0)
Hepatitis	2 (0.6)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Transaminases increased	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatotoxicity	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-mediated hepatitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Hyperthyroid events						
Hyperthyroidism	9 (2.7)	0 (0)	4 (1.2)	1 (0.3)	1 (0.3)	0 (0)
Pneumonitis						
Pneumonitis	9 (2.7)	3 (0.9)	10 (3.0)	4 (1.2)	1 (0.3)	1 (0.3)
Interstitial lung disease	2 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.3)
Other rare/miscellaneous						
Arthralgia	6 (1.8)	0 (0)	0 (0)	0 (0.0)	2 (0.6)	1 (0.3)
Vasculitis	2 (0.6)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatic events						
Lipase increased	3 (0.9)	3 (0.9)	2 (0.6)	2 (0.6)	0 (0)	0 (0)
Pancreatitis	2 (0.6)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)
Adrenal insufficiency						
Adrenal insufficiency	7 (2.1)	2 (0.6)	4 (1.2)	1 (0.3)	0 (0)	0 (0)

Hypophysitis						
Hypopituitarism	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Thyroiditis						
Thyroiditis	2 (0.6)	0	2 (0.6)	0	0 (0)	0
Autoimmune thyroiditis	2 (0.6)	0	1 (0.3)	0	0 (0)	0
Renal events						
Autoimmune nephritis	2 (0.6)	0	0 (0.0)	0	0 (0.0)	0
Blood creatinine increased	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type 1 diabetes mellitus						
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)

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. See Section 12.2.3.12, POSEIDON CSR, Module 5.3.5.1 for further information. In the T + D + Chemo pool and the T + D pan-tumor pool, AESIs of infusion related reaction were reported in 17 patients (2.9%) and 45 patients (2.0%), respectively. The incidence of these AESIs were low that no meaningful comparison can be made (see Table 2.7.4.6.3A and Table 2.7.4.6.3B, Module 5.3.5.3).

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. See Section 12.2.3.12, POSEIDON CSR, Module 5.3.5.1 for further information. 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. The incidence of these AESIs were low, so no meaningful comparison can be derived (see Table 2.7.4.6.3A and Table 2.7.4.6.3B, Module 5.3.5.3).

The FDA's Assessment:
FDA evaluated infusion-related reactions (IRRs) using a grouped term of "infusion-related reactions" and "hypersensitivity". FDA agrees with the Applicant's reporting of the rates of IRRs for the T + D + SoC and SoC arms in POSEIDON. FDA agrees that IRRs were rare events in both treatment arms, and that the majority of the events were Grade 1 or 2.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 40 Overview of Adverse Events in POSEIDON and the two safety pools (Safety Analysis Set)

Category of AE	Number (%) of patients				
	POSEIDON		T + D + Chemo pool (N = 596)	Chemo Pool (N = 599)	T + D Pan-tumor pool (N = 2280)
	T + D + SoC (N = 330)	SoC (N = 333)			
Any AE	321 (97.3)	320 (96.1)	585 (98.2)	578 (96.5)	2160 (94.7)
Any AE of maximum CTCAE Grade 3 or Grade 4	176 (53.3)	172 (51.7)	345 (57.9)	330 (55.1)	1127 (49.4)
Any AE with outcome = death	41 (12.4)	30 (9.0)	68 (11.4)	45 (7.5)	153 (6.7)
Any SAE (including events with outcome = death)	146 (44.2)	117 (35.1)	267 (44.8)	214 (35.7)	1020 (44.7)
Any AE leading to discontinuation of any study treatment	73 (22.1)	51 (15.3)	130 (21.8)	76 (12.7)	367 (16.1)
Any AE leading to discontinuation of durvalumab or tremelimumab	57 (17.3)	0	108 (18.1)	0	367 (16.1)
Any AE leading to dose modification of any study treatment	206 (62.4)	179 (53.8)	338 (56.7)	303 (50.6)	622 (27.3)
Any AE leading to dose modification of durvalumab or tremelimumab	174 (52.7%)	0	285 (47.8%)	0	622 (27.3%)

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.

Source: see Table 2.7.4.2.1, Module 5.3.5.3.

The integrated analysis of AEs for the safety pools was based on all treatment emergent adverse events (TEAEs) as defined in each individual study. There are some minor differences in data conventions provided in Module 2.7.4.

Since the design of the POSEIDON study, and all other studies included in the pools was open-label, the causality assessment of AEs to any of the study treatments, as assessed by Investigator, are subject to bias and are not discussed in this document. For AEs causally related to study treatment in POSEIDON, see Section 12.2.1.2, POSEIDON CSR, Module 5.3.5.1. For AEs possibly related to study treatment or tremelimumab/durvalumab in the safety pools, see Table 2.7.4.2.7.1A to Table 2.7.4.2.9.2B, Module 5.3.5.3.

POSEIDON**:** The incidence of AEs across the AE profile was similar in the T + D + SoC and SoC alone arms for the categories of any AE, and maximum CTCAE Grade 3 or 4 (Table 40). Incidence was higher in the T + D + SoC arm compared to the SoC alone arm for AEs with outcome of death (12.4% vs 9.0%), SAEs (44.2% vs 35.1%), AEs leading to discontinuation of any study treatment (22.1% vs 15.3%), and AEs leading to dose modification of any study treatment (62.4% vs 53.8%).

POSEIDON vs T + D + Chemo Pool**:** Incidence of AEs across the AE profile was similar for the T + D + SoC

arm of POSEIDON and the T + D + Chemo pool; the only notable difference was for AEs leading to dose modification of any study treatment (62.4% vs 56.7%) and to dose modification of tremelimumab or durvalumab (52.7% vs 47.8%), which were more frequent in POSEIDON.

POSEIDON vs T + D Pan-Tumor Pool**:** Incidence of AEs was similar in the T + D + SoC arm of POSEIDON and the T + D pan tumor pool for the categories any AE, AEs of maximum CTCAE Grade 3 or 4, and SAEs. Incidence was higher in the T + D + SoC arm of POSEIDON than in the T + D pan-tumor pool for AEs with outcome of death (12.4% vs 6.7%). The higher incidence of these AEs in the T + D + SoC arm of POSEIDON may be influenced by the additional toxicity burden of chemotherapy. Adverse events leading to any study treatment discontinuation were also higher in the T + D + SoC arm of POSEIDON compared to the T + D pan-tumor pool (22.1% vs 16.1%). This is possibly due to discontinuation of SoC chemotherapy, as the incidence of AEs leading to discontinuation of tremelimumab or durvalumab was comparable between the T + D + SoC arm of POSEIDON and the T + D pan-tumor pool. In addition, AEs leading to any study treatment dose modification were also higher in the T + D + SoC arm of POSEIDON compared to the T + D pan-tumor pool (62.4% vs 27.3%); dose modification of the chemotherapy agents accounts for some of this difference but there remained a higher incidence of dose modifications for tremelimumab and durvalumab alone in the T + D + SoC arm of POSEIDON than in the T + D pan-tumor pool (52.7% vs 27.3%). This may be due to the longer treatment duration in POSEIDON and management of toxicities by dose modifications

Commonly reported adverse events

POSEIDON**:** The most common AEs were generally comparable between the T + D + SoC and SoC alone arm. Adverse events associated with chemotherapy were reported at similar rates in the T + D + SoC and SoC alone arms of POSEIDON, indicating that the addition of tremelimumab and durvalumab to SoC chemotherapy did not potentiate chemotherapy-related toxicity. The most common AEs were anaemia, nausea, and neutropenia (all ≥30% in the T + D + SoC arm of POSEIDON) that are associated with SoC chemotherapy.

The PTs neutropenia, diarrhea, rash, pyrexia, arthralgia, hypothyroidism, pruritus, and hyperthyroidism were reported in a higher proportion of patients (≥5% difference between arms) in the T + D + SoC arm than the SoC alone arm (see Table 7 and Table 2.7.4.2.5A, Module 5.3.5.3). Neutrophil count decreased was reported in a lower proportion of patients in the T + D + SoC arm than the SoC alone arm.

POSEIDON vs T + D + Chemo Pool**:** Overall, the most common AEs in the POSEIDON T + D + SoC arm were also common in the T + D + Chemo pool, and anaemia was the only PT with an incidence ≥ 5% higher in the POSEIDON T + D + SoC arm compared to the T + D + Chemo pool.

POSEIDON vs T+D Pan-tumor Pool**:** A difference in incidence and type of some of the most commonly reported AEs was observed between the T + D + SoC arm of POSEIDON and the T + D pan-tumor pool; this difference was principally associated with the toxicity profile associated with cytotoxic chemotherapy agents. The AEs that differed between the T + D + SoC arm of POSEIDON vs the T + D pan-tumor pool were primarily hematologic and gastrointestinal in nature, reflecting the chemotherapies administered in the T + D + SoC arm of POSEIDON. In contrast, the incidence of AEs such as hypothyroidism that are observed with immunotherapies were comparable between the 2 arms. The incidence of AEs such as diarrhoea, rash and transaminase increases that are observed with both

chemotherapies and immunotherapies were generally comparable, especially when the event rate adjusted for exposure is taken into account, suggesting that chemotherapies do not intensify the typical safety profiles of the IO agents (see Table 2.7.4.2.5B, Module 5.3.5.3).

CTCAE Grade 3 or 4 adverse events

POSEIDON**:** The incidence and the most common maximum CTCAE Grade 3 or 4 AEs by PT were generally similar between the treatment arms (Table 9). The most common PTs (reported for ≥ 10% of patients) were anaemia and neutropenia. The only PTs with a higher incidence (≥ 3% difference) in the T + D + SoC arm compared with the SoC alone arm were neutropenia and pneumonia. The incidence of maximum CTCAE Grade 3 or 4 AEs for other hematologic PTs was similar between the T + D + SoC and SoC alone arms, showing that the addition of tremelimumab and durvalumab to SoC did not increase the severity of chemotherapy-related events.

POSEIDON vs T + D + Chemo Pool**:** The incidence of maximum CTCAE Grade 3 or 4 AEs was similar in the T + D + SoC arm of POSEIDON and the T + D + Chemo pool. Neutropenia was reported for fewer patients in POSEIDON than in the T + D + Chemo pool (17% vs 23.7%). This could be partly attributed to the different SoC chemotherapies administered in POSEIDON and CASPIAN and could also be possibly due to the reporting differences for laboratory abnormalities between the 2 studies.

POSEIDON vs T + D Pan-Tumor Pool**:** The overall incidence of maximum CTCAE Grade 3 or 4 AEs was similar in the T + D + SoC arm of POSEIDON and the T + D pan-tumor pool. The most common PTs (anaemia, neutropenia, neutrophil count decreased, and thrombocytopenia) of maximum CTCAE Grade 3 or 4 AEs were higher in frequency (> 5% difference) in the POSEIDON T + D + SoC arm compared to the T + D pan-tumor pool, which is to be expected as they are possibly due to the chemotherapy in POSEIDON.

The Applicant's Position:
Overall, combination of tremelimumab, durvalumab and SoC chemotherapy demonstrated a manageable safety and tolerability profile. The nature and incidence of AEs in the POSEIDON D+T+SOC arm generally reflect the safety profile of the combination of Durvalumab, Durvalumab plus tremelimumab and the chemotherapeutic agents. The most common reported events and events grade ¾ were hematologic or Gastrointestinal in nature reflecting the chemotherapeutic agents safety pofile and were manageable in accordance with standard management guidelines. The closer similarity to the T + D + Chemo pool provides reassurance of the safety profile of the proposed association of D+T+SOC in a population affected by throracic malignancies and the differences observed with the T + D pan-tumor pool are likely reflecting the different indications of studies in this pool, the different exposures as a consequence and the lack of exposure to chemotherapeutic agents in this pool.

The FDA's Assessment:
FDA agrees that the safety and tolerability of T + D + SoC are acceptable in the setting of a life-threatening disease. While FDA agrees that the incidences of the most common AEs were generally similar between the T + D + SoC and SoC alone arms, the following AEs occurred with greater frequency (≥5%) in the T + D + SoC arm compared to the SoC arm: nausea, diarrhea, hypothyroidism, pruritis, pyrexia, pneumonia, upper respiratory tract infection, musculoskeletal pain, and rash. The severity of these more frequently occurring AEs was generally mild; only Grade 3-4 events of pneumonia occurred

at a substantially greater rate compared to the SoC arm (8% vs. 4.2%).

AEs that occurred with ≥5 % incidence in the T + D + SoC arm as compared to the D + SoC arm included nausea, diarrhea, pyrexia, decreased appetite, pneumonia, and rash. While the addition of tremelimumab to the D + SoC regimen may increase the frequency of these AEs, it did not lead to more severe AEs. The difference between the rates of Grade 3 or 4 AEs did not exceed 2% for any AE category when comparing the T + D + SoC and D + SoC arms.

Adverse drug reactions

Adverse drug reactions (ADRs) related to durvalumab and tremelimumab are identified by ongoing signal evaluation based on emerging safety data from all data sources (nonclinical findings, clinical data from ongoing clinical trial program, and post-marketing safety reports for durvalumab), as well as by comparative analyses of randomized comparator/placebo controlled pivotal trials in the target populations. The risks with durvalumab identified prior to analysis of data from POSEIDON are summarized in the IMFINZI prescribing information. The identified risks for durvalumab are also considered identified risks for the durvalumab + tremelimumab combination. Additional identified risks for durvalumab plus tremelimumab combination therapy include: lipase increased and amylase increased, intestinal perforation and large intestine perforation.

Recently, the ADRs of pancreatitis and encephalitis have been identified for durvalumab based on global safety data from all currently available information, including spontaneous reports, clinical trial data, clinical trial comparator arm analysis, and data from other agents with similar mechanisms of action. In the POSEIDON study, comparative analyses were conducted to identify AEs with an increased frequency in the T +D + SoC arm compared with the SoC alone arm. A Bayesian framework method was used to identify AEs with 95% posterior probability that the relative risk-ratio is > 1. Analyses included AEs by severity, AEs leading to discontinuation, SAEs, and laboratory abnormalities that worsened from baseline and individual case/case series review for evidence strongly indicative of a causal association. Based on the analysis and review, no ADRs were identified specific for durvalumab in combination with tremelimumab and SoC chemotherapy (abraxane + carboplatin; gemcitabine + cisplatin; gemcitabine + carboplatin; pemetrexed + carboplatin; pemetrexed + cisplatin).

In the POSEIDON study, review of common AEs including nature of the events, frequency and severity, time to onset, temporal relation with durvalumab, tremelimumab or SoC chemotherapy and outcome as well as in the context of known mechanism of action and established ADRs reported in the respective current individual prescribing information of abraxane, carboplatin, cisplatin, gemcitabine or pemetrexed suggested that the following events were considered consistent with their safety profile and are included in the T + D + SoC safety profile: neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia, pancytopenia, nausea, constipation, vomiting, alopecia, fatigue, decreased appetite, stomatitis and peripheral neuropathy. These were all considered ADRs for durvalumab in combination with etoposide and platinum chemotherapy in the CASPIAN study, with the exception of peripheral neuropathy.

Although these events are included in the safety profile for T + D + SoC in the "Undesirable Effects" section of the product's reference safety information, the characteristics of these ADRs were similar between T + D + SoC, or higher in SoC groups, consistent with the individual prescribing information of SoC components in the POSEIDON study, and manageable according to guidelines in the individual prescribing information. Therefore, they are not considered new important safety concerns for inclusion in the "Warnings and Precautions" section. For additional details, see Section 2.1.9, Module 2.7.4.

The Applicant's Position:

It is recognized that ADRs known to occur with durvalumab, tremelimumab or each SoC chemotherapy given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in the T + D + SoC arm of POSEIDON. Overall, no additional new safety concerns were identified for the combination of T + D + SoC. The proposed ADR table for POSEIDON is submitted with the annotated label in Module 1.

The FDA's Assessment:
FDA agrees that no new safety concerns were identified during the review of treatment-emergent adverse events in the T + D + SoC arm of POSEIDON. The safety profile of T + D + SoC is consistent with the known mechanism of action and established adverse reactions for the drug classes of chemotherapy and immune checkpoint inhibitors. However, FDA's safety review evaluated adverse events irrespective of causality.

Treatment emergent adverse events reported in ≥10% of patients in the primary safety population and pooled safety population are presented in Table 41

Table 41: Adverse reactions in ≥ 10% of patients enrolled on POSEIDON (FDA review)

	T + D + SoC N = 330		SoC N = 333		D + SoC N = 334	
Adverse Reaction	**All Grades (%)**	**Gr 3 or 4 (%)**	**All Grades (%)**	**Gr 3 or 4 (%)**	**All Grades (%)**	**Gr 3 or 4 (%)**
Cough/ Productive Cough[a]	12	0	8	0.3	15	0
Nausea	42	1.8	37	2.1	37	0.6
Diarrhea	22	1.5	15	1.5	20	2.1
Constipation	19	0	24	0.6	22	0
Vomiting	18	1.2	14	1.5	16	1.2
Stomatitis[b]	10	0	6	0.3	13	0.3
Hypothyroidism[c]	13	0	2.1	0	8	0
Rash[d]	27	2.4	10	0.6	20	1.5
Alopecia	10	0	6	0	11	0
Pruritus	11	0	4.5	0	10	0

	T + D + SoC N = 330		SoC N = 333		D + SoC N = 334	
Adverse Reaction	**All Grades (%)**	**Gr 3 or 4 (%)**	**All Grades (%)**	**Gr 3 or 4 (%)**	**All Grades (%)**	**Gr 3 or 4 (%)**
Fatigue/Asthenia[e]	36	5	32	4.5	33	5
Pyrexia[f]	19	0	8	0	11	0
Edema[g]	10	0	10	0.6	10	0.6
Musculoskeletal pain[h]	29	0.6	22	1.5	23	2.4
Decreased appetite	28	1.5	25	1.2	22	0.6
Pneumonia[i]	17	8	12	4.2	13	6
Upper respiratory tract infections[j]	15	0.6	9	0.9	9	0.6
Headache[k]	11	0	8	0.6	7.2	0

Sources: ADSL (Subject-Level Analysis Dataset)_Overall Survival, ADAE (Adverse Events Analysis Dataset)_Overall Survival. Variables used: ACTARM, AEDECOD, AETOXGRN, USUBJID.
[a] Includes cough and productive cough.
[b] Includes mucosal inflammation and stomatitis.
[c] Includes blood thyroid stimulating hormone increased and hypothyroidism.
[d] Includes eczema, erythema, dermatitis, drug eruption, erythema multiforme, pemphigoid, rash, rash maculo-papular, rash papular, rash pruritic and rash pustular.
[e] Includes asthenia and fatigue.
[f] Includes body temperature increased, hyperpyrexia, hyperthermia, and pyrexia.
[g] Includes face edema, localized edema, and edema peripheral.
[h] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain,s pinal pain
[i] Includes lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial.
[j] Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.
[k] Includes headache, migraine.

Laboratory Findings

Data:
Clinical laboratory results were evaluated separately for haematology, clinical chemistry, and urinalysis variables. Within each of these categories, results were examined in 3 ways: changes in mean values over time, changes in individual patients over time, and individual clinically important abnormalities.

Hematology

POSEIDON**:** The incidence of changes to CTCAE Grade 3 or 4 was higher in the T + D + SoC arm than the SoC alone arm for neutrophils and leukocytes. For other parameters, incidence of changes to CTCAE Grade 3 or 4 was similar in the 2 treatment arms.

POSEIDON vs T + D + Chemo Pool**:** Data were similar for the T + D + SoC arm in POSEIDON and the T + D

+ Chemo pool. As expected, differences in hematology parameters are most likely due to chemotherapy.

POSEIDON vs T + D Pan-Tumor Pool**:** There were fewer changes in CTCAE Grade in the T + D pan-tumor pool than in the T + D + SoC arm of POSEIDON.

Clinical chemistry

No unexpected changes from baseline or trends in clinical laboratory chemistry values over time were observed in either POSEIDON T + D + SoC arm, or in the T + D + Chemo pool or T + D pan-tumor pool (see Table 2.7.4.7.1A and Table 2.7.4.7.1B, Module 5.3.5.3).

POSEIDON: There was a higher incidence of changes to CTCAE Grade 3 or 4 in the T + D + SoC arm than the SoC alone arm for the parameters amylase, AST, creatinine, high glucose, lipase, and low potassium. For other parameters, there was numerical difference between the treatment arms. See Section 12.4.2, POSEIDON CSR, MODULE 5.3.5.1 for further information on creatinine clearance, further information on amylase and lipase increased, which are ADRs for tremelimumab in combination with durvalumab.

POSEIDON vs T + D + Chemo Pool**:** The incidence of clinically important changes was very similar in the T + D + SoC arm of POSEIDON and the T + D + Chemo pool.

POSEIDON vs T + D Pan-tumor pool**:** Overall, incidence of changes to CTCAE Grade 3 or 4 were similar in the POSEIDON T + D + SoC arm the T + D pan-tumor pool. Incidence was higher in POSEIDON for creatinine and low potassium, but given the totality of safety data, these differences do not appear clinically meaningful.

Magnesium and GGT were evaluated regularly in some studies in the T + D pan-tumor pool, and only as clinically indicated in POSEIDON T + D + SoC arm and T + D + Chemo pool. Consequently, the incidence of changes in these parameters is more common in the T + D pan-tumor pool than in the POSEIDON T + D + SoC arm

Hepatic function abnormalities on treatment

In POSEIDON T + D + SoC arm and the safety pools, the majority of elevations in ALT or AST were ≥ 3 to ≤ 5 x ULN, and most elevations in total bilirubin were ≥ 2 to ≤ 3 x ULN (Table 42).

Cases of liver function test abnormalities meeting the criteria of potential Hy's Law (ALT or AST ≥ 3 × ULN, and total bilirubin ≥ 2 × ULN) were reported for a small percentage of patients in POSEIDON T + D + SoC arm and the safety pools. There were no confirmed cases of Hy's Law in either treatment group in POSEIDON. See Section 12.4.2.5, POSEIDON CSR, Module 5.3.5.1 for abbreviated narratives of patients who met potential Hy's Law criteria.

There were no confirmed cases of Hy's Law in CASPIAN. See CASPIAN CSR, Module 5.3.5.1 for further information.

In the T + D pan-tumor pool, a total of 51 patients (2.2%) had PHL cases. Of the 51 patients, 14 patients were from Study 22; following a detailed independent review of these cases, no cases were confirmed as true Hy's law cases due to factors indicating the presence of an alternative etiology, complications of hepatocellular carcinoma progression and/or a pattern of cholestatic liver injury at the time when PHL

criteria were met. Hy's Law was ruled out for 36 of the remaining 37 patients whose test results met the criteria. The remaining patient was enrolled in MYSTIC. The patient had a fatal AE of acute hepatic failure related to durvalumab, and Hy's Law could not be ruled out with the information provided. See the individual CSRs in Module 5.3.5.1 and Module 5.3.5.2 for more information on PHL cases.

Table 42 Liver Function Abnormalities on Treatment (Safety Analysis Set)

	Number (%) of patients				
	POSEIDON				
Category	T + D + SoC (N = 330)	SoC (N = 333)	T + D + Chemo pool (N = 596)	Chemo pool (N = 599)	T + D Pan-tumor pool (N = 2280)
ALT or AST					
≥3× to ≤5× ULN	38 (11.5)	25 (7.5)	67 (11.2)	45 (7.5)	145 (6.4)
>5× to ≤8× ULN	21 (6.4)	14 (4.2)	36 (6.0)	20 (3.3)	67 (2.9)
>8× to ≤10× ULN	3 (0.9)	3 (0.9)	6 (1.0)	3 (0.5)	18 (0.8)
>10× to ≤20× ULN	6 (1.8)	1 (0.3)	7 (1.2)	1 (0.2)	24 (1.1)
>20× ULN	1 (0.3)	1 (0.3)	9 (1.5)	2 (0.3)	24 (1.1)
Total bilirubin					
≥2× to ≤3× ULN	6 (1.8)	2 (0.6)	7 (1.2)	3 (0.5)	22 (1.0)
>3× to ≤5× ULN	3 (0.9)	0	6 (1.0)	2 (0.3)	22 (1.0)
>5× ULN	0	1 (0.3)	2 (0.3)	1 (0.2)	16 (0.7)
Potential Hy's law [a]	**3 (0.9)**	**1 (0.3)**	**9 (1.5)**	**2 (0.3)**	**51 (2.2)**

[a] The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin evaluation.
Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first).
Patients are counted only once in the worst reported sub-category. Source: see Table 2.7.4.7.3A and Table 2.7.4.7.3B, Module 5.3.5.3.

Urinalysis

No clinically meaningful changes in urinalysis parameters were observed over time in either the T + D + SoC arm or the SoC alone arm of POSEIDON (see Section 12.4.3, POSEIDON CSR, Module 5.3.5.1). Urinalysis results are presented at the individual study-level and not at a pooled level for the safety pools and are available in the individual CSRs in Modules 5.3.5.1 or 5.3.5.2.

The Applicant's Position:
There were no clinically meaningful changes observed in laboratory parameters. As expected, differences in hematology parameters were most likely due to chemotherapy.

The FDA's Assessment:
The most common lab abnormalities of all grades that occurred in the primary safety population were increased creatinine (89%), neutropenia (71%), lymphocytopenia (63%), increased alanine aminotransferase (ALT) (6%), increased aspartate aminotransferase (AST) (63%), hyponatremia (55%), hyperkalemia (49%), hyperglycemia (42%), increased amylase (41%), and increased lipase (35%). The most common (≥10%) grade 3 or 4 lab abnormalities observed in patients treated with T + D + SoC were neutropenia (37%), anemia (24%), lymphocytopenia (20%), increased lipase (14%), and thrombocytopenia (11%).

FDA agrees with the Applicant's assessment of the potential Hy's law cases.

The laboratory abnormality profile associated with T + D + SoC treatment was similar to that of patients treated with SoC alone, largely reflecting the known toxicity profile of cytotoxic chemotherapy. FDA's assessment of the common laboratory abnormalities worsening from baseline is provided in Table 43.

Table 43: Select laboratory abnormalities that worsened from baseline in ≥ 10% of patients enrolled on POSEIDON (FDA review)

Laboratory Abnormality[1]	T + D + SoC[2] n=330		SOC[3] n=333	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Lipase increased	35	14	25	5
Hyponatremia	55	13	50	11
Hypernatremia	15	0	14	0
Amylase increased	41	9	25	6
Hypokalemia	21	7	17	2.8
Hyperglycemia	42	6	37	3.1
Increased ALT	64	6	56	4.7
Increased AST	63	5	55	2.2
Blood creatinine increased	89	4.0	83	1.9
Increased Alkaline Phosphatase	33	3.4	26	1.2
Gamma Glutamyl Transferase increased	38	2.2	35	4.7
Hyperkalemia	49	2.2	35	2.8
Albumin decreased	27	1.9	18	0.9
Hypocalcemia	58	0.9	49	0.9
Hypomagnesemia	12	4	23	0
Bilirubinemia	16	0.9	8	0.3
Hematology				
Neutropenia	71	37	69	32
Anemia	84	24	84	25
Leukopenia	77	21	81	18
Lymphocytopenia	67	20	60	19
Thrombocytopenia	53	11	54	12

[1] Graded according to NCI CTCAE version 4.03

[2] The denominator used to calculate the rate varied from 45 to 326 based on the number of patients with a baseline value and at least one post-treatment value.
[3] The denominator used to calculate the rate varied from 43 to 323 based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs

Data:
In POSEIDON, summary statistics over time for blood pressure, heart rate, and respiratory rate showed no clinically meaningful changes for either the T + D + SoC arm or the SoC alone arm (see Table 14.3.8.1, POSEIDON CSR, Module 5.3.5.1). Vital signs and physical findings results are presented at the individual study-level and not at a pooled level for the safety pools and are available in the individual CSRs in Modules 5.3.5.1 or 5.3.5.2.

The Applicant's Position:
There were no clinically meaningful changes observed in vital signs.

The FDA's Assessment:
FDA agrees.

Electrocardiograms (ECGs)

Data:

The POSEIDON study was not designed to formally assess ECG interval, rhythm, rate, or morphology. ECGs were collected at baseline or as clinically indicated throughout the study. There were no clinically meaningful findings (see Section 12.5, POSEIDON CSR, Module 5.3.5.1). ECG results are presented at the individual study-level and not at a pooled level for the safety pools and are available in the individual CSRs in Module 5.3.5.1 or 5.3.5.2.

The Applicant's Position:
There were no clinically meaningful changes observed in ECG.

The FDA's Assessment:
FDA agrees.

QT

Data:

In Study 06, there was an in-depth assessment of digital centrally-read ECGs in 313 patients who received T + D. There was no evidence of clinically meaningful cardiac effects associated with T + D treatment. The concentration-baseline adjusted QTcF (ΔQTcF) relationship was also evaluated. For this analysis, 67 and 66 patients for durvalumab and tremelimumab, respectively, had centrally read triplicate ECG and concentration-matched observations. The modeling results demonstrated no

significant linear relationship between durvalumab or tremelimumab concentrations and ΔQTcF (see Appendix 16.1.13, Study 06 CSR, Module 5.3.5.2).

The Applicant's Position:
No safety concerns pertaining to and associated with the elongation QT interval were identified.

The FDA's Assessment:
FDA agrees.

Anti-drug antibody-related adverse events

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

T + D + Chemo Pool: Of the 456 tremelimumab ADA-evaluable patients, 55 (12.1%) tested positive for tremelimumab at any visit. Of the 477 durvalumab-evaluable patients, 48 (10.1%) tested positive for durvalumab at any visit.

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

See Table 2.7.4.9.1.1 and Table 2.7.4.9.1.2, Module 5.3.5.3 for details. See the Integrated Summary of Immunogenicity (ISI), Module 5.3.5.3 and Section 12.6, POSEIDON CSR, Module 5.3.5.1 for further information.

The Applicant's Position:

The frequency of tremelimumab ADA-positive patients was comparable across the T + D + SoC arm of POSEIDON, T + D + chemo pool and the pan-tumor pool (<5% difference). The frequency of durvalumab ADA-positive patients was comparable between the T + D + SoC arm of POSEIDON and the T + D + chemo pool (<5% difference); however, when compared to the T + D pan-tumor pool, the frequency of durvalumab ADA-positive patients was numerically higher in the T + D + SoC arm of POSEIDON (6.2% vs 14.7%).

Across the AE profile, in the majority of AE categorical data, the percentage of AEs between ADA-positive patients for tremelimumab or durvalumab was generally comparable with ADA-negative patients for tremelimumab or durvalumab in the POSEIDON T + D + SoC arm, T + D + chemo pool, and T + D pan-tumor pool.

The FDA's Assessment:
See Section 6 for FDA's assessment of anti-drug antibody-related adverse events.

Safety results – Contribution of Components

In a combination treatment regimen, the individual components are required to establish their distinct contributions to the overall treatment effect. The 3-arm additive design of the pivotal POSEIDON study supports a clear evaluation of the contribution of each component of the proposed regimen – chemotherapy, durvalumab, and tremelimumab – within the pivotal study supporting the submission. This section describes the contribution of components from the safety and tolerability perspective.

Contribution of chemotherapy to the safety and tolerability profile of T + D + SoC

The contributions of chemotherapy to the overall safety and tolerability profile of T + D + SoC were characterized based on the safety and tolerability profile observed in the SoC alone arm in the POSEIDON study. Adverse events reported in the SoC arm were in line with the known safety profiles of individual chemotherapies and were manageable with standard treatment guidelines. For additional details, see Section 12, POSEIDON CSR, Module 5.3.5.1.

Contribution of durvalumab to the safety and tolerability profile of T + D + SoC

Overall, D + SoC demonstrated a manageable safety and tolerability profile. The AEs reported in the D + SoC arm were consistent with the known safety and tolerability profile of durvalumab and chemotherapies. As anticipated, the most commonly reported AEs by PT (≥20% of patients in either arm) were hematologic or gastrointestinal in nature reflecting the chemotherapies administered with the treatment. For additional details, see Section 12, POSEIDON CSR, Module 5.3.5.1.

Contribution of tremelimumab to the safety and tolerability profile of T + D + SoC

Comparison of safety data from the T + D + SoC arm and the D + SoC arm gives an insight into the contribution of tremelimumab to the safety profile of T + D + SoC. Adverse events by PT that were reported in a higher percentage of patients (≥5% difference between arms) in the T + D + SoC arm compared with the D + SoC arm, respectively were nausea (41.5% vs 36.2%), neutropenia (30.0% vs 23.7%), decreased appetite (28.2% vs 21.6%), rash (19.4% vs 14.1%), thrombocytopenia (18.2% vs 12.9%), asthenia (17.0% vs 9.9%), pyrexia (16.1% vs 9.3%), and hypothyroidism (11.8% vs 6.3%) (Table 2.7.4.2.5A). The most commonly reported AEs were hematologic in nature and in line with the concomitant use of chemotherapies. Maximum Grade 3 or 4 AEs were reported in a similar percentage of patients in the T + D + SoC and SoC arms (53.3% vs 54.8%). The incidence of SAEs were numerically higher in the T + D + SoC arm compared with the D + SoC arm (44.2% vs 40.1%). AEs leading to death were reported in a higher percentage of patients in the T + D + SoC arm compared with the D + SoC arm (12.4% vs 10.2%). There was no particular pattern in the type of AEs that lead to treatment discontinuation or death.

The AEs reported on T + D + SoC and D + SoC arms were consistent with the known safety profiles of tremelimumab, durvalumab and SoC chemotherapies. See Section 12.3.2.1, POSEIDON CSR, Module 5.3.5.1 for further information.

As expected, the incidence of imAEs was numerically higher in the T + D + SoC arm than the D + SoC arm (see Table 2.7.4.9.1, Module 5.3.5.3). Although the overall incidence of imAEs was higher, the incidence of maximum Grade 3 or 4 imAEs, imAEs with outcome of death, and imAEs leading to discontinuation of

any study treatment were generally similar in both arms. A higher percentage of patients had an imAE that required treatment intervention with systemic corticosteroids, high-dose steroids, immunosuppressants and endocrine therapy in the T + D + SoC arm compared to the D + SoC arm. This suggests that although imAEs were more common in the T + D + SoC arm than the D + SoC arm, Investigators could successfully manage them with existing treatment guidance. For further information see Section 12.2.3, POSEIDON CSR, Module 5.3.5.1.

The FDA's Assessment:
An assessment of the contribution of tremelimumab to the toxicity profile of the T + D + SoC treatment regimen was made by evaluating safety data from the D + SoC arm. Across these arms, increases in the incidences of specific TEAEs, TEAEs leading to treatment interruption or discontinuation, imAEs, SAEs, and laboratory abnormalities that occurred in the T + D + SoC arm compared to the D + SoC arm were minor. In summary, the addition of tremelimumab to D + SoC does not appear to significantly change the toxicity profile of the regimen. Furthermore, although the overall incidence of imAEs was higher in the T + D + SoC arm compared to the D + Soc arm, the increase in imAE severity was minimal. FDA views the toxicity profile of T + D + SoC to be consistent with the mechanism of action for this combination of therapies.

Analysis of Submission-Specific Safety Issues

Data:
Not applicable

The FDA's Assessment:
FDA agrees.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
No information has been collected in the current application.

The FDA's Assessment:
FDA agrees.

Safety Analyses by Demographic Subgroups

The Applicant's Position:
There were no clinically meaningful differences in the safety profile of tremelimumab, durvalumab and SoC chemotherapy combination with respect to sex, race and geographic region. For additional details see Section 5, Module 2.7.4.

The FDA's Assessment:
Of the 330 patients with metastatic NSCLC treated with T + D + SoC, 143 (43%) patients were older than 65 years and 35 (11%) patients were 75 years or older. Grade 3 or 4 TEAEs occurred at a slightly higher rate in patients >65 years old (65% vs 59%).

The patient population that received T + D + SoC was predominantly male (80%). The incidence of Grade 3 or 4 TEAEs was slightly higher in females treated with T + D + SoC (68% vs 60%).

In general, FDA agrees that the differences in incidences of adverse events with respect to age and sex were not clinically meaningful.

The size of racial and ethnic subgroups were too small to to draw substantial conclusions about whether this demographic factor had an effect on safety.

Specific Safety Studies/Clinical Trials

The Applicant's Position:
No safety specific clinical studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
No new information concerning human carcinogenicity or tumor development is provided in this supplement.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

Pregnancy

No pregnancies were reported during the POSEIDON study as of the DCO date.

There are no data on the use of tremelimumab and durvalumab in pregnant women and tremelimumab and durvalumab are not recommended during pregnancy or in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose of durvalumab or tremelimumab.

Based on the mechanism of action, durvalumab or tremelimumab has the potential to affect maintenance of pregnancy and may cause fetal harm when administered to a pregnant woman.

Although antibodies such as tremelimumab and durvalumab are not expected to be able to cross the blood-testes barrier, male contraception is required from the time of informed consent through 90 days after the last dose of tremelimumab or durvalumab and male patients must refrain from sperm donation from the time of informed consent through 90 days after the last dose of tremelimumab or

durvalumab.

Lactation

There is no information regarding the presence of tremelimumab or durvalumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants from durvalumab or tremelimumab, a lactating woman should be advised not to breast-feed during treatment and for at least 3 months after the last dose.

Fertility

There are no data on the potential effects of tremelimumab or durvalumab on fertility in humans or animals. In repeat-dose toxicology studies of up to 3 months duration with durvalumab in sexually mature cynomolgus monkeys, and in 6-month studies with tremelimumab there were no notable effects on the male and female reproductive organs.

The FDA's Assessment:
See FDA's response under Toxicology (Section 5.5.4).

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
Not applicable.

The FDA's Assessment:
The safety and effectiveness of tremelimumab have not been established in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose: Tremelimumab and durvalumab do not have any particular effect or characteristic that might increase the likelihood of intentional overdose. There is no specific treatment in the event of tremelimumab or durvalumab overdose, and possible symptoms have not been established.

Drug abuse: Based on the clinical setting of use, mode of action, physiological and pharmacological activity, and lack of stimulant properties, tremelimumab in combination with durvalumab is unlikely to be abused.

Withdrawal and rebound: Because tremelimumab and durvalumab have no known potential for dependence and are not dosed continuously, withdrawal or rebound events are not relevant to treatment with tremelimumab and durvalumab.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

As of the date of this application, tremelimumab is not approved in any region.

As of 05 October 2021, durvalumab is approved in 75 countries for Stage III, unresectable, NSCLC, in 64 countries for ES-SCLC, and 17 countries for metastatic UC. The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) since launch to 30 June 2021 has been estimated to be (b) (4) patient-years.

The Applicant's Position:

No new safety concern was identified based on the post-marketing safety reports.

Tremelimumab is not yet approved for use in any country

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

Tremelimumab was approved in the U.S. on October 21, 2022, in combination with durvalumab for the treatment of adult patients with unresectable HCC.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
AstraZeneca has comprehensive processes for signal detection, regular safety reviews identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the reference safety information). In addition, these processes enable the identification of safety topics that need to be kept under close surveillance. The safety signal detection activities include review of reported AEs from postmarketed sources, and a review of the published literature relevant to durvalumab. The postmarket data for durvalumab are regularly reviewed for new findings or trends. The Applicant will employ the same measures for tremelimumab.

The FDA's Assessment:
A REMS is not required to ensure safe and effective use of tremelimumab in combination with durvalumab and platinum-based chemotherapy. T + D + SoC will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

Integrated Assessment of Safety

The Applicant's Position:

- The combination of tremelimumab, durvalumab, and SoC chemotherapy demonstrated a manageable safety and tolerability profile.
- The overall safety findings were consistent with the known safety profiles of tremelimumab + durvalumab, durvalumab, and chemotherapy. The addition of tremelimumab and durvalumab did not compromise the ability to administer chemotherapy.
- Immune-mediated AEs were manageable with standard treatment guidelines.
- No new safety concerns were identified.

The FDA's Assessment:
In general, FDA agrees with the Applicant's position. No new safety concerns were identified during FDA's review.

Based on FDA review of safety data from both the POSEIDON primary safety population (n=330) and the pooled safety population of patients from POSEIDON and CASPIAN (n=596), D + T + SoC is generally well tolerated and has a toxicity profile that is consistent with other combinations of (an) immune checkpoint inhibitor(s) with platinum-based chemotherapy. As immune checkpoint inhibitors have been utilized for the treatment of lung cancer for several years, oncologists are experienced with identifying and managing imAEs. The addition of tremelimumab to D + SoC did not lead to a significant increase in adverse reactions leading to treatment discontinuation. Furthermore, the overall low rates of TEAEs leading to treatment discontinuation in the T + D + SoC indicates acceptable tolerability of this treatment regimen.

SUMMARY AND CONCLUSIONS

Statistical Issues

The FDA's Assessment
The statistical assessment of efficacy was based on the submitted data and results of the primary endpoints of BICR-assessed PFS per RECIST 1.1 and OS for the comparison of D + SoC and SoC and the key secondary endpoints of BICR-assessed PFS and OS comparing T + D + SoC and SoC in the intent-to-treat population comprised of adult patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations in POSEIDON. Alpha was split between the two primary endpoints (2-sided alpha of 1% and 4% for PFS and OS, respectively), and the overall study-wise Type I error control was achieved using an O'Brien-Fleming alpha-spending method for interim analyses and a hierarchical testing approach for testing additional pre-specified endpoints. The study met statistical significance for the comparison D + SoC vs. SoC for the primary endpoint of BICR-assessed PFS, but a statistically significant OS benefit for this treatment comparison was not observed. Alpha from the statistically significant endpoint of PFS was re-allocated to test the key secondary endpoints BICR-assessed PFS and OS comparing T + D + SoC to SoC. A statistically significant and clinically meaningful treatment benefit was observed for both PFS and OS for these key secondary comparisons. A post-hoc finding of higher BICR-assessed ORR and longer median DOR in the T + D + SoC arm compared to the SoC arm provides further supportive evidence of the efficacy of T + D + SoC in the indicated patient population.

There were no major statistical issues identified during the review of this application. While a statistically significant PFS and OS benefit was observed in patients treated with T + D + SoC compared to SoC alone, the descriptive analyses of PFS and OS results were numerically similar and marginally higher in the T + D + SoC arm compared to the D + SoC arm. Although there was not a formal statistical comparison of PFS and OS results in these two experimental arms, the Kaplan-Meier plot for OS showed separation of the survival curves between the T + D + SoC and D + SoC arms during the trial follow-up period extending to approximately 44 months from randomization. It is important to recognize that this data involves a small number of patients in each treatment arm; however, the incremental difference in OS between the T + D + SoC and D + SoC arms appears to be sustained over time.

The statistically significant and clinically meaningful improvement in OS observed in patients who received T + D + SoC compared with SoC, supported by the descriptive comparison of the T + D + SoC and D + SoC arms as well as the mechanistic plausibility of dual immune checkpoint blockade in NSCLC, provides substantial evidence of effectiveness supporting regular approval of the T + D + SoC treatment regimen.

Conclusions and Recommendations

The FDA's Assessment:

POSEIDON is an international, open-label, three-arm, randomized (1:1:1) clinical trial evaluating the efficacy and safety of durvalumab in combination with platinum-based chemotherapy with or without tremelimumab compared to platinum-based chemotherapy in 1013 patients with advanced, previously untreated NSCLC that did not harbor an ALK or EGFR mutation.

Treatment with T + D + SoC demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of OS over SoC with a HR for OS of 0.77 (95% CI: 0.65, 0.92) and a median OS of 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC arm. These results are supported by a statistically significant improvement in the key secondary endpoint of BICR-assessed PFS with a HR of 0.72 (95% CI: 0.60, 0.86) favoring T + D + SoC over SoC and a median PFS of 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 4.8 months (95% CI 4.6, 5.8) in the SoC arm.

The safety profile of the T + D + SoC regimen is acceptable in the context of a life-threatening condition and is manageable with product labeling. Based on a favorable risk:benefit assessment, the FDA review teams recommend regular approval of tremelimumab in combination with durvalumab and platinum-based chemotherapy for the following indication:

Tremelimumab in combination with durvalumab and platinum-based chemotherapy is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

X	X
Primary Statistical Reviewer Arup Kumar Sinha	Statistical Team Leader Pallavi Mishra-Kalyani

X X

Primary Clinical Reviewer
Erica Nakajima

Clinical Team Leader
Nicole Drezner

Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
FDA did not refer this supplemental application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

Pediatrics

The Applicant's Position:

Tremelimumab in combination with durvalumab and platinum-based chemotherapy was not studied in pediatric NSCLC.

An amended initial Pediatric Study Plan (iPSP-12) for tremelimumab was agreed by the FDA on 23-March-2021. In the amended iPSP, the Applicant plans to

request a full waiver for pediatric studies for tremelimumab in combination with durvalumab and platinum based chemotherapy for treatment of 1L NSCLC [redacted (b) (4)]

AstraZeneca submitted the request for waiver [redacted (b) (4)] in the tremelimumab BLA and durvalumab sBLA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Labeling Recommendations

Data:
This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labelling.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
The proposed prescribing information has been edited in accordance with 21 Code of Federal Regulations (CFR), final and draft labeling guidances to ensure safe and effective use of tremelimumab and durvalumab.

Labeling Section	Applicant Proposal	FDA Revisions
1 INDICATIONS AND USAGE	TRADENAME, in combination with durvalumab and platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.	TRADENAME, in combination with durvalumab and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. FDA removed "first-line" to broaden the indicated population to those who may receive clinical benefit.
2 DOSAGE AND ADMINISTRATION	Foot notes under Table 1: (b) (4)	The sponsor proposed a dosing chart that had the important dosing details in footnotes. FDA proposed revised dosing tables. New, agreed upon tables are: Table 1 Recommended Dosage Schedule Table 2: Recommended (b) (4) Dosage These new tables move important details out of the footnotes and clarify weight-based dosing and histology-specific chemotherapy agents. weight-based dosing. Preparation and Administration section re-written for clarity of

	(b) (4)	administration of single-agent or combination regimens.
5 WARNINGS AND PRECAUTIONS		FDA revised the pooled safety population to 596 patients with lung cancer who received T + D + SoC in POSEIDON and CASPIAN, as this is representative of the indicated dose administered to patients with lung cancer.
6 ADVERSE REACTIONS	Description of the safety data from the POSEIDON study. Adverse reaction and laboratory abnormality tables described IMJUDO with durvalumab and platinum-based chemotherapy versus platinum-based chemotherapy.	Inclusion of description of the appropriate safety pool and primary safety populations described in Warnings and Precautions section. Revised adverse reaction tables to include the appropriate comparator arm: durvalumab plus platinum-based chemotherapy. Revised inclusion of adverse reactions leading to death.
6.2 Immunogenicity	Text proposed to describe immunogenicity.	Text moved to Section 12.6 and revised based on the draft guidance Immunogenicity

		Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling.
8 USE IN SPECIFIC POPULATIONS	Clinical and non-clinical pregnancy and lactiation data proposed.	Pregnancy statement that IgG2 has potential to transfer from mother to fetus. Animal data added regarding CTLA-4 effect on pregnancy. FDA revised language for consistency with current labeling practice.
8.5 Geriatric Use	Text proposed (b) (4) ". (b) (4)	Text revised for consistency with 21 CFR 201.57(c)(9)(v).
10 OVERDOSAGE		Section omitted for consistency with 21 CFR 201.56(d)(4).
11 DESCRIPTION	Text describing product description.	Text revised for consistency with current labeling practice, molecular weight included.
12 CLINICAL PHARMACOLOGY		Elimination section revised to include information on terminal half like and clearance. Specific populations was revised to include more racial data, Pharmacodynamics section included to state that response for effectiveness has not been fully characterized.
13 NONCLINICAL TOXICOLOGY	13.2 Animal Toxicolgy and / or Pharmacology section	FDA removed this section for consistency with current labeling practice.
14 CLINICAL STUDIES		Clarified drug dosing used in POSEIDON according to weight and histology. Revised language for consistency with current labeling practice for describing efficacy endpoints. Kaplan-

		Meier plot revised for legibility. Request to increase font size for legibility of figures. Deletion of KM curves for PFS, OS curves retained.
16 HOW SUPPLIED/STORAGE AND HANDLING	Supplied and storage information.	No revisions.
17 PATIENT COUNSELING INFORMATION	Text proposed for consistency with durvalumab.	No revisions.

Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team determined that a REMS is not indicated.

Postmarketing Requrements and Commitment

The FDA's Assessment:
As the Applicant has submitted the final overall survival analysis and other updated efficacy results with associated datasets for POSEIDON, there will be no post-marketing requirements or commitments for this application.

Division Director (DHOT) (NME ONLY)

X

Division Director (OCP)

X _____

Division Director (OB)

X _____

Division Director (Clinical)

X _____

Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Appendices

References

The Applicant's References:

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The FDA's References:

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4. US FDA: YERVOY USPI.
5. US FDA: OPDIVO USPI.

Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed in the table for the three covered studies. No concerns were raised regarding the overall integrity of the data.

Covered Clinical Study (Name and/or Number):* POSEIDON (D419MC00004)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1458		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* Mystic (D419AC00001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1526		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* NEPTUNE (D419AC00003)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1306		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

	Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
	Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
	Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 21			
	Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No new information concerning nonclinical pharmacology/toxicology.

The FDA's Assessment:
FDA agrees.

OCP Appendices (Technical documents supporting OCP recommendations)

Population PK Analysis

Executive Summary

The FDA's Assessment:

In support of this BLA, the applicant submitted reports of the updated population pharmacokinetic (PPK) analyses for durvalumab and tremelimumab. The PPK model for tremelimumab was developed 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 every 4 weeks (Q4W) or every 12 weeks (Q12W). The final tremelimumab PPK model was a 2-compartment model with linear and time-dependent clearance (CL). The time dependency of CL was only observed in patients who received durvalumab and tremelimumab as combination therapy; tremelimumab serum concentrations in patients on monotherapy were adequately described by a 2-compartment PK model with linear CL.

Data from 5 clinical trials was used for durvalumab PPK model development, including CD-ON-MEDI4736-1108 (Phase 1/2), D4191C00003 (ATLANTIC, Phase 3), D4191C00001 (PACIFIC, Phase 3), D419QC00001 (CASPIAN, Phase 3), and D419MC00004 (POSEIDON, Phase 3). The studied dose range was 0.1-20 mg/kg every 2 weeks (Q2W), every 3 weeks (Q3W), or Q4W, or 1500 mg Q3W. The applicant claimed that a 2-compartment PPK model with time-dependent elimination best described durvalumab PK.

The PPK analyses showed that no clinically significant differences in the pharmacokentics of durvalumab and tremelimumab were found based on body weight (31 to 175 kg), age (19 to 96 years), sex, race (White, Black, Asian, Native Hawaiian or other Pacific Islander, or American Indian/Alskan Native), serum albumin levels (0.3-396 g/L), lactate dehydrogenase levels (12 to 15800 IU/L), soluble PD-L1 (67.1 to 3470 pg/mL), combination therapy (tremelimumab, durvalumab + tremelimumab, and durvalumab + tremelimumab + chemotherapy), ECOG status (normal activity, restricted activity, and in bed less than or equal to 50% of the time), primary indication (advanced NSCLC, pleural, BTC, EC, HPV positive anogenital cancer, MSI-H CRC, ovarian, STS, and peritoneal), region (Europe, Asia, North America, South America, Africa, and other), creatinine CL (CLcr 22.5 to 299 mL/min), and mild to moderate hepatic impairment (NCI scale).

In general, the applicant's PPK analyses for durvalumab and tremelimumab are deemed acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Specifically, the developed PPK models are acceptable to be used to derive exposure metrics for exposure-response (E-R) analyses, and to support applicant's proposed labeling statements regarding general PK information including intrinsic and extrinsic factors in the current submission.

PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	***PPK For Tremelimumab*** • *Characterize the PK of **Tremelimumab** in various indications* • *Assess the correlation between pre-defined categorical and continuous covariates and individual Empirical Bayes Estimates (EBEs)* • *Predict individual exposure metrics of tremelimumab for E-R assessment* • *Justify the tremelimumab fixed dosing of 75 mg Q3W*
Study Included	*D4190C00002 (Study 02), D4190C00006 (Study 06), D4190C00010 (Study 10), D4880C00003 (DETERMINE), D4884C00001, D419MC00004 (POSEIDON)*
Dose(s) Included	*1 mg/kg, 3 mg/kg, 10 mg/kg, 75 mg, 750 mg Q4W*
Population Included	*Patients with advanced solid tumors (BTC, EC, and SCCHN, UBC, TNBC, PMM, PDAC, NSCLC), and with metastatic NSCLC in POSEIDON study*

Population Characteristics (*See Table 19-20, Population PK and Exposure-Response Report, Module 5.3.3.5.*)	General	*Age (years) median (range, % subj >=65 yr, % subj >=75 yr): 64.0 (22.0-87.0, 48.0%, 11.0%);* *Weight (kg) median (range): 70.2 (34.0-149);* *n (%) male: 1063 (66.2%);* *n (%) in each race: White 1143 (71.2%), Black 29 (1.81%), Asian 357 (22.2%), Native Hawaiian or Other Pacific Islander 6 (0.374%), American Indian/Alaskan Native 12(0.748%), other 57 (3.55%), multiple 1 (0.0623%).*
	Organ Impairment	*Hepatic (NCI) - n (%) in each category: Normal 1435 (89.4%), mild 146 (9.1%), moderate 3 (0.187%)* *Renal (CrCL in mL/min) - median (range): 80.3 (22.5-299)*
	Pediatrics (if any)	*None*
No. of Patients, PK Samples, and BLQ		*1605 patients with 5455 PK samples for tremelimumab available: 178 (3.3%) post-dose BLQ and 39 (0.7%) outlying observations were excluded.*
Sampling Schedule	Rich Sampling	Pre-dose: Weeks 0, 1, 2, 4, 8, 12, 24, 36, 48 Post-dose (end of infusion - EOI): Weeks 0, 4, 8, 12, 24
	In ITT Population	Pre-dose: Weeks 0, 4, 12 Post-dose: Week 0 (EOI), and one additional sample at 3 months after tremelimumab discontinuation
Covariates Evaluated	Static	*baseline demographics (age, sex, race, region, body weight), primary indication, tumor type, ECOG, Smoking status, ADA status post-baseline, Hepatic function NCI, combination therapy, baseline albumin, baseline LDH, CrCL*
	Time-varying	*N/A*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM 7.4.3	Yes
Model Structure	*2-compartment model with linear and time-varying clearance (no time-varying clearance for tremelimumab monotherapy)*	Yes
Model Parameter Estimates	*(See Table 24, Population PK and Exposure-Response Report, Module 5.3.3.5.)*	Yes, see Table 44
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*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 Tmax, respectively. Shrinkage was <25% for CL and V1, and high for V2 (37%) and Tmax -maximum change of CL over time (69%).*	Yes, See Table 44
BLQ for Parameter Accuracy	*178 (3.3%) tremelimumab concentrations below the limit of quantification (BLQ) during active treatment were excluded, corresponding to the M1 method, and the minimum impact of BLQ on PK is anticipated due to the low BLQ percentage (<5%).*	Yes
GOF, VPC	*See Figure 45-46, Population PK and Exposure-Response Report, Module 5.3.3.5. (GOF); See Figure 48 and Appendix 22, Population PK and Exposure-Response Report, Module 5.3.3.5. (VPC)*	Yes, see Figure 21, Figure 22, Figure 23, Figure 24
Significant Covariates and Clinical Relevance	*See Figure 51-52, Population PK and Exposure-Response Report, Module 5.3.3.5. (forest plots of significant covariates on exposure)*	Yes The effects of significant covariates on tremelimumab CL and V1 are shown in Figure 25 and Figure 26, respectively. The same

		plots illustrating effects on AUC and Cmax are shown in Figure 27 and Figure 28, respectively. With the exception of low serum ALB, all other tested covariates appear to have little to moderate impact (< 25% change for corresponding PK parameter or metrics) based on univariate analyses.
Analysis Based on Simulation (optional)	*See Figure 67, Population PK and Exposure-Response Report, Module 5.3.3.5. (Flat dosing of 75mg Q3W vs. body weight based dosing of 1 mg/kg Q3W)*	Yes. Figure 29 showed substantial PK profile overlap between 75mg Q3W and 1mg/kg Q3W.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4)	Yes. Refer to Assessment Aid for BLA 761289 and sBLA 761069

Abbreviations: BTC=biliary tract carcinoma, EC=esophageal carcinoma, NSCLC=non-small cell lung cancer; PDAC=pancreatic ductal adenocarcinoma, PMM=pleural or peritoneal malignant mesothelioma, SCCHN=squamous cell carcinoma of the head and neck, TNBC=triple-negative breast cancer, UBC=urothelial bladder cancer.

*Note: **Durvalumab PPK** model was updated by adding POSEIDON data, and consistent with the previous submitted (BLA761069/Original and BLA761069/S-002) PPK analysis of 2-compartment, linear PK model with time-varying CL. There were no clinically relevant effects of baseline patient characteristics of body weight, age, race, renal function, and hepatic function and other intrinsic/extrinsic factors on PK of durvalumab.*

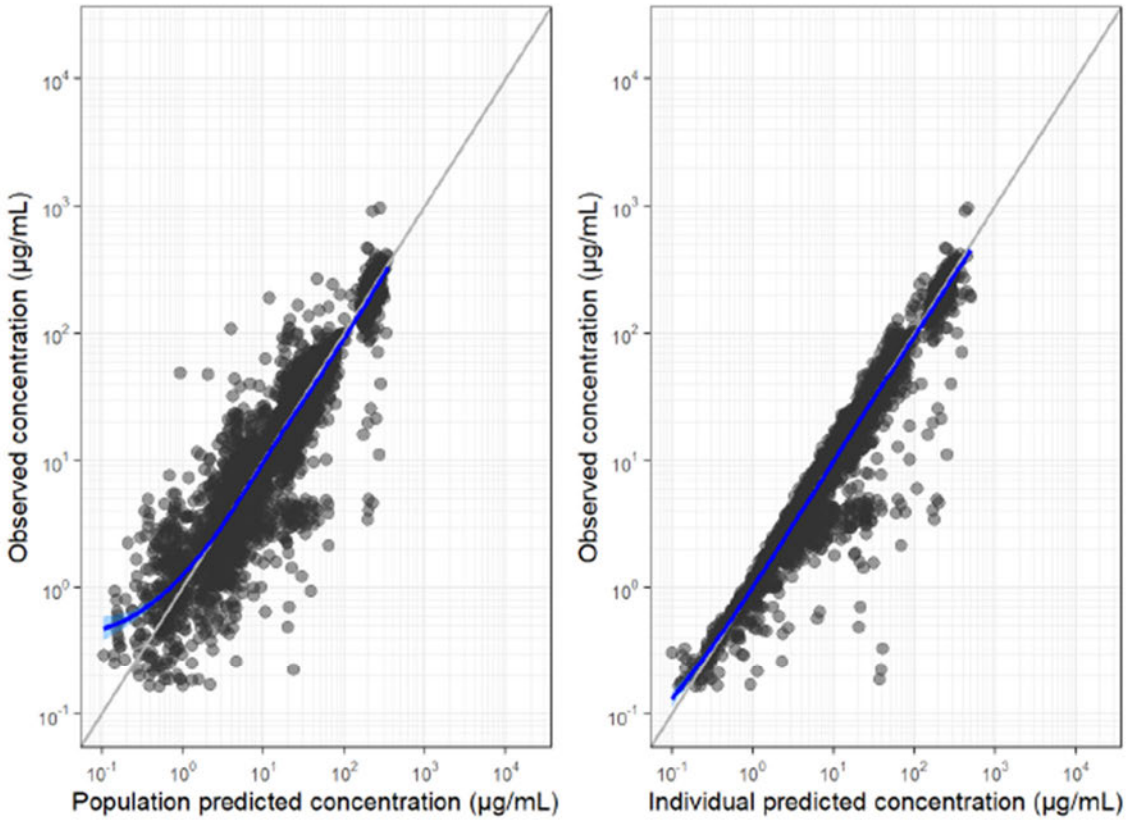
Table 44: Population PK Model Parameter Estimates for Tremelimumab (FDA review)

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.

Source: d419mc00004-pop-pk-eres-report, Table 24

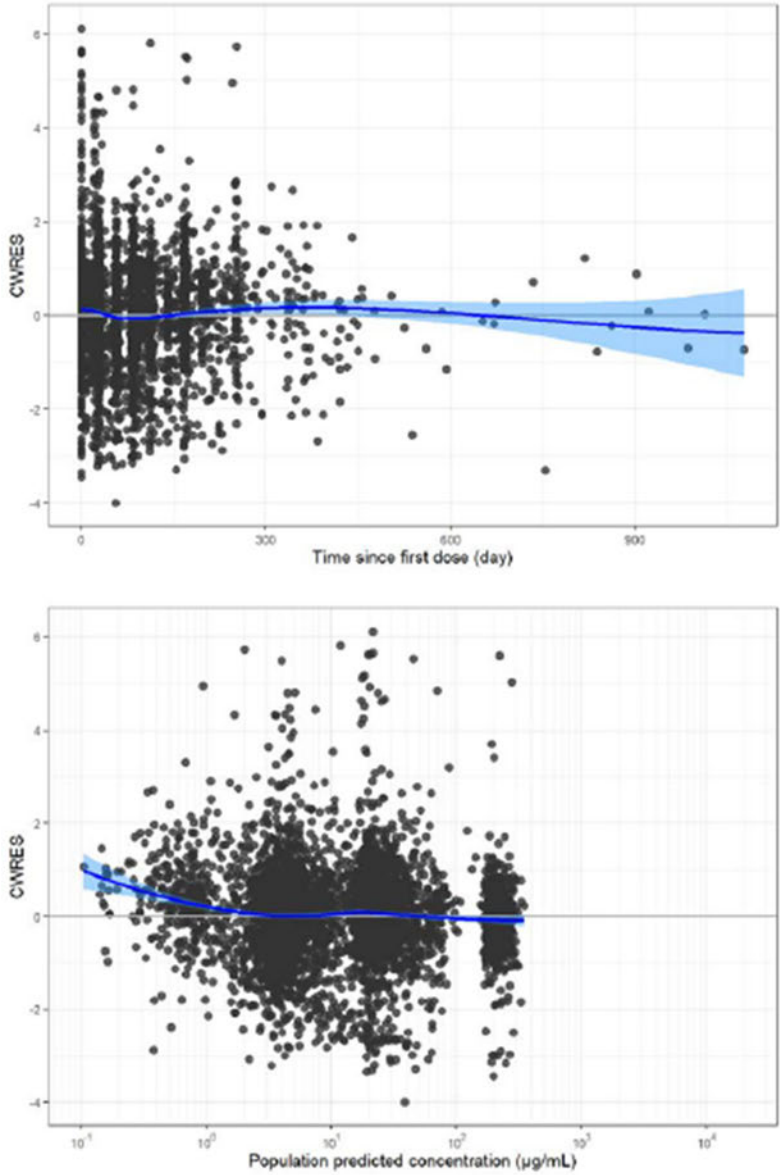
Figure 21. Tremelimumab Final PPK Model Goodness-of-Fit Plots: Observations vs Predictions



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

Source: d419mc00004-pop-pk-eres-report, Figure 45

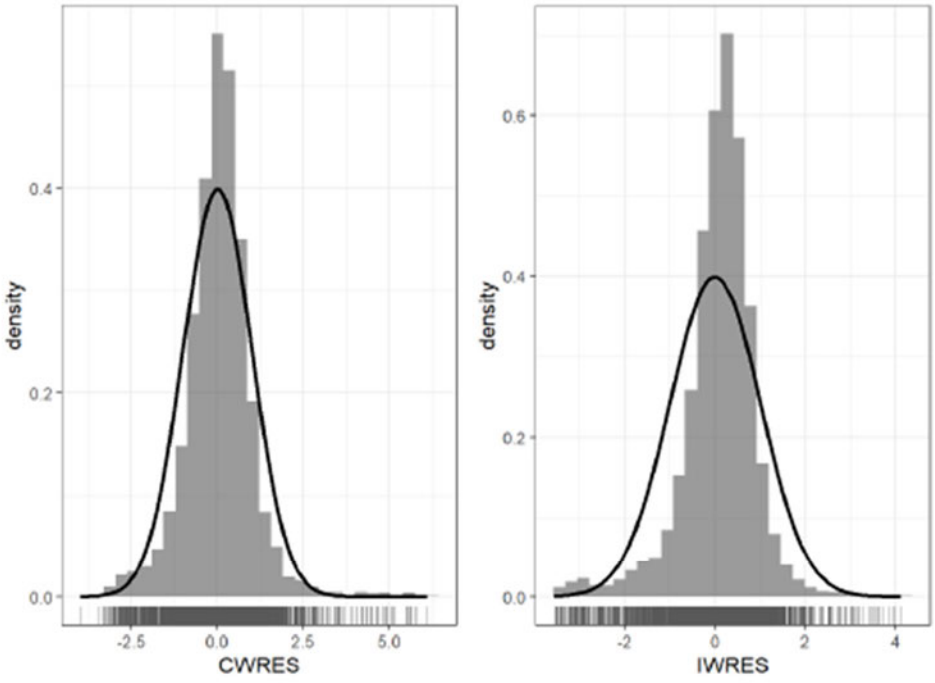
Figure 22. Tremelimumab Final PPK Model Goodness-of-Fit Plots: Residuals vs Time and vs Concentrations



Source: az-tremelimumab-pk-gof-v10.docx, References: 38da4d:1efca5 and 2209f2:c2f075
Note: Dots are individual data; the grey solid lines mark x=0. Blue solid lines are smoothed LOESS lines, with confidence areas shown as light blue areas. Predictions below the LLOQ are not shown.
Abbreviation: CWRES=conditional weighted residuals. LLOQ=lower limit of quantification.

Source: d419mc00004-pop-pk-eres-report, Figure 46

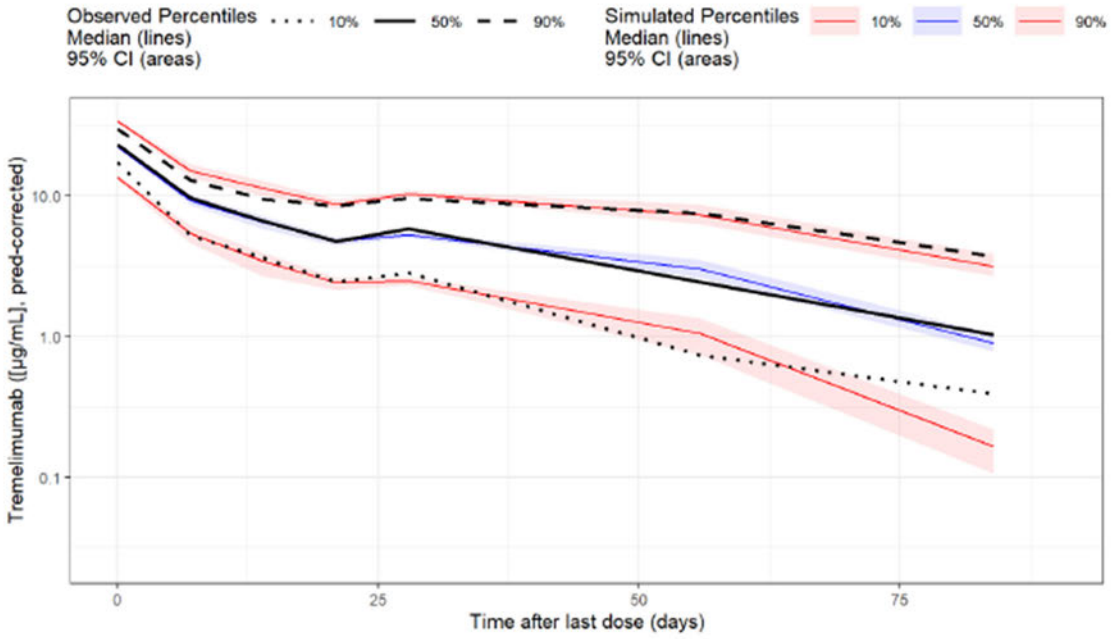
Figure 23. Tremelimumab Final PPK Model Goodness-of-Fit Plots: CWRES and IWRES Distributions



Source: az-tremelimumab-pk-gof-v10.docx, Reference: 9f4317:652d68
Note: the bold black lines are density lines of a normal distribution with a mean of 0 and a standard deviation of 1.
Abbreviations: CWRES=conditional weighted residuals, IWRES=individual weighted residuals

Source: d419mc00004-pop-pk-eres-report, Figure 47

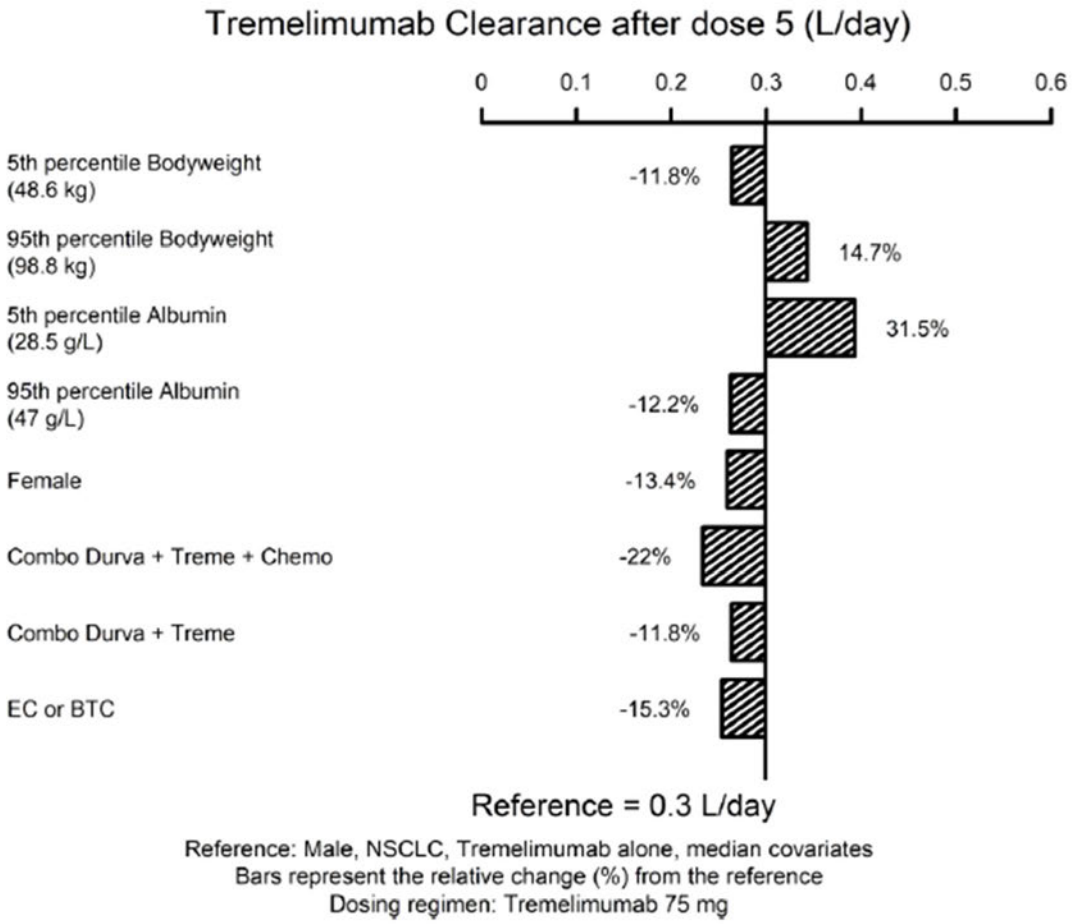
Figure 24. VPC of the Tremelimumab Final PPK Model, POSEIDON Study



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

Source: d419mc00004-pop-pk-eres-report, Figure 48

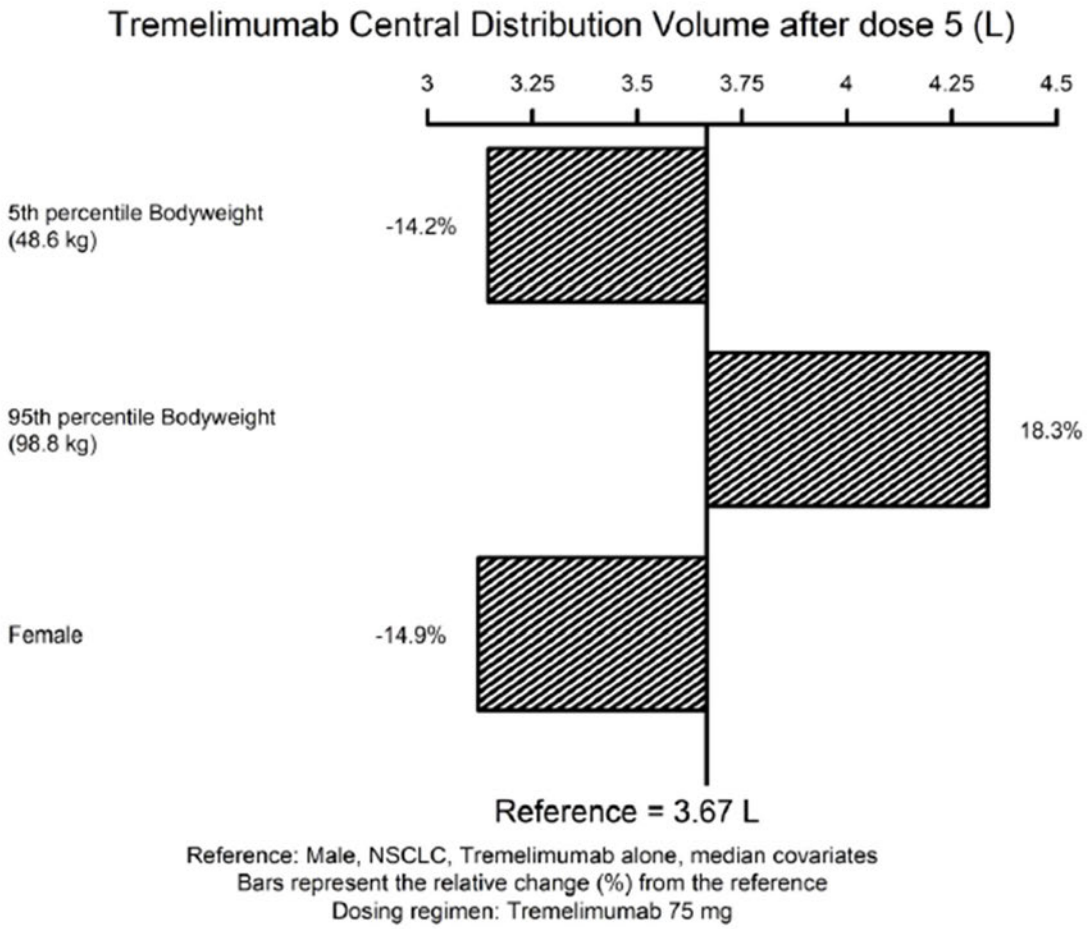
Figure 25. Univariate Impact of Covariates on Tremelimumab Clearance



Source: Source: az-treme-pk-univariate-simulations-covariates-poseidon-v6.docx, Reference: d1a844:858150
Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual clearance values between the 5th and 95th percentiles, respectively, of the median observed covariate values.
Abbreviations: Chemo=chemotherapy, BTC=biliary tract carcinoma , Durva=durvalumab, EC=esophagus carcinoma, NSCLC=non-small cell lung cancer, Treme=tremelimumab

Source: d419mc00004-pop-pk-eres-report, Figure 49

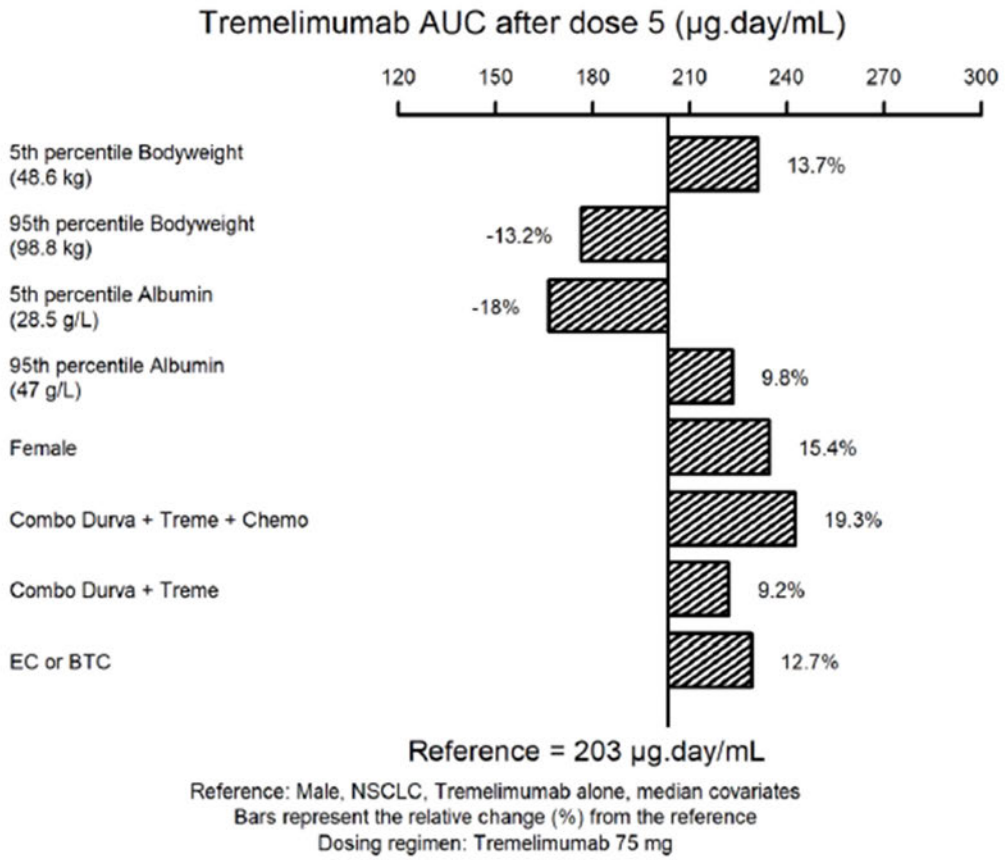
Figure 26. Univariate Impact of Covariates on Tremelimumab Central Volume of Distribution



Source: Source: az-treme-pk-univariate-simulations-covariates-poseidon-v6.docx, Reference: d1a844:948ac4
Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual central volumes of distribution between the 5th and 95th percentiles, respectively of median observed covariate values.
Abbreviations: NSCLC=non-small cell lung cancer

Source: d419mc00004-pop-pk-eres-report, Figure 50

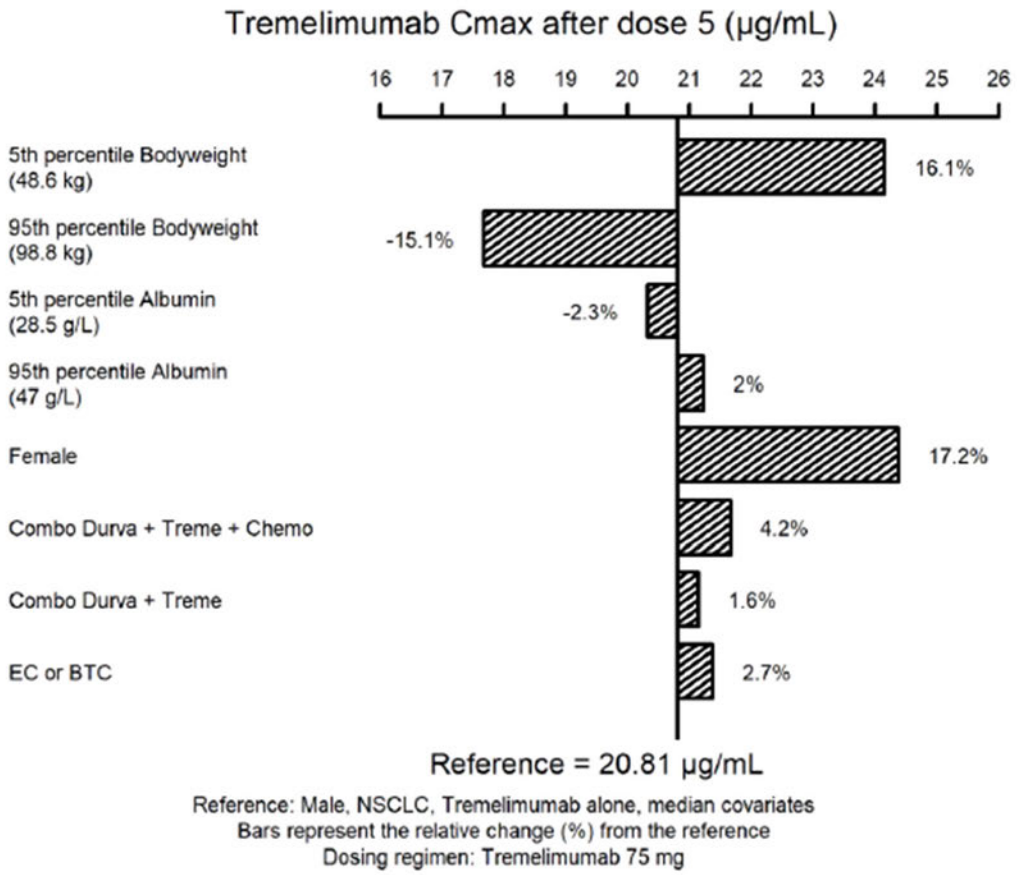
Figure 27. Univariate Impact of Covariates on Tremelimumab AUC



Source: az-treme-pk-univariate-simulations-covariates-poseidon-v7.docx, Reference: 8db541:1a0498
Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual clearance values between the 5th and 95th percentiles, respectively, of median observed covariate values.
Abbreviations: AUC=area under the serum concentration-time curve, Chemo=chemotherapy, BTC=biliary tract carcinoma, Durva=durvalumab, EC=esophagus carcinoma, NSCLC=non-small cell lung cancer, Treme=tremelimumab

Source: d419mc00004-pop-pk-eres-report, Figure 51

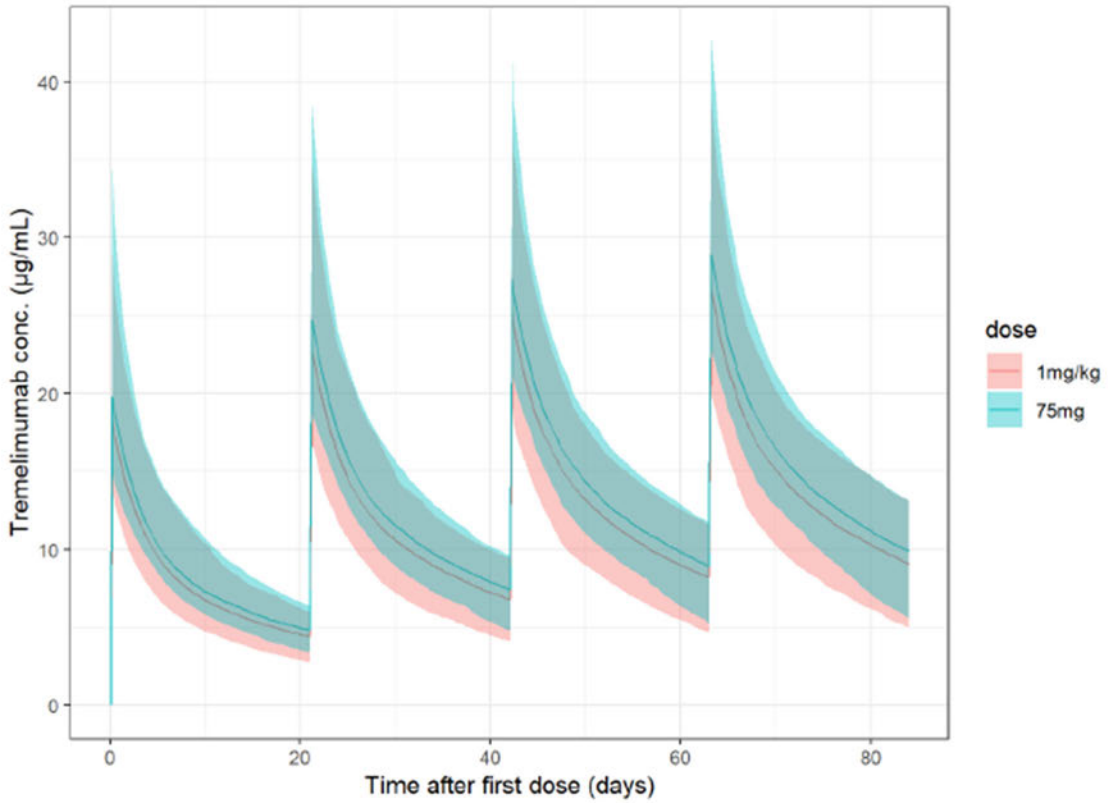
Figure 28. Univariate Impact of Covariates on Tremelimumab Cmax



Source: az-treme-pk-univariate-simulations-covariates-poseidon-v7.docx, Reference: 573a70:57ed8a
Note: Covariate effects were expressed as a percentage change from the typical value of the reference patient. For continuous covariates, bars represent the range of individual clearance values between the 5th and 95th percentiles, respectively, of the median observed covariate values.
Abbreviations: Chemo=chemotherapy, Cmax=maximum concentration, BTC=biliary tract carcinoma, Durva=durvalumab, EC=esophagus carcinoma, NSCLC=non-small cell lung cancer, Treme=tremelimumab

Source: d419mc00004-pop-pk-eres-report, Figure 52

Figure 29. Comparison of 75 mg Q3W and 1 mg/kg Q3W



Source: az-treme-sim-dosing.Rmd
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
Abbreviations: conc.=concentration, Q=every, W=week

Source: d419mc00004-pop-pk-eres-report, Figure 69

The FDA's Assessment: In general, the applicant's PPK analyses for durvalumab and tremelimumab are deemed acceptable. In addition, to support labeling statements mentioned above, applicant also provided the single dose and multiple dose PK information derived from population PK models (see Table 35, Table 36, Table 37, and Table 38 in Assessment Aid for BLA 761289 and sBLA 761069), which based on POSEIDON combined with data in various indications (D4190C00002, D4190C00006, D4190C00010, DETERMINE, D4884C00001, D419CC00002, and HIMALAYA). The proposed labeling language in Section 12.3 is acceptable.

PPK Review Issues

None

Reviewer's Independent Analysis

None

Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

In support of this BLA, the applicant submitted reports of exposure-response (E-R) analyses for efficacy based on data from 326 patients in durvalumab + tremelimumab + SoC arm of the Phase III study POSEIDON (D419MC0004). The E-R analysis dataset covered a body weight range between 34 and 134 kg and an age range of 27 and 87 years old and based on individual PK exposures derived from an applicant's PPK model. For the efficacy analysis, the relationships of efficacy endpoints, overall survival (OS) and progression-free survival (PFS), with PK metrics (Cmax, Cmin, and AUC of durvalumab or tremelimumab following first dose or at steady-state) were assessed.

Kaplan-Meier (KM) estimates stratified by the exposure quantiles for any of the PK metrics indicated no E-R relationship between OS or PFS vs. durvalumab expsoures. For tremelimumab, there was a trend showing increased PK exposures may lead to better OS and PFS based on KM plots. The KM plots also suggested the patients with lowest tremelimumab expousres (1st quantile) potentially had worse OS and PFS compared with the patients receiving SoC only. However, further case-matching analyese indicated that 1) the potential E-R relationship for trememlimumab could be confounded by covariates, 2) the patients with lowest tremelimumab exposures had comparable OS and PFS with patients receiving SoC only.

The cox proportional hazard (CPH) models were developed to further explore the correlation between efficacy endpoints, OS and PFS, and the tremelimumab PK exposures (Cmin after 1st cycle). The results suggested tremelimumab Cmin after 1st cycle was significantly correlated with OS. However, such E-R relationship was confounded by other covariates, e.g. albumin and neutrophil-to-lymphocyte ratio (NLR). Tremelimumab Cmin after 1st cycle was not correlated with PFS based on CPH analysis.

In summary, Applicant's E-R for efficacy analyses appear to be adequate. No E-R relationship was identified for durvalumab and the E-R correlation between OS and tremelimumab exposure was confounded. Therefore, the Applicant's E-R analyses for efficacy support the proposed dosing regimens for durvalumab and tremelimumab in patients with previously untreated metastatic NSCLC and no need of dose adjustment for durvalumab or tremelimumab in specific patient populations.

ER (efficacy) Assessment Summary

The Applicant's Position:

General Information

Goal of ER analysis		• assess the durvalumab/tremelimumab E-R (efficacy) relationship using POSEIDON study data. • support the evidence of effectiveness and justify the dosages and dosing regimens in the ITT population • evaluate the intrinsic and extrinsic factors, and adjustments of dosages and dosing regimens in subpopulations	
Study Included		*POSEIDON (Individual predicted exposure metrics of patients and efficacy data from POSEIDON study)*	
Endpoint		*Primary: overall survival (OS) from POSEIDON study data* *Secondary: progression-free survival (PFS) and objective response rate (ORR) from POSEIDON study data*	
No. of Patients (total, and with individual PK)		*Total 330 patients from T + D + SoC arm: 326 patients with durvalumab and tremelimumab PK*	
Population Characteristics (*See Table 26-27, Population PK and Exposure-Response Report, Module 5.3.3.5.*)	General	*Age (years) median (range): 63.0 (27.0-87.0)* *Weight (kg) median (range): 68.2 (34.0-134)* *n (%) male: 261 (80.1%)* *n (%) race: White 197 (60.4%), Black 8 (2.45%), Asian 97 (29.8%), Native Hawaiian or Other Pacific Islander 2 (0.613%), American Indian/Alaskan Native 11 (3.37%), Other 11 (3.37%).*	
	Pediatrics (if any)	*None*	
Dose(s) Included		*tremelimumab 75 mg+durvalumab 1500 mg+SoC Q3W x4 cycles; followed by durvalumab 1500 mg Q4W; additional one tremelimumab 75 mg dose at week 16*	
Exposure Metrics Explored (range)		*durvalumab exposure:* *Cmin, Dose 1 Durva (µg/mL): 69.0-207* *Cmax,Dose 1 Durva (µg/mL): 278-1060* *AUC,Dose 1 Durva (µg.day/mL): 2950-7150* *Cmin,ss Durva (µg/mL): 118-660* *Cmax,ss Durva (µg/mL): 458-1150* *AUC,ss Durva (µg.day/mL): 6150-22700* *tremelimumab exposure:* *Cmin,Dose 1 Treme (µg/mL): 1.24-9.65* *Cmax,Dose 1 Treme (µg/mL): 10.0-62.5* *AUC,Dose 1 Treme (µg.day/mL): 114-319* *Cmin,Dose 5 Treme (µg/mL): 1.68-32.2* *Cmax,Dose 5 Treme (µg/mL): 15.6-62.6* *AUC,Dose 5 Treme (µg.day/mL): 163-755*	
Covariates Evaluated		*sex, race, smoking status, baseline ECOG, hepatic function NCI method, ADA status post-baseline to durva, ADA status post-baseline to treme, tumor mutation burdens (mutations per megabase >= 20, 16, or 12), PD-L1 TC (<50, 25, or 1%), chemotherapy type, tumor histology type, age, body weight, AST, ALT, albumin, bilirubin, creatinine, baseline LDH, baseline NLR, baseline tumor size per investigator, exposure metrics*	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Primary endpoint OS:* *Cox Proportion-Hazard-CPH Model with Cmin,treme Dose5 and Tumor histology type as significant covariates;* *Secondary endpoint PFS:*	Since the exposure-response analyses with exposure metrics

	CPH Model with Cmin,treme Dose5, Tumor histology type, logNLR, PD-L1TC < 25%, and TMB<12 as significant covariates; *Case-matching analysis for OS and PFS:* *To supplement the CPH models for both OS and PFS, patients from the SOC arm were matched with those in Q1 of Cmin,Dose 5 Treme of the durvalumab + tremelimumab + SOC arm. Matching was performed based on the distributions* *of the following 10 disease-related covariates: baseline tumor size, ECOG score at baseline,* *aspartate aminotransferase (AST), albumin (ALB), LDH, NLR, tumor burden (> or < 12 mutations per megabase), tumor type (nonsquamous vs squamous), 25% of PD-L1 TC and the chemotherapy used in SOC (Abraxane based vs Gemcitabine based vs Pemetrexed based). Using the matched data, patients in the lowest quartile (Q1)* *were compared with SOC-treated patients using the final CPH model for OS and PFS.* *Secondary endpoint ORR:* *The ORR was dichotomized as PR or CR, vs SD or PD, and analyzed using a logistic regression model relating the probability of being a responder to durvalumab or tremelimumab* *exposure metrics.*	derived from the later phase of the treatment could be highly confounded by the post-treatment outcome, we requested the applicant to perform additional CPH analyses based on Cmin of tremelimumab after 1st cycle. The histology type, AST, albumin, and tremelimumab Cmin after 1st cycle were potential covaraites for OS (Table 45). Histology type, NLR, and baseline PD-L1 expression > 25% were identified as significant covaraites for PFS (Table 46). Tremelimumab Cmin after 1st cycle was correlated with albumin and NLR, suggesting the potential exposure-response between tremelimumab PK exposure and OS could be confounded.
Model Parameter Estimates	*See Table 28-31, Population PK and Exposure-Response Report, Module 5.3.3.5. (primary and major secondary endpoints)*	The parameter estimates for exposure-response

		between OS and PFS vs. tremelimumab Cmin after 1st cycle are listed in Table 45 and Table 46
Model Evaluation	*OS and PFS: graphical exploration of OS and PFS by exposure metrics of durvalumab and tremelimumab; evaluated by the change of objective function values (ofv) and significant p-value for CPH model when incorporating covariates.* *ORR: evaluated by plots showing the model-predicted response and its CI compared to observations stratified by exposure quartiles and other covariates.*	Yes
Covariates and Clinical Relevance	*No relationship between durvalumab exposure and OS or PFS was identified in the POSEIDON triplet combination arm. The Cmin after the 5th tremelimumab dose significantly influenced OS and PFS in patients enrolled in the POSEIDON study, but case matching analysis suggested that the observed relationship with tremelimumab exposure is possibly confounded by disease-related covariates.* *There appears to be no clear trend between durvalumab and tremelimumab exposure and the probability of being a responder with no statistically significant impact in the ORR logistic regression analysis ($p>0.05$).* *There appears to be no association between durvalumab or tremelimumab exposure vs. the body weight (quantiles) or ADA status (positive or negative).*	No exposure-response relationship for durvalumab (Figure 30 and Figure 31). KM plots (Figure 32 and Figure 33) and CPH analyses (Table 45) suggested potential correlation between efficacy and tremelimumab PK exposure. However, the tremelimumab PK was also correlated with disease related covariates, e.g. albumin and NLR (Figure 34), suggesting the potential exposure-reponse relationship for tremelimumab could be confounded. The KM plot for tremelimumab

		also showed the patients with lowest tremelimumab exposures (Quantile 1) had worse OS compared with patients receiving SoC only (Figure 32). Additional case-matching analyses indicated patients with low tremelimumab PK exposure had comparable OS and PFS with patients with SoC only (Table 47, Table 48, Figure 35, and Figure 36).
Simulation for Specific Population	*N/A*	
Visualization of E-R relationships	*See Figure 72, 74 (OS vs. Exposure quantiles KM plots), Figure 78, 80, (PFS vs. Exposure quantiles KM plots), Figure 84, 85 (case matching analysis for OS and PFS), Figure 89 (ORR vs. Exposure quantiles logistic regression), Appendix 25-Figure 119, 120, 121 (OS vs. Body weight quantiles or ADA Status KM plots), Population PK and Exposure-Response Report, Module 5.3.3.5.* *See Appendix 27, Population PK and Exposure-Response Report, Module 5.3.3.5. for baseline demographics stratified by quantiles*	See Figure 30, Figure 31, Figure 32, Figure 33, Figure 35, and Figure 36
Overall Clinical Relevance for ER	No need for adjustments of dose regimen as no clinical relevant E-R (efficacy) relationship identified at the dose regime in POSEIDON	Yes
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	*N/A*	

Table 45. Final CPH model parameter estimates OS vs. tremelimumab Cmin after 1st cycle

Approach 1					
Predictor	**β**	**exp(β)**	**95% CI β**	***Wald p* value**	**AIC**
TUMTYP22	0.509	1.66	[0.249 ; 0.769]	<0.001	2484.01
logAST	0.418	1.51	[0.186 ; 0.638]	<0.001	
PCMIN1T	-0.338	0.713	[-0.487 ; -0.189]	<0.001	
Approach 2					
Predictor	**β**	**exp(β)**	**95% CI β**	***Wald p* value**	**AIC**
TUMTYP22	0.590	1.80	[0.331 ; 0.849]	<0.001	2489.93
logAST	0.378	1.46	[0.157 ; 0.599]	<0.001	
logALB	-1.61	0.199	[-2.43 ; -0.794]	<0.001	

AIC=Akaike Information Criterion; ALB=albumin; AST=aspartate aminotransferase; β=estimate coefficient for a covariate; CI=confidence interval; log=log-transformed values; PCMIN1T=Cmin, cycle 1 Tremelimumab; TUMTYP22=tumor histology type (non-squamous vs squamous).

Source: Applicant's response to Information Request issued on 02/17/2022, Table 1

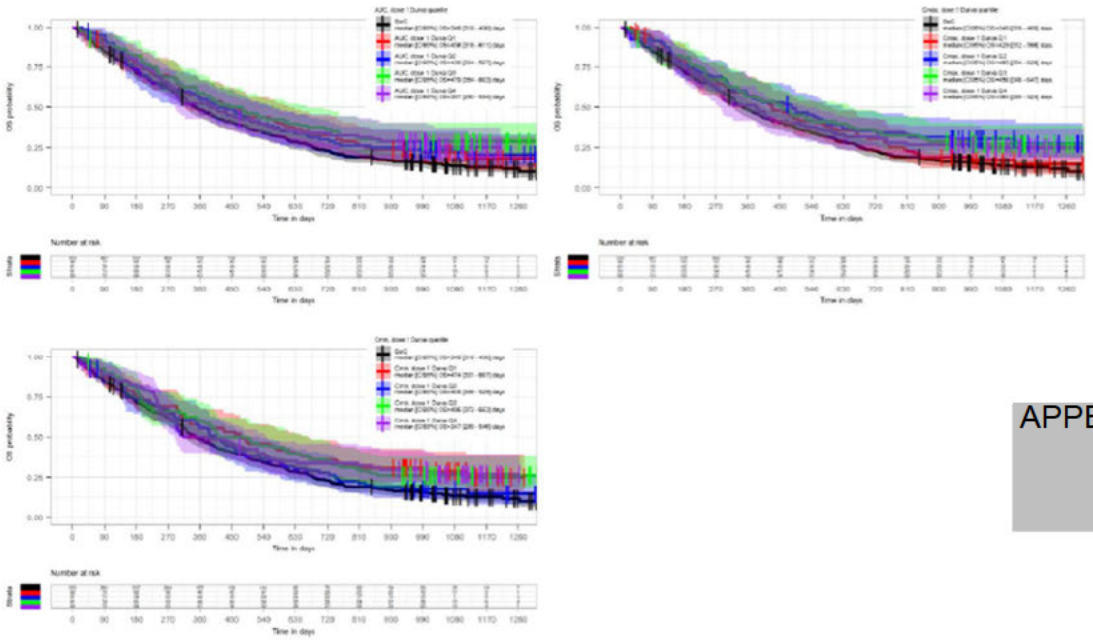
Table 46. Final CPH model parameter estimates PFS vs. tremelimumab Cmin after 1st cycle

Predictor	**β**	**exp(β)**	**95% CI β**	***Wald p* value**	**AIC**
TUMTYP22	0.692	2.00	[0.440 ; 0.943]	<0.001	2717.71
PDTC251	-0.523	0.593	[-0.783 ; -0.264]	<0.001	
logNLR	0.495	1.64	[0.273 ; 0.716]	<0.001	

AIC=Akaike Information Criterion; β=estimate coefficient for a covariate; CI=confidence interval; log=log-transformed values; NLR=neutrophil-to-lymphocyte ratio; PDTC251=baseline PD-L1 expression > 25%; TUMTYP22=tumor histology type (non-squamous vs squamous).

Source: Applicant's response to Information Request issued on 02/17/2022, Table 3

Figure 30. OS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Dose 1

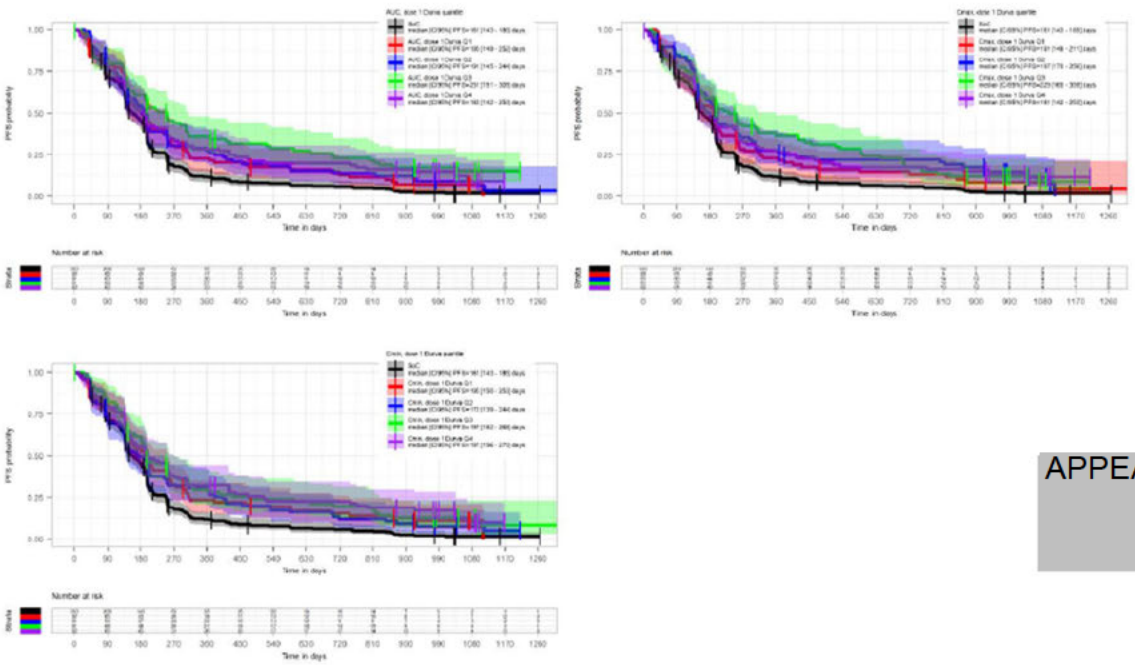


APPEARS THIS WAY ON ORIGINAL

Source: az-durvalumab-os-triplet-v25.Rmd, Reference: f8e6f3:929021
Note: Shaded areas are the 95% confidence interval around the KM curves. Vertical ticks represent the right censoring.
Abbreviations: OS=overall survival, Cmin=minimum serum concentration, Cmax=maximum serum concentration, AUC=area under the serum concentration-time curve, SOC=Standard of Care

Source: d419mc00004-pop-pk-eres-report, Figure 71

Figure 31. PFS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Dose 1

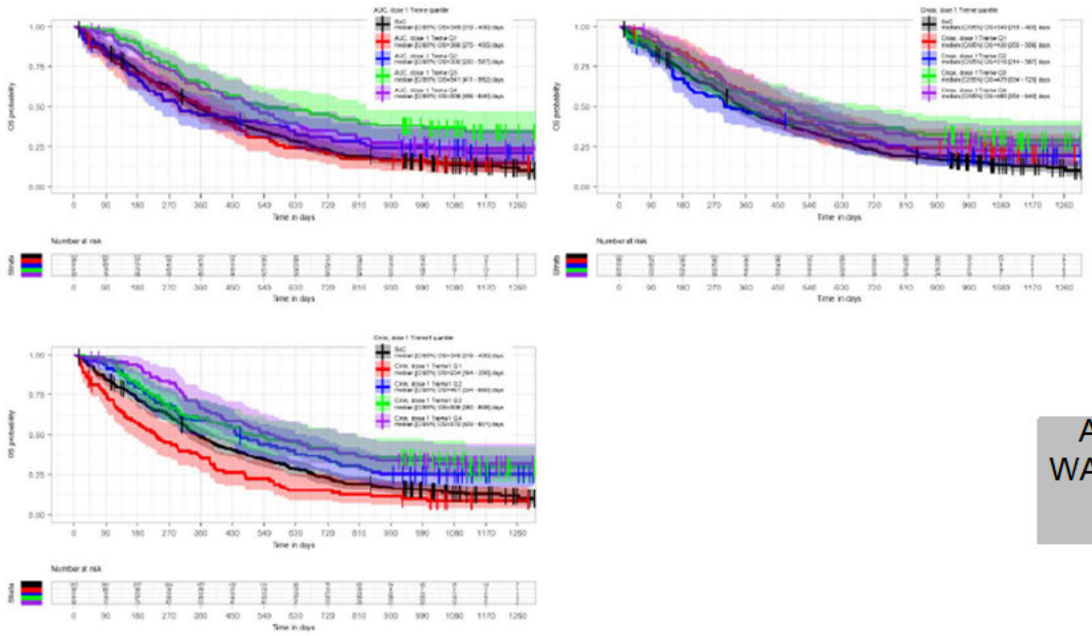


APPEARS THIS WAY ON ORIGINAL

Source: az-durvalumab-pfs-triplet-v25.Rmd, Reference: f8e6f3:165cfa
Note: Shaded areas are the 95% confidence interval around the KM curves. Vertical ticks represent the right censoring.
Abbreviations: PFS=progression-free survival, Cmin=minimum serum concentration, Cmax=maximum serum concentration, AUC=area under the serum concentration-time curve, SOC=Standard of Care

Source: d419mc00004-pop-pk-eres-report, Figure 77

Figure 32. OS Kaplan-Meier Plots for Tremelimumab Exposure Metrics by Quartiles at Dose 1

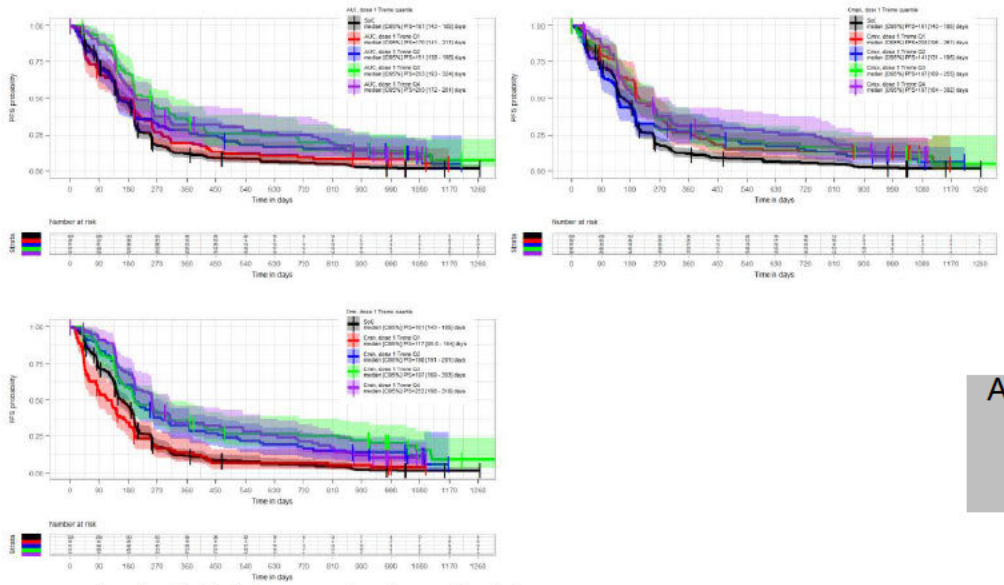


APPEARS THIS WAY ON ORIGINAL

Source: az-durvalumab-os-triplet-v25.Rmd, Reference: f8e6f3:8d65e0
Note: Shaded areas are the 95% confidence interval around the KM curves. Vertical ticks represent the right censoring.
Abbreviations: OS=overall survival, Cmin=minimum serum concentration, Cmax=maximum serum concentration, AUC=area under the serum concentration-time curve, SOC=Standard of Care

Source: d419mc00004-pop-pk-eres-report, Figure 73

Figure 33. PFS Kaplan-Meier Plots for Tremelimumab Exposure Metrics by Quartiles at Dose 1

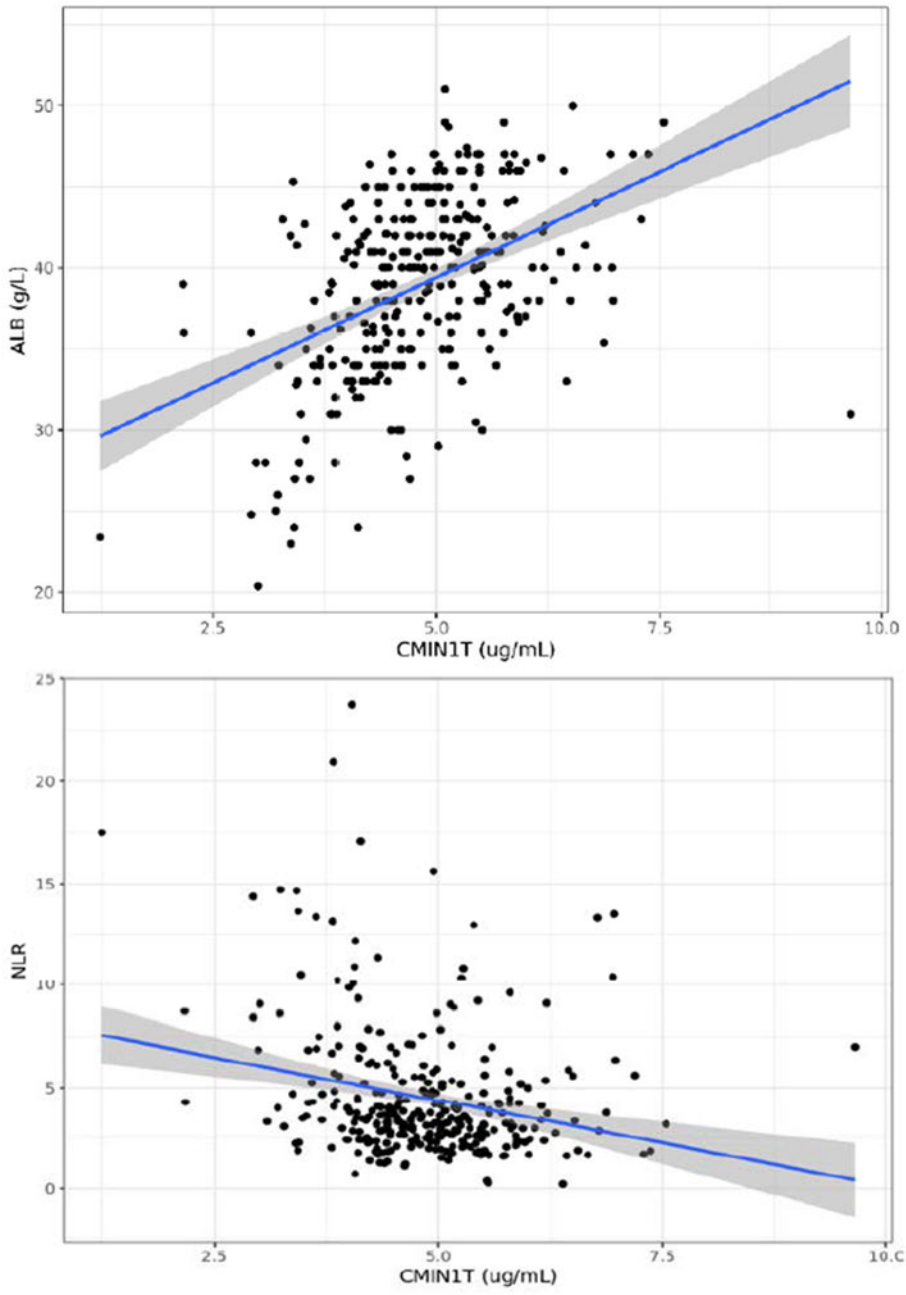


APPEARS THIS WAY ON ORIGINAL

Source: az-durvalumab-pfs-triplet-v25.Rmd, Reference: f8e6f3:f8ac47
Note: Shaded areas are the 95% confidence interval around the KM curves. Vertical ticks represent the right censoring.
Abbreviations: PFS=progression-free survival, Cmin=minimum serum concentration, Cmax=maximum serum concentration, AUC=area under the serum concentration-time curve, SOC=Standard of Care

Source: d419mc00004-pop-pk-eres-report, Figure 79

Figure 34. Correlation between ALB, NLR vs. Cmin, cycle 1 Tremelimumab



ALB: albumin; NLR: neutrophil-to-lymphocyte ratio, CMIN1T: Cmin, cycle 1 Treme.

Source: Applicant's response to Information Request issued on 02/17/2022, Figure 1

Table 47. HR for OS in Patients of Cmin, cycle 1 Tremelimumab Q1, Q2, Q3, Q4 Subgroup and SoC Group

	Median overall survival (days)				Median overall survival (days)		
Comparison	Control	Treatment	HR (CI 95%)	Comparison	Control	Treatment	HR (CI 95%)
Q1 vs. SoC	n=333 349	n=82 234	1.42 (1.10-1.84)	Q1 vs. Matched Control	n=82 321	n=82 234	1.19 (0.86-1.64)
Q2 vs. SoC	n=333 349	n=81 461	0.71 (0.54-0.94)	Q2 vs. Matched Control	n=81 315	n=81 461	0.59 (0.42-0.83)
Q3 vs. SoC	n=333 349	n=81 506	0.60 (0.45-0.80)	Q3 vs. Matched Control	n=81 323	n=81 506	0.58 (0.41-0.83)
Q4 vs. SoC	n=333 349	n=82 570	0.56 (0.42-0.75)	Q4 vs. Matched Control	n=82 394	n=82 570	0.66 (0.46-0.95)

HR=hazard ratio; OS=overall survival; Q=quartile; SoC=standard of care; CI= confidence interval
OS DCO: 12 March 2021; a hazard ratio <1 favors Durva + Treme + SoC over SoC alone

Source: Applicant's response to Information Request issued on 02/17/2022, Table 4

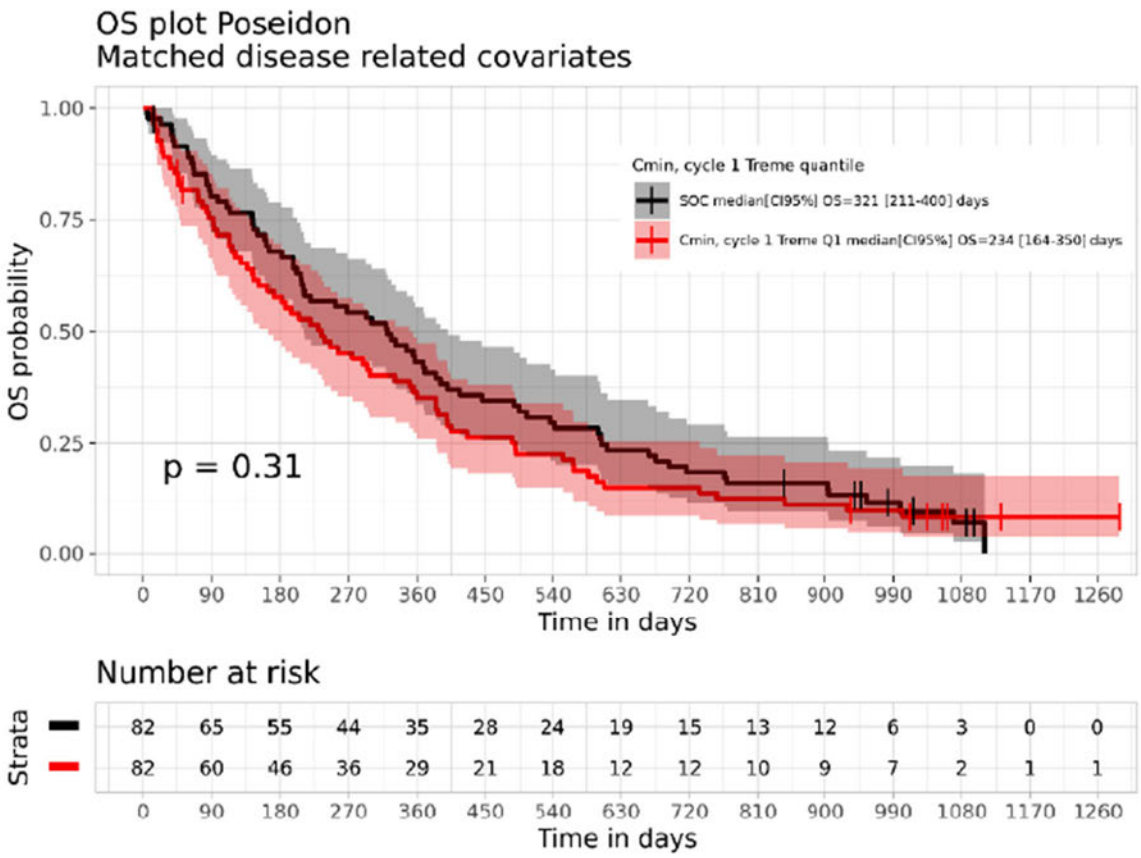
Table 48. HR for PFS in Patients of Cmin, cycle 1 Tremelimumab Q1, Q2, Q3, Q4 Subgroup and SoC Group

	Median overall survival (days)				Median overall survival (days)		
Comparison	Control	Treatment	HR (CI 95%)	Comparison	Control	Treatment	HR (CI 95%)
Q1 vs. SoC	n=333 161	n=82 117	1.16 (0.90-1.50)	Q1 vs. Matched Control	n=82 150	n=82 117	1.00 (0.72-1.38)
Q2 vs. SoC	n=333 161	n=81 198	0.58 (0.44-0.75)	Q2 vs. Matched Control	n=81 141	n=81 198	0.44 (0.32-0.62)
Q3 vs. SoC	n=333 161	n=81 197	0.51 (0.39-0.68)	Q3 vs. Matched Control	n=81 140	n=81 197	0.50 (0.35-0.70)
Q4 vs. SoC	n=333 161	n=82 253	0.51 (0.39-0.66)	Q4 vs. Matched Control	n=82 195	n=82 253	0.62 (0.44-0.87)

HR=hazard ratio; OS=overall survival; Q=quartile; SoC=standard of care; CI= confidence interval
PFS DCO: 24 July 2019; a hazard ratio <1 favors Durva + Treme + SoC over SoC alone

Source: Applicant's response to Information Request issued on 02/17/2022, Table 5

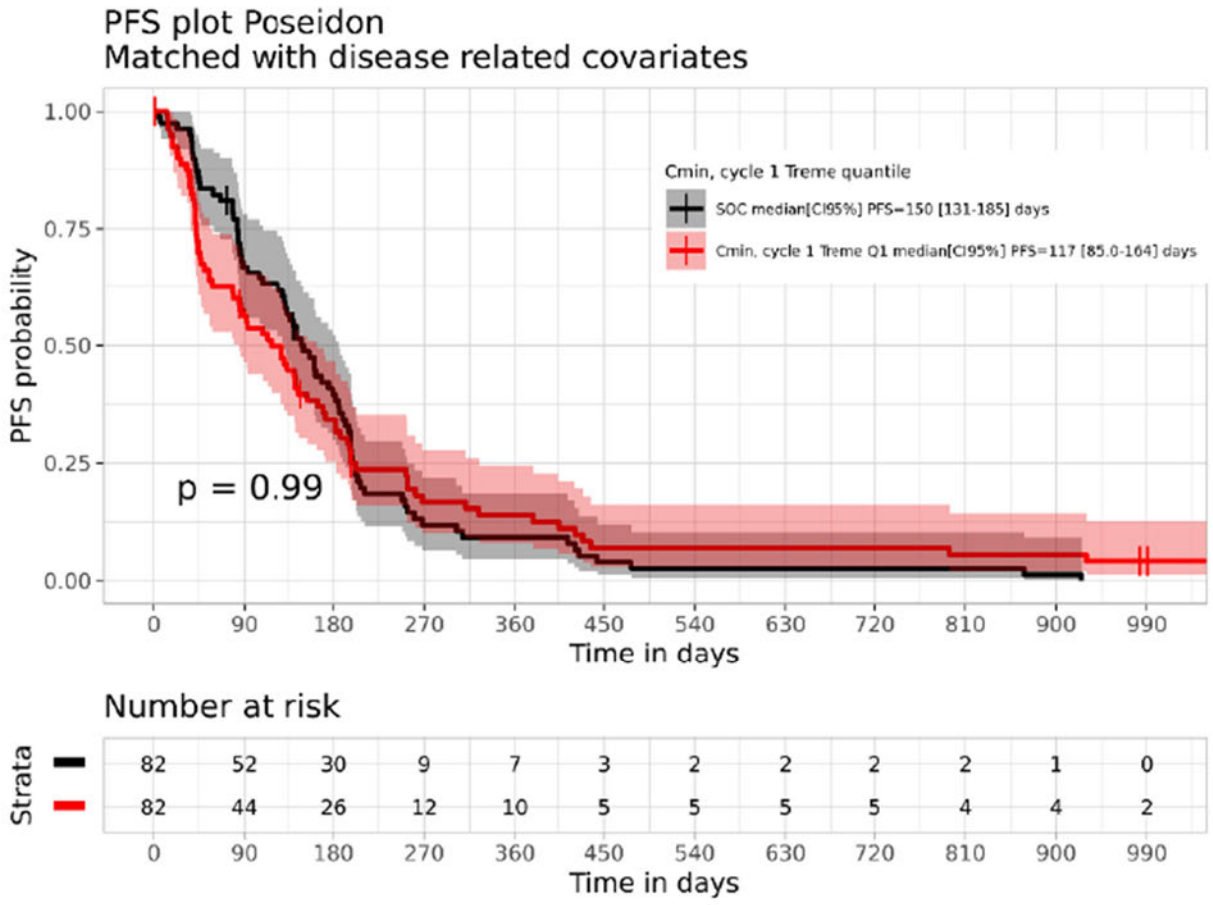
Figure 35. OS Kaplan-Meier Plot of Cmin, cycle 1 Tremelimumab Q1 vs. SoC in the Matched Population



OS=overall survival, Q=quartile, SoC=standard of care, p=*P* value based on a log rank test

Source: Applicant's response to Information Request issued on 02/17/2022, Figure 6

Figure 36. PFS Kaplan-Meier Plot of Cmin, cycle 1 Tremelimumab Q1 vs. SoC in the Matched Population



PFS=Progression-free survival, Q=quartile, SoC=standard of care, p=*P* value log rank test

Source: Applicant's response to Information Request issued on 02/17/2022, Figure 10

ER (safety) Executive Summary

The FDA's Assessment:

In support dosing recommendation of this BLA, the applicant also submitted reports of exposure-response (E-R) for safety analyses. The Applicant's E-R for safety analyses for durvalumab and tremelimumab were conducted with data from 327 patients for durvalumab and 326 patients for tremelimumab from durvalumab + tremelimumab + SoC group in the Phase III study D419MC00004. The E-R analysis dataset covered a body weight range between 34 and 134 kg and an age range from 27 to 87 years old.

Assessment of durvalumab/tremelimumab E-R relationships for safety included the following safety endpoints: Grade 3+ treatment -related adverse events (AE), Grade 3+ drug-related AE of special interest (AESI), and AE leading to treatment discontinuation. No clinically relevant E-R relationship was observed for durvalumab or tremelimumab PK exposure and the above listed safety endpoints at pre-specified significance level of α=0.001. Applicant's E-R analyses for safety appear to be adequate. Therefore, Overall, no dose adjustment for durvalumab or tremelimumab is needed based on exposure-response analyses for safety.

ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		• assess the durvalumab/tremelimumab E-R (safety) relationship using POSEIDON study data. • support the acceptance of safety profile, and justify the dosages and dosing regimens in the ITT population
Study Included		*POSEIDON (Individual predicted exposure metrics of patients and safety data from POSEIDON study)*
Population Included		*Patients with advanced metastatic NSCLC in POSEIDON study*
Endpoint		*Grade 3+ AE, Grade 3+ AESI, AE leading to treatment discontinuation from POSEIDON study data*
No. of Patients (total, and with individual PK)		*Total 330 patients from T + D + SoC arm: 327 and 326 patients with durvalumab and tremelimumab PK, respectively*
Population Characteristics (*See Table 26-27, Population PK and Exposure-Response Report, Module 5.3.3.5.*)	General	*Age (years) median (range): 63.0 (27.0-87.0)* *Weight (kg) median (range): 68.2 (34.0-134)* *n (%) male: 261 (80.1%)* *n (%) race: White 197 (60.4%), Black 8 (2.45%), Asian 97 (29.8%), Native Hawaiian or Other Pacific Islander 2 (0.613%), American Indian/Alaskan Native 11 (3.37%), Other 11 (3.37%).*
	Organ impairment	*Hepatic (NCI) - n (%) in each category: Normal 1435 (89.4%), mild 146 (9.1%), moderate 3 (0.187%)* *Renal (CrCL in mL/min) - median (range): 80.3 (22.5-299)*
	Pediatrics (if any)	*None*
	Geriatrics (if any)	*Age (years) median (range, % subj >=65 yr, % subj >=75 yr): 63.0 (27.0-87.0, 43.3%, 10.4%)* *n (%) male: 261 (80.1%)*
Dose(s) Included		*tremelimumab 75 mg+durvalumab 1500 mg+SoC Q3W x4 cycles; followed by durvalumab 1500 mg Q4W; additional one tremelimumab 75 mg dose at week 16*
Exposure Metrics Explored (range)		*durvalumab exposure:* *Cmin, Dose 1 Durva (µg/mL): 69.0-207* *Cmax,Dose 1 Durva (µg/mL): 278-1060* *AUC,Dose 1 Durva (µg.day/mL): 2950-7150* *Cmin,ss Durva (µg/mL): 118-660* *Cmax,ss Durva (µg/mL): 458-1150* *AUC,ss Durva (µg.day/mL): 6150-22700* *tremelimumab exposure:* *Cmin,Dose 1 Treme (µg/mL): 1.24-9.65* *Cmax,Dose 1 Treme (µg/mL): 10.0-62.5*

	AUC,Dose 1 Treme (µg.day/mL): 114-319 *Cmin,Dose 5 Treme (µg/mL): 1.68-32.2* *Cmax,Dose 5 Treme (µg/mL): 15.6-62.6* *AUC,Dose 5 Treme (µg.day/mL): 163-755*	
Covariates Evaluated	sex, race, region, smoking status, baseline ECOG, hepatic function NCI method, ADA status post-baseline to durva, ADA status post-baseline to treme, tumor mutation burdens (mutations per megabase >= 20, or 16), PD-L1 TC (<50, 25, or 1%), age group, age, body weight, baseline albumin, baseline LDH, baseline NLR, baseline tumor size per investigator, exposure metrics	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*The safety endpoints (Grade 3+ AE, Grade 3+ AESI, AE leading to treatment discontinuation) were converted to binary responses and analyzed with linear logistic regression models relating the probability of responses to durvalumab or tremelimumab exposure metrics.*	**Yes**
Model Parameter Estimates	*See Table 33-36, Population PK and Exposure-Response Report, Module 5.3.3.5. (logistic regressions for probability of safety endpoints vs. exposure quantiles)*	Yes See Table 49, Table 50, Table 51, and Table 52
Model Evaluation	The probability of *safety endpoints (Grade 3+ AE, Grade 3+ AESI, AE leading to treatment discontinuation)* calculated in quartiles of the various durvalumab and tremelimumab exposure metrics were graphically explored with overlaid model predictions from the logistic regression model fit. The logistic regression results assessing the impact of exposure on the probability of safety endpoints were tabulated with P values associated with exposure effects in comparison to the pre-specified significance level of α =0.001.	Yes See Figure 37, Figure 38, Figure 39, Figure 40, Figure 41, Figure 42, Figure 43, and Figure 44
Covariates and Clinical Relevance	In general, there appears to be no clear trend between increasing exposure of durvalumab or tremelimumab and the probability of all safety endpoints. The P values associated with exposure effects were relatively large (in comparison to the pre-specified significance level of α =0.001), indicating that the relationship was not statistically significant. In addition, there appears to be no association between covariates (e.g., among baseline bodyweight quartiles, ADA status and other covariates explored) and the percentages of patients having safety endpoints (Grade 3+ AE, Grade 3+ AESI, AE leading to treatment discontinuation).	Yes
Simulation for Specific Population	*N/A*	
Visualization of E-R relationships	*See Figure 97, 101, 107, 113, Population PK and Exposure-Response Report, Module 5.3.3.5. (logistic regression of probabilities of AEs vs. exposure plots)*	Yes See Figure 37, Figure 38, Figure 39, Figure 40,

	See Appendix 26-Figure 173, 183, Population PK and Exposure-Response Report, Module 5.3.3.5. (additional covariates exploratory analysis)	Figure 41, Figure 42, Figure 43, and Figure 44
Overall Clinical Relevance for ER	No need for adjustments of dose regimen as no clinical relevant E-R (safety) relationship identified at the dose regime in POSEIDON	Yes
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	*N/A*	

Table 49. Summary of the Effect of Different Exposures Metrics on the Probability of Having Grade 3 and Above Treatment-Related AE

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P-value (based on LRT)	Loglikelihood	AIC	Number of patients
Durvalumab Cmax after first dose	-0.00066 (139)	(-0.00247, 0.00114)	0.471	-224.5	453	327
Durvalumab Cmin after first dose	-0.00081 (566)	(-0.00983, 0.00818)	0.86	-224.8	453.5	327
Durvalumab AUC after first dose	-9.28e-05 (182)	(-0.000425, 0.000238)	0.582	-224.6	453.3	327
Durvalumab Cmax steady-state	-0.000392 (171)	(-0.00171, 0.000925)	0.559	-224.6	453.2	327
Durvalumab Cmin steady-state	-0.000111 (1060)	(-0.00242, 0.0022)	0.925	-224.8	453.6	327
Durvalumab AUC steady-state	-8.63e-06 (439)	(-8.32e-05, 6.59e-05)	0.82	-224.8	453.5	327
Tremelimumab Cmax after first dose	0.00642 (254)	(-0.0253, 0.0391)	0.693	-224.1	452.2	326
Tremelimumab Cmin after first dose	0.0542 (220)	(-0.179, 0.29)	0.649	-224.1	452.2	326
Tremelimumab AUC after first dose	0.000605 (522)	(-0.00558, 0.00686)	0.848	-224.2	452.3	326
Tremelimumab Cmax,Dose 5	0.00313 (555)	(-0.0309, 0.0378)	0.857	-224.2	452.3	326
Tremelimumab Cmin,Dose 5	-0.0207 (242)	(-0.125, 0.0798)	0.679	-224.1	452.2	326
Tremelimumab AUC,Dose 5	-0.00101 (220)	(-0.00555, 0.00342)	0.649	-224.1	452.2	326

Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: b2d741:0e11c0
Abbreviations: AE=adverse event, AIC=Akaike's information criteria, AUC=area under the serum concentration-time curve, Cmax=maximum serum concentration, Cmin=minimum serum concentration, LRT=likelihood ratio test.

Source: d419mc00004-pop-pk-eres-report, Table 33

Table 50. Summary of the Effect of Different Exposures Metrics on the Probability of Having Grade 3 and Above AESI

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P-value (based on LRT)	Loglikelihood	AIC	N
Durvalumab Cmax after first dose	0.000604 (222)	(-0.00218, 0.00311)	0.656	-121.4	246.8	327
Durvalumab Cmin after first dose	0.00148 (469)	(-0.0121, 0.0152)	0.831	-121.5	246.9	327
Durvalumab AUC after first dose	0.000123 (205)	(-0.000381, 0.000611)	0.628	-121.4	246.7	327
Durvalumab Cmax steady-state	0.000488 (204)	(-0.00153, 0.00239)	0.626	-121.4	246.7	327
Durvalumab Cmin steady-state	0.000508 (349)	(-0.00302, 0.00395)	0.775	-121.4	246.9	327
Durvalumab AUC steady-state	2.2e-05 (259)	(-9.16e-05, 0.000133)	0.7	-121.4	246.8	327
Tremelimumab Cmax after first dose	0.0174 (129)	(-0.0302, 0.0594)	0.452	-121.1	246.2	326
Tremelimumab Cmin after first dose	0.124 (143)	(-0.228, 0.468)	0.485	-121.1	246.2	326
Tremelimumab AUC after first dose	0.0041 (111)	(-0.00515, 0.0128)	0.374	-121	245.9	326
Tremelimumab Cmax,Dose 5	0.0163 (152)	(-0.0354, 0.0626)	0.518	-121.2	246.3	326
Tremelimumab Cmin,Dose 5	-0.0111 (712)	(-0.187, 0.123)	0.887	-121.3	246.7	326
Tremelimumab AUC,Dose 5	0.000741 (434)	(-0.00641, 0.00651)	0.821	-121.3	246.7	326
Durvalumab Cmax after first dose	-0.00066 (139)	(-0.00247, 0.00114)	0.471	-224.5	453	327
Durvalumab Cmin after first dose	-0.00081 (566)	(-0.00983, 0.00818)	0.86	-224.8	453.5	327
Durvalumab AUC after first dose	-9.28e-05 (182)	(-0.000425, 0.000238)	0.582	-224.6	453.3	327
Durvalumab Cmax steady-state	-0.000392 (171)	(-0.00171, 0.000925)	0.559	-224.6	453.2	327
Durvalumab Cmin steady-state	-0.000111 (1060)	(-0.00242, 0.0022)	0.925	-224.8	453.6	327
Durvalumab AUC steady-state	-8.63e-06 (439)	(-8.32e-05, 6.59e-05)	0.82	-224.8	453.5	327

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P-value (based on LRT)	Loglikelihood	AIC	N
Tremelimumab Cmax after first dose	0.00642 (254)	(-0.0253, 0.0391)	0.693	-224.1	452.2	326
Tremelimumab Cmin after first dose	0.0542 (220)	(-0.179, 0.29)	0.649	-224.1	452.2	326
Tremelimumab AUC after first dose	0.000605 (522)	(-0.00558, 0.00686)	0.848	-224.2	452.3	326
Tremelimumab Cmax,Dose 5	0.00313 (555)	(-0.0309, 0.0378)	0.857	-224.2	452.3	326
Tremelimumab Cmin,Dose 5	-0.0207 (242)	(-0.125, 0.0798)	0.679	-224.1	452.2	326
Tremelimumab AUC,Dose 5	-0.00101 (220)	(-0.00555, 0.00342)	0.649	-224.1	452.2	326

Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 06b67a:61cafe
Abbreviations: AE=adverse event, AIC=Akaike's information criteria, AUC=area under the serum concentration-time curve, Cmax=maximum serum concentration, Cmin=minimum serum concentration, LRT=likelihood ratio test.

Source: d419mc00004-pop-pk-eres-report, Table 34

Table 51. Summary of the Effect of Different Exposures Metrics on the Probability of Having AE Leading to Durvalumab Treatment Discontinuation

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	P-value (based on LRT)	Loglikelihood	AIC	Number of patients
Durvalumab Cmax after first dose	-7.07e-05 (1760)	(-0.00264, 0.00226)	0.955	-144.9	293.8	327
Durvalumab Cmin after first dose	0.000341 (1810)	(-0.0118, 0.0125)	0.956	-144.9	293.8	327
Durvalumab AUC after first dose	-1.19e-05 (1920)	(-0.000466, 0.000429)	0.958	-144.9	293.8	327
Durvalumab Cmax steady-state	8.46e-05 (1070)	(-0.00174, 0.00181)	0.925	-144.9	293.8	327
Durvalumab Cmin steady-state	0.000379 (416)	(-0.00275, 0.00345)	0.81	-144.9	293.7	327
Durvalumab AUC steady-state	9.89e-06 (516)	(-9.15e-05, 0.000109)	0.846	-144.9	293.8	327

Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: d464f2:d399b1
Abbreviations: AE=adverse event, AIC=Akaike's information criteria, AUC=area under the serum concentration-time curve, Cmax=maximum serum concentration, Cmin=minimum serum concentration, LRT=likelihood ratio test

Source: d419mc00004-pop-pk-eres-report, Table 35

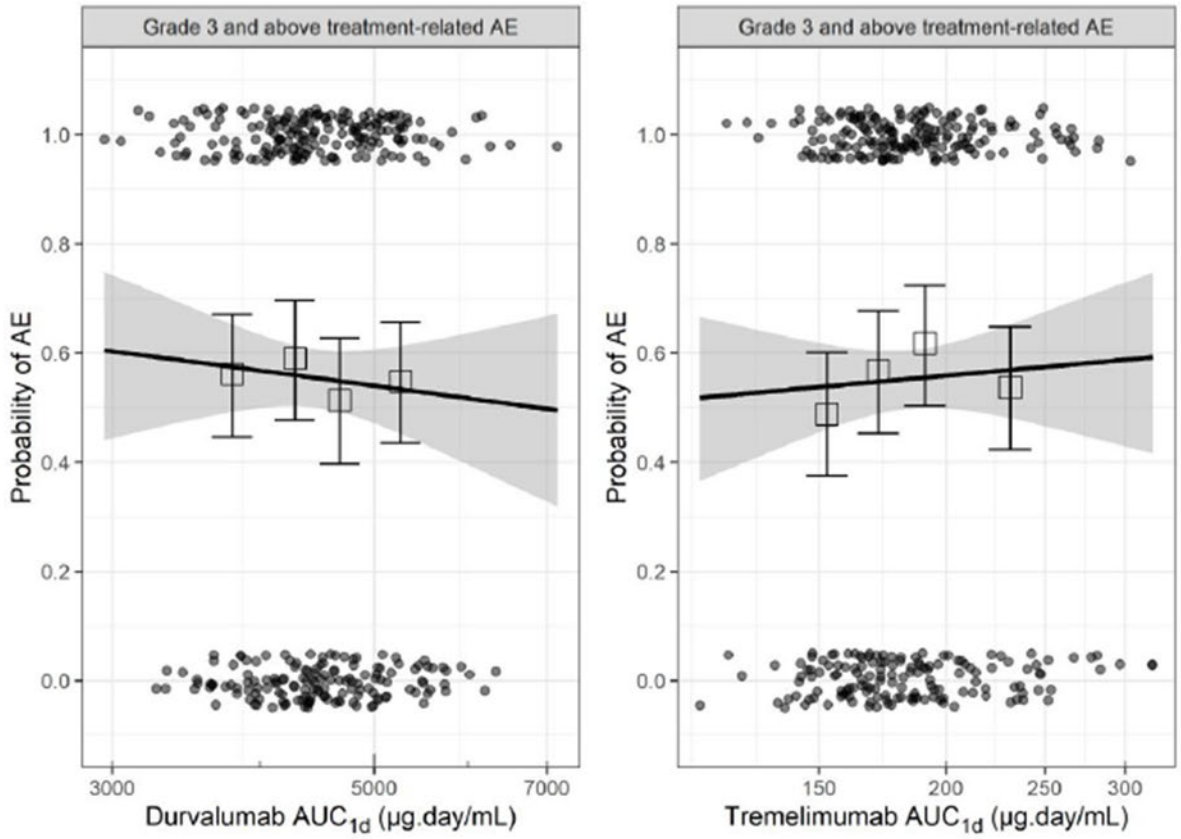
Table 52. Summary of the Effect of Different Exposures Metrics on the Probability of Having AE Leading to Tremelimumab Treatment Discontinuation

Exposure metric	Estimate (% Relative standard error)	95% Confidence interval	*P* value (based on LRT)	Loglikelihood	AIC	Number of patients
Tremelimumab Cmax after first dose	0.046 (48)	(0.000395, 0.0884)	0.048	-102.7	209.4	326
Tremelimumab Cmin after first dose	-0.62 (34.5)	(-1.05, -0.209)	0.003	-100.2	204.4	326
Tremelimumab AUC after first dose	0.00294 (172)	(-0.00748, 0.0125)	0.566	-104.5	213	326
Tremelimumab Cmax,Dose 5	0.03 (86)	(-0.0241, 0.0783)	0.262	-104	212	326
Tremelimumab Cmin,Dose 5	-0.468 (24.8)	(-0.702, -0.245)	0	-95.87	195.7	326
Tremelimumab AUC,Dose 5	-0.0109 (46.5)	(-0.0213, -0.00143)	0.022	-102	208.1	326

Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 98e845:b67ef0
Abbreviations: AE=adverse event, AIC=Akaike's information criteria, AUC=area under the serum concentration-time curve, Cmax=maximum serum concentration, Cmin=minimum serum concentration, LRT=likelihood ratio test

Source: d419mc00004-pop-pk-eres-report, Table 36

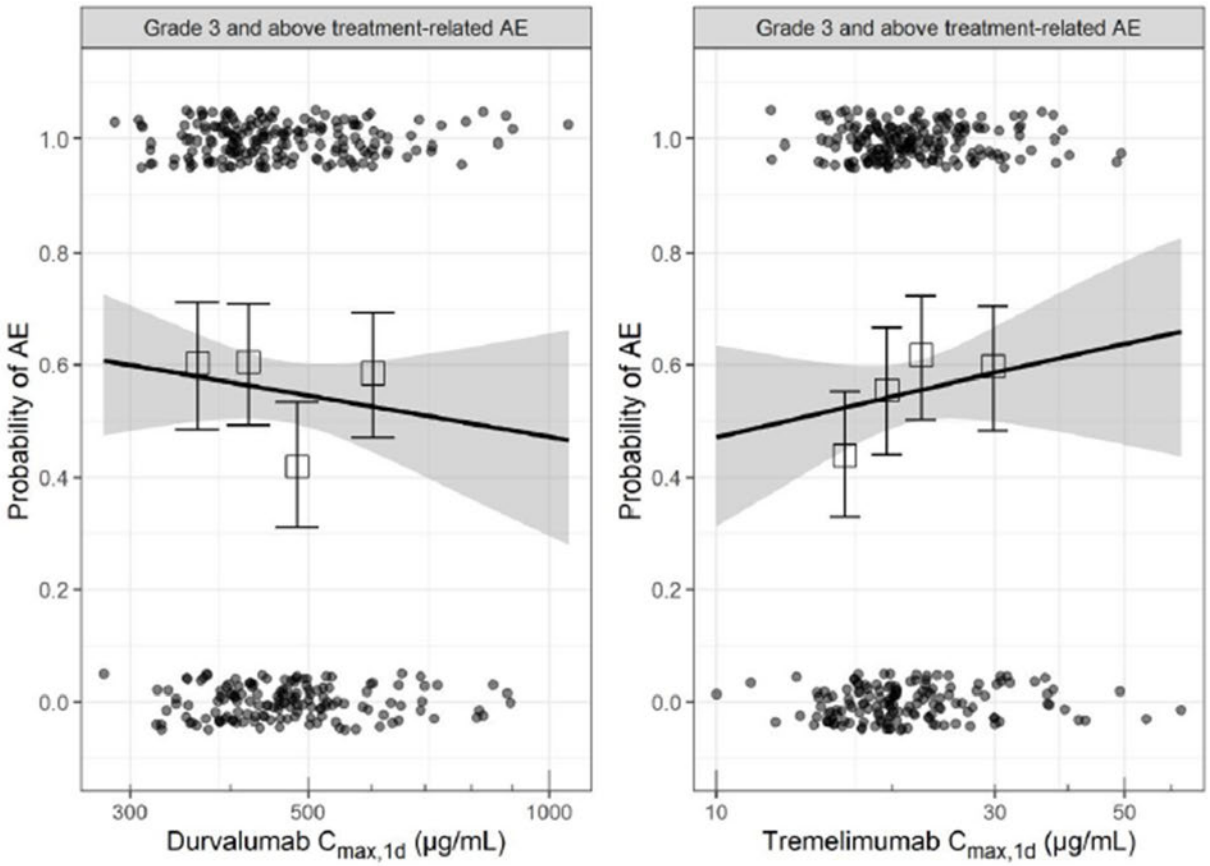
Figure 37. Relationship Between the Probability of Having Grade 3 and Above Treatment-Related AEs and AUC after the First Dose of Durvalumab and Tremelimumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 400028:af5db1
Abbreviations: AE=adverse event, 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.

Source: d419mc00004-pop-pk-eres-report, Figure 96

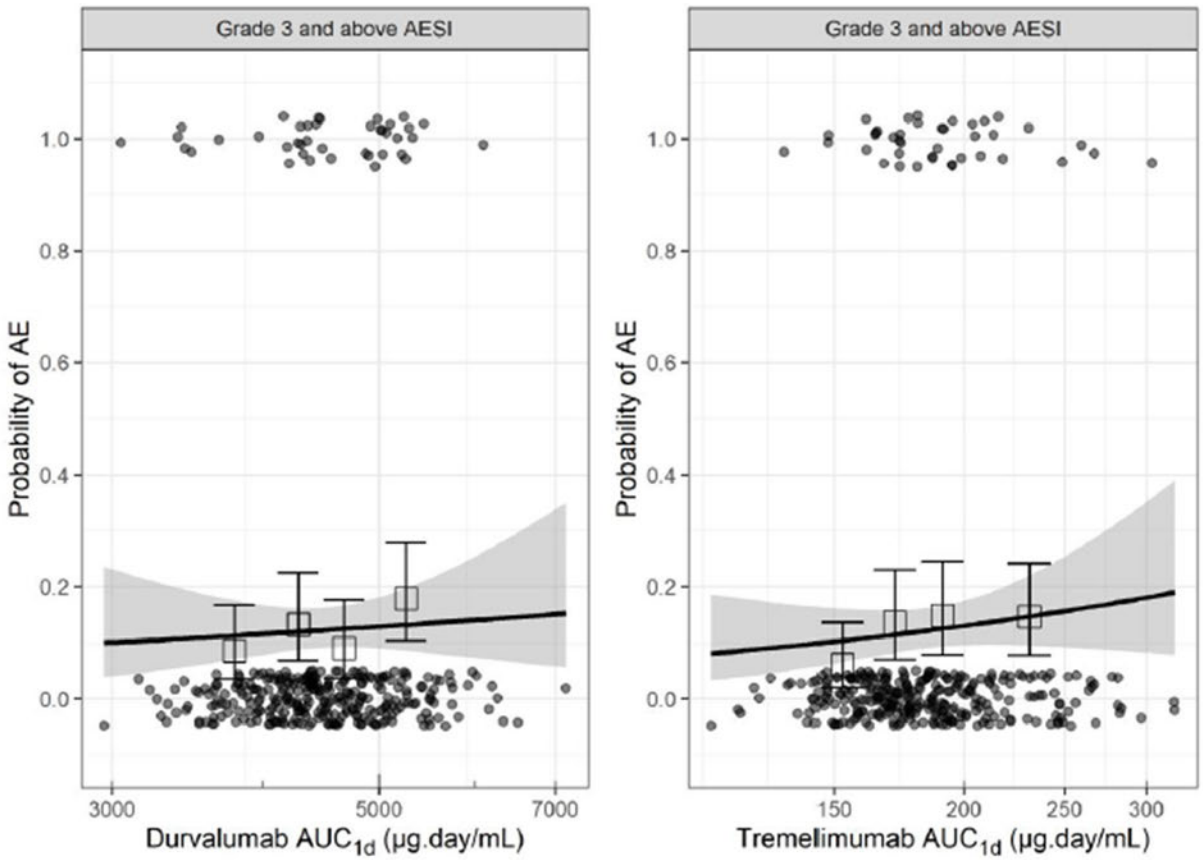
Figure 38. Relationship Between the Probability of Having Grade 3 and Above Treatment-Related AEs and Maximum Concentration After the First Dose of Durvalumab and Tremelimumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: d9eaeb:a51b62
Abbreviations: AE=adverse event, Cmax=maximum serum concentration
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.

Source: d419mc00004-pop-pk-eres-report, Figure 100

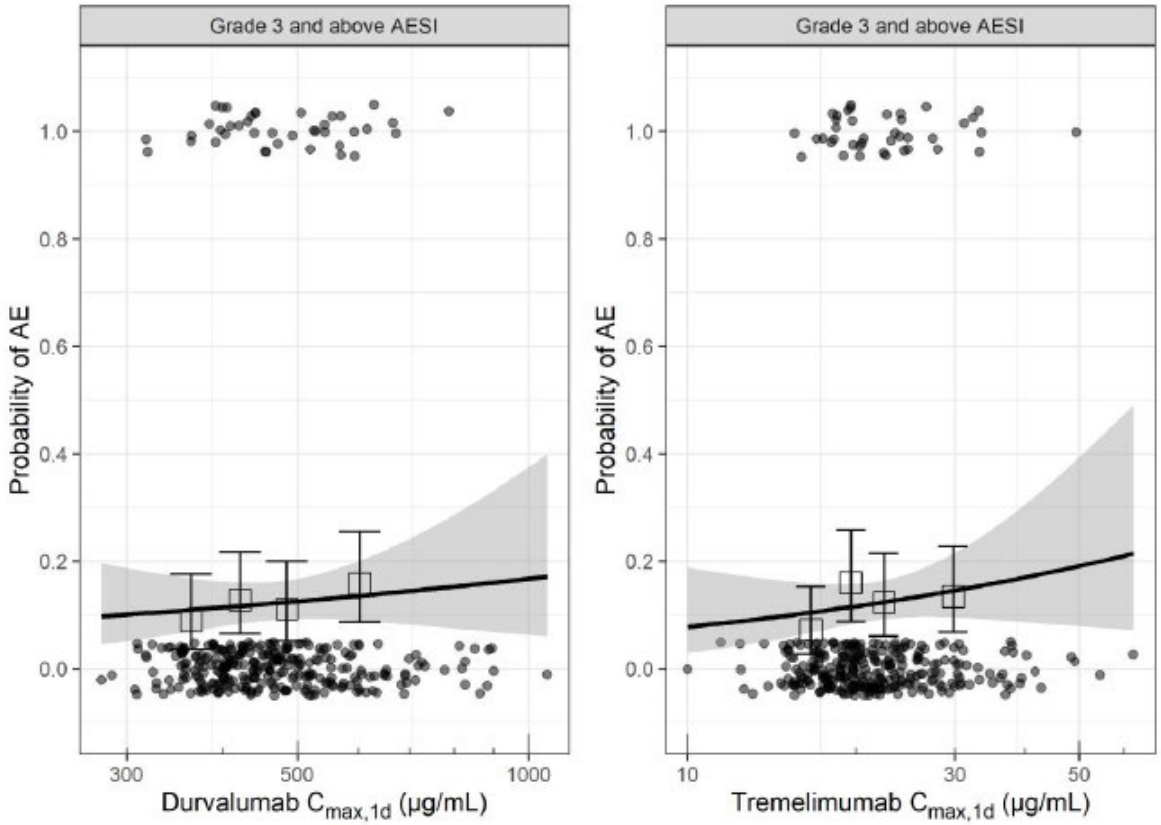
Figure 39. Relationship Between the Probability of Having Grade 3 and Above AESI and AUC After First Dose for Durvalumab and Tremelimumab



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

Source: d419mc00004-pop-pk-eres-report, Figure 102

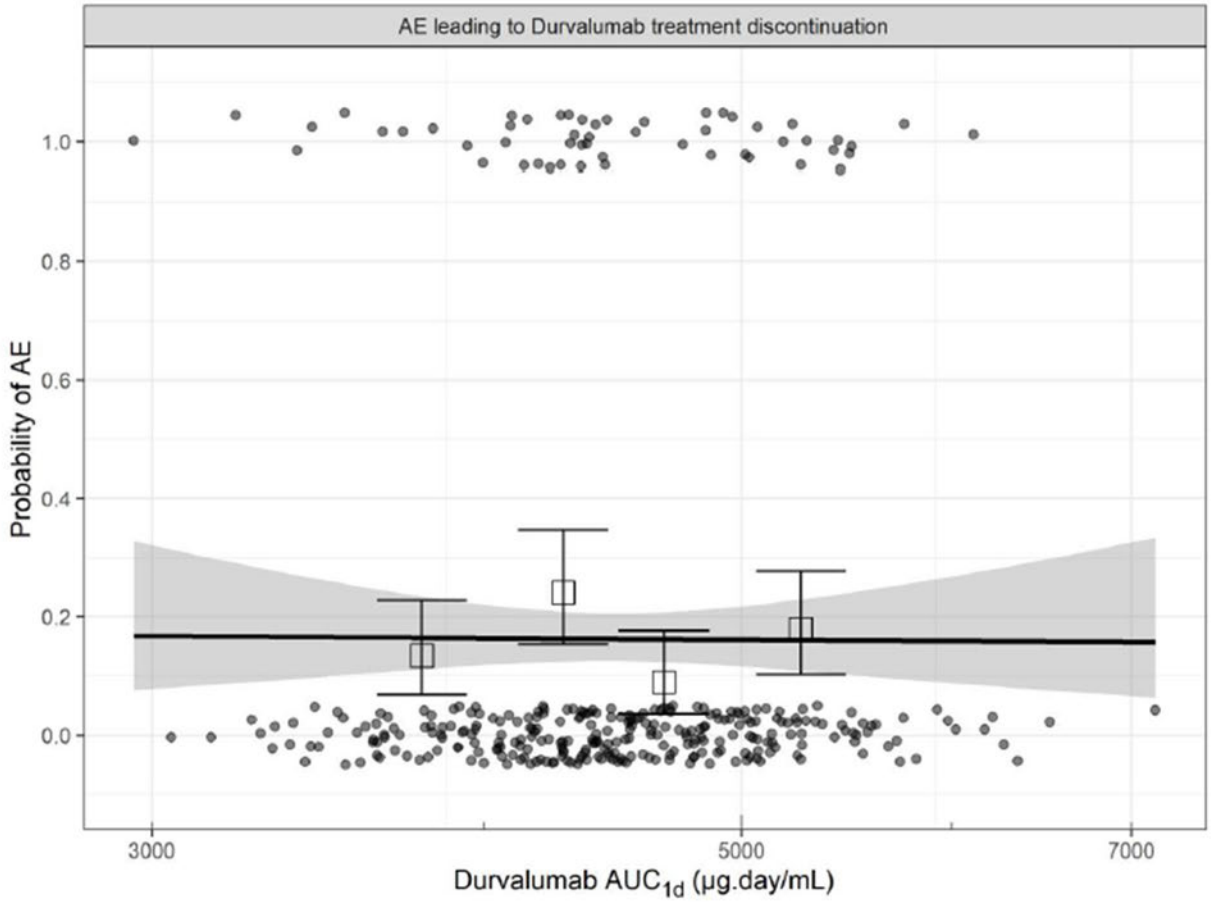
Figure 40. Relationship Between the Probability of Having Grade 3 and Above AESI and Maximum Concentration After First Dose of Durvalumab and Tremelimumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: d9eaeb:bd4602
Abbreviations: AE=adverse event, AESI=adverse event of special interest, Cmax=maximum serum concentration
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.

Source: d419mc00004-pop-pk-eres-report, Figure 106

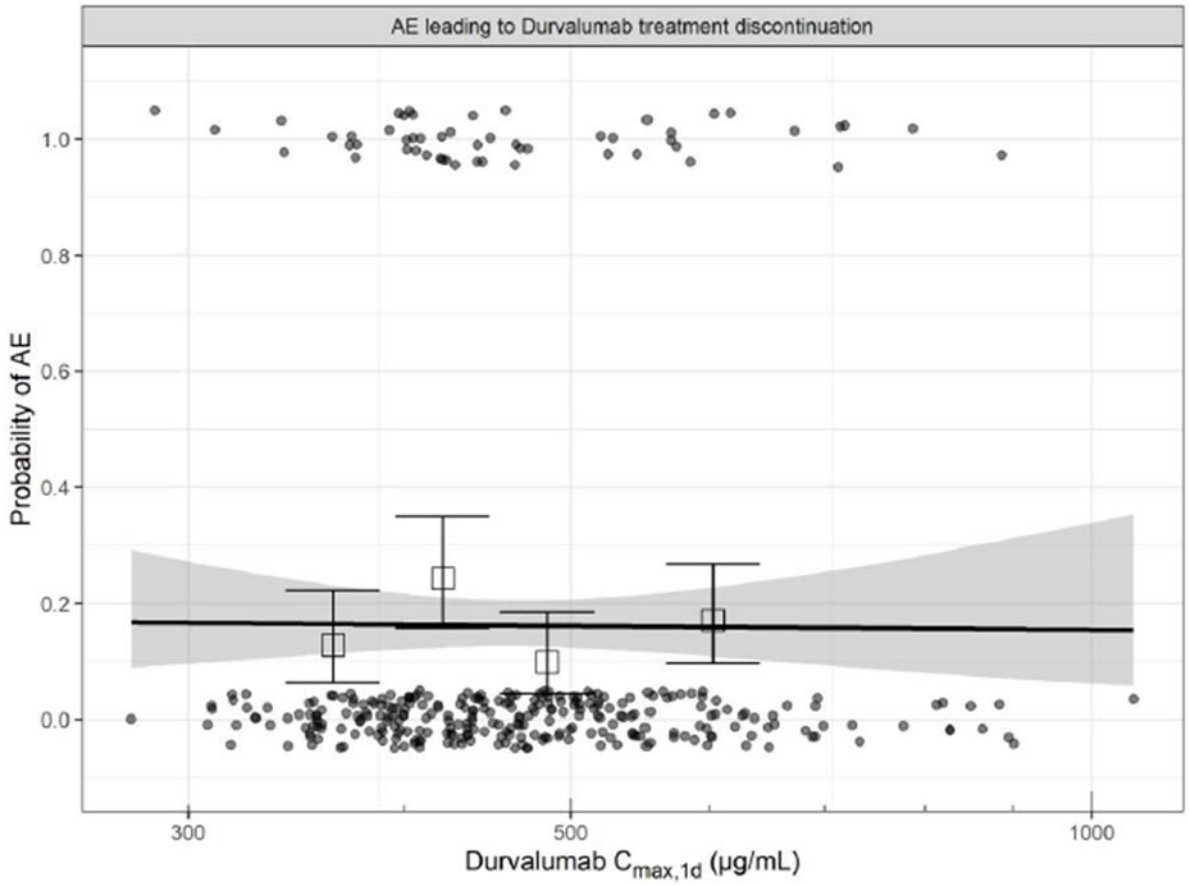
Figure 41. Relationship Between Probability of Having AEs Leading to Durvalumab Treatment Discontinuation and AUC After First Dose of Durvalumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 0d1807:9ed8ab
Abbreviations: AE=adverse event, 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.

Source: d419mc00004-pop-pk-eres-report, Figure 108

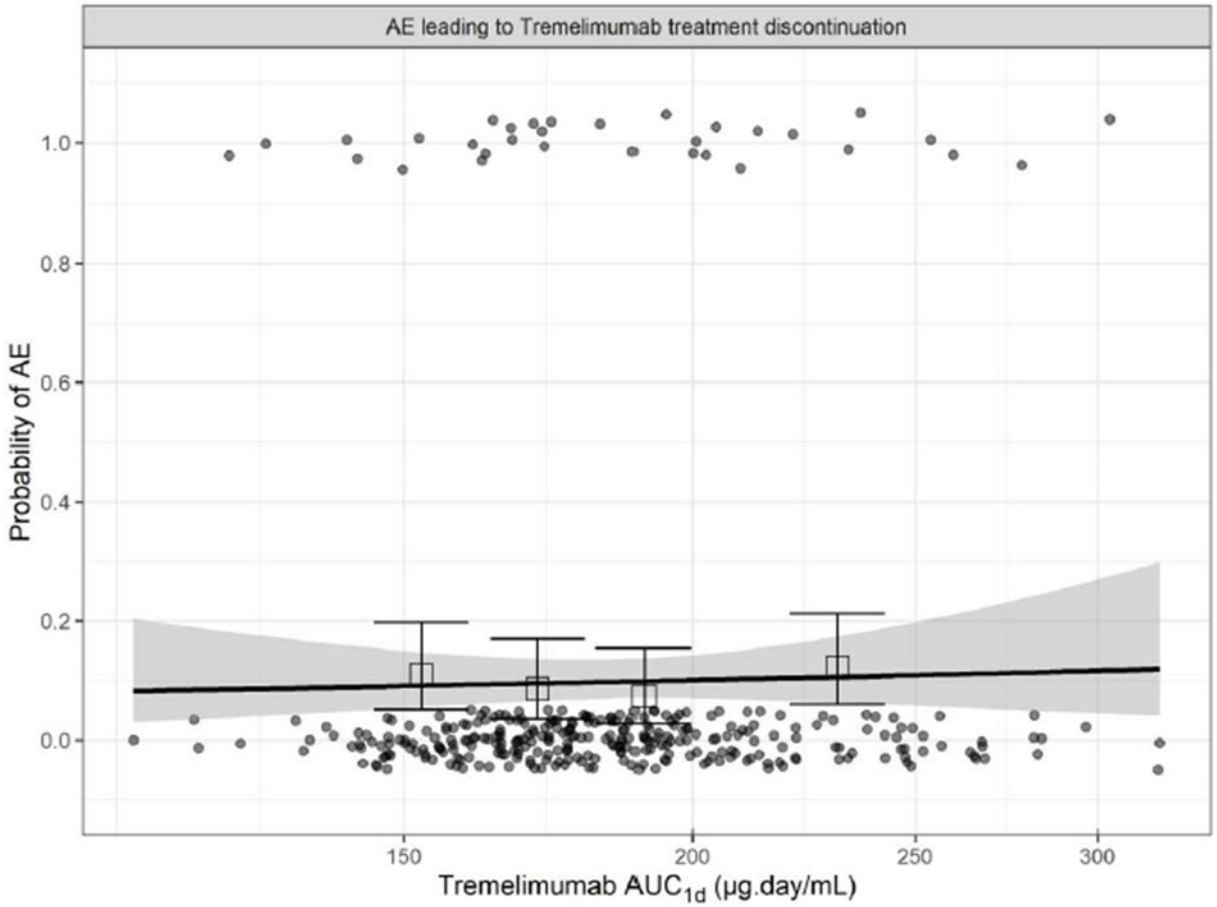
Figure 42. Relationship Between Probability of Having AEs Leading to Durvalumab Treatment Discontinuation and Maximum Concentration after First Dose of Durvalumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: b0ae9b:c17b0c
Abbreviations: AE=adverse event, Cmax=maximum serum concentration
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.

Source: d419mc00004-pop-pk-eres-report, Figure 112

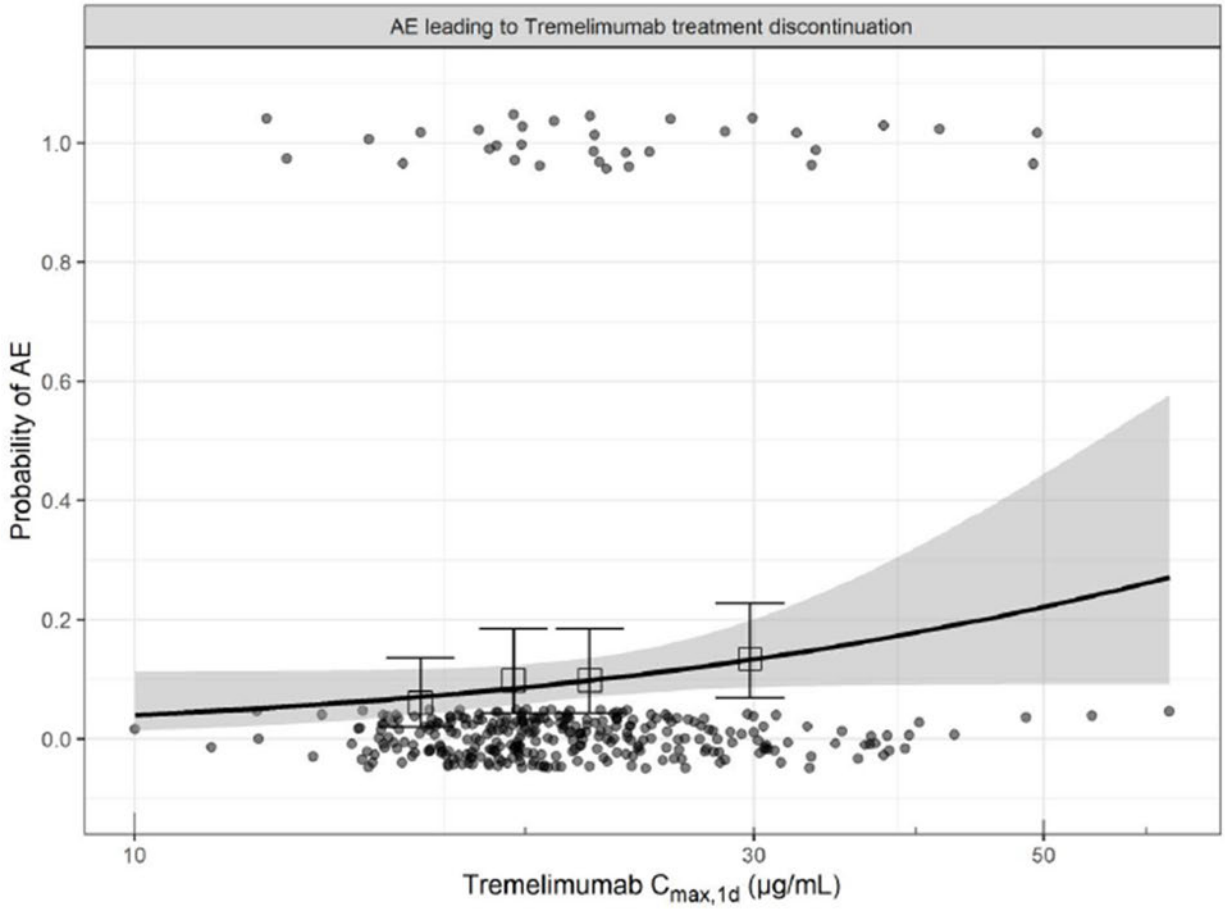
Figure 43. Relationship Between Probability of Having AEs Leading to Tremelimumab Treatment Discontinuation with AUC After First Dose of Tremelimumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 1a8a2a:ed387f
Abbreviations: AE=adverse event, 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.

Source: d419mc00004-pop-pk-eres-report, Figure 114

Figure 44. Relationship Between Probability of Having AEs Leading to Tremelimumab Treatment Discontinuation and Maximum Concentration After First Dose of Tremelimumab



Source: az-durvalumab-ae-poseidon-v5.Rmd, Reference: 549bd3:4245d1
Abbreviations: AE=adverse event, Cmax=maximum serum concentration
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.

Source: d419mc00004-pop-pk-eres-report, Figure 118

The FDA's Assessment:

In general, the applicant's ER analysis for durvalumab and tremelimumab is considered acceptable for the purpose of supporting analyses objectives. There appears no correlation between the durvalumab or tremelimumab PK exposures and probability of having Grade 3+ treatment-related AE, Grade 3+ AESI, AE leading to treatment discontinuation at pre-specified significance level of α=0.001.

ER Review Issues

Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:
See Section 0 for details on overall benefit-risk evaluation based on E-R analyses.

The FDA's Assessment:
Overall, the Applicant's E-R analyses for both efficacy and safety support the proposed dosing regimens for durvalumab and tremelimumab in patients with previously untreated metastatic NSCLC and no need of dose adjustment for durvalumab or tremelimumab in specific patient populations.

Reviewer's Independent Analysis

The FDA's assessment

Bioanalytical Methods

The Office of Clinical Pharmacology review team has assessed the acceptability of the following bioanalytical methods used in the pivotal study (poseidon), 20 supportive durvalumab and tremelimumab studies.
Summaries of method performance are provided in Table 53 and Table 54

Table 53 Summary method performance of a bioanalytical method to measure tremelimumab in human serum

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of the Quantitative ELISA Assay for Measurement of MEDI-1123 Concentrations in Human Serum (Report AR4785). Selectivity in human serum from patients with solid tumors from: Validation of the Quantitative ELISA Assay for Measurement of MEDI-1123 Concentrations in Human Serum Amendment 4 (Report VR4785 Amendment 4). Long-term stability data from: Long Term Stability of MEDI-1123 Quality Control Samples in Human Serum Using an Enzyme Linked Immunosorbent Assay (ELISA) (Report AR4785 Addendum 2).
Method description	This method utilizes an indirect ELISA format to measure the concentrations of tremelimumab in human serum. Standards, controls, and test samples are incubated with recombinant CTLA-4 (human CD152 muIg) that has been immobilized on a microtiter plate. After incubation, unbound material is washed away and tremelimumab is detected using biotinylated mouse monoclonal antibody to human IgG2, followed by HRP-streptavidin conjugate, and tremelimumab is visualized with peroxidase substrate TMB. The color development was stopped, and the intensity of the color was measured at 450 nm with wavelength correction set to 650 nm.

Materials used for calibration curve & concentration	Tremelimumab in human serum at final concentrations (in 5% human serum) of 3.9, 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0 ng/mL		
Validated assay range	156 ng/mL to 5000 ng/mL in 100% human serum		
Material used for QCs & concentration	Tremelimumab in 100% human serum at concentrations of 156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL		
Minimum required dilutions (MRDs)	1:20		
Source & lot of reagents (LBA)	Tremelimumab Lot:PS01 CD152-mulg (Coat) Lot: 202603 Biotinylated Mouse Monoclonal Antibody IgG2 Lot: 977038A Streptavidin-HRP Conjugate Lot: 1094380 Pooled Human Serum Lot: (b) (4) 673682 Selectivity in human serum from patients with solid tumors from Report VR4785 Amendment 4: Tremelimumab Lot:PS01 CD152-mulg (Coat) Lot: 243102 Biotinylated Mouse Monoclonal Ab IgG2 Lot: QK221423 Streptavidin-HRP Conjugate Lot: 1711869 Pooled Human Serum Lot: (b) (4) 1222126		
Regression model & weighting	Data were fit using a linear adjusted variance weighted five-parameter logistic function.		
Validation parameters	**Method validation summary**		**Accetapability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	6	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.4 to 0.5%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.9%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL	−8.7 to −2.3%	Yes
	Inter-batch %CV QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL	≤ 19.4%	Yes
	Total Error (TE) QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL	≤ 21.7%	Yes

Selectivity & matrix effect	Normal serum Ten individual human serum samples of mixed gender were analyzed in an assay together with 3 replicate spikes of the pool matrix. The individual samples and the pool spikes were tested both unspiked and spiked with 0.20 µg/mL (10 ng/mL in 5% human serum) tremelimumab. 100% of the unspiked serum samples and the unspiked matrix returned values below the LLOQ and 100% of the spiked serum samples measured between -13.8% and 13.8% of the mean value of the spiked pool matrix. Human serum from patients with solid tumors Selectivity in disease state matrix was evaluated using 18 serum samples from human individuals with solid tumors: Three different lots of breast, lung, bladder, ovarian, head/neck, and gastric cancer sera were used. The individual serum samples were tested both unspiked and spiked with tremelimumab at a concentration (200 ng/mL) between LLOQ and the LQC levels. For controls, pooled normal human serum was tested both unspiked (3 duplicate determinations) and spiked (3 separate aliquots each tested in duplicate), using the same spike solution used for the samples. Specificity (unspiked samples) and selectivity (spiked samples) of tremelimumab measurement in samples from patients with solid tumors met the acceptance criteria in 100% of the lots tested.	Yes
Interference & specificity	Specificity of tremelimumab measurement was tested in the presence of several co-drugs (including durvalumab) in prepared QCs. The assay was found to be specific to the measurement of tremelimumab.	Yes
Hemolysis effect	Not applicable	Yes
Lipemic effect	Not applicable	Yes
Dilution linearity & hook effect	Dilution linearity tested and passed at 10 µg/mL (dilution factor = 200), 100 µg/mL (dilution factor = 2000), and 1000 µg/mL (dilution factor = 2000)	Yes
Bench-top/process stability	24 hours in human serum at room temperature	Yes
Freeze-Thaw stability	5 cycles in human serum at -70°C	
Long-term storage	Tremelimumab is stable in human serum for 733 days at -70°C ± 10°C Tremelimumab is stable in human serum for 121 days at -20°C ± 5°C	Yes

Parallelism	Not applicable	Yes
Carry over	Not applicable	Yes
Method performance in study D419MC00004 (POSEIDON)		
Assay passing rate	40 out of 50 (80%)	Yes
Standard curve performance	• Cumulative bias range: -1.4 to 0.9% (from LLOQ to ULOQ) • Cumulative precision: ≤ 8.7% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -12.6 to -4.4% • Cumulative precision: ≤ 12.7% CV • TE: ≤ 25.3% [a]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C	Yes
Method performance in study D4190C00006 (Study 06)		
Assay passing rate	95 out of 103 (92%)	Yes
Standard curve performance	• Cumulative bias range: -3.4 to 0.6% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 6.1% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -7.0 to -2.7% [b] • Cumulative precision: ≤ 6.1% CV • TE: ≤ 14.9% [c]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples (except for 4 samples) were analyzed within the established stability of 733 days at -70°C ± 10°C. The 4 samples that exceeded the long-term stability were reported as Non-Reportable Result.	Yes
Method performance in study D4190C00022 (Study 22)		
Assay passing rate	53 out of 64 (83%)	Yes
Standard curve performance	• Cumulative bias range: -0.1 to 0.3% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 8.7% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -7.0 to -3.0% [b, d] • Cumulative precision: ≤ 14.4% CV [d] • TE: ≤ 21.4% [c, d]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C	Yes
Method performance in study D419AC00001 (MYSTIC)		

Assay passing rate	51 out of 72 (71%)	Yes
Standard curve performance	• Cumulative bias range: -3.4 to 0.8% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 6.4% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -5.8 to -0.7% [b] • Cumulative precision: ≤ 9.3% CV • TE: ≤ 15.1% [c]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C	Yes
Method performance in study D419AC00003 (NEPTUNE)		
Assay passing rate	56 out of 71 (79%)	Yes
Standard curve performance	• Cumulative bias range: -2.1 to 1.3% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 6.6% CV (from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -4.2 to 2.7% [b] • Cumulative precision: ≤ 9.9% CV • TE: ≤ 14.1% [c]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C	Yes
Method performance in study D4191C00004 (ARCTIC)		
Assay passing rate	35 out of 50 (70%)	Yes
Standard curve performance	• Cumulative bias range: -4.8 to 1.3% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 4.2% CV(from LLOQ to ULOQ)	Yes
QC performance	• Cumulative bias range: -4.9 to 0.7% [b] • Cumulative precision: ≤ 10.1% CV • TE: ≤ 15.0% [c]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 733 days at -70°C ± 10°C	Yes
Method performance in study D419QC00001 (CASPIAN)		
Assay passing rate	27 out of 29 (93%)	
Standard curve performance	• Cumulative bias range: -5.7 to 2.1% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 3.9% CV(from LLOQ to ULOQ)	Yes

QC performance	• Cumulative bias range: -8.8 to -4.1% [b] • Cumulative precision: ≤ 11.4% CV • TE: ≤ 20.2% [c]	Yes
Method reproducibility	Incurred sample reanalysis was not performed for this study	Yes
Study sample analysis/ stability	All standards, QCs, and study samples (except for two samples) were analyzed within the established stability of 733 days at -70°C ± 10°C. The two samples that exceeded the long-term stability was reported as Non-Reportable Result.	Yes

[b] Cumulative accuracy (%bias) in QCs calculated from Table 5 of Report 5028, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
[c] Total error (TE) calculated from Table 5 of Report 5028, using the equation of %TE= %CV + |%RE|.
[d] Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated from Table 3 of Report 6323, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
[e] Cumulative accuracy (%bias) in QCs calculated from Table 5 of Report 6323, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration* 100%.
[f] Total error (TE) calculated from Table 5 of Report 6323, using the equation of %TE= %CV + |%RE|.

Table 54 Summary method performance of a bioanalytical method to measure durvalumab in human serum ((b) (4) Method (b) (4) 17-078-230)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an ECL Method for the Quantification of MEDI4736 in Human Serum (Report (b) (4) -17-078-230-REP)
Method description	MSD Streptavidin Multi Array 96-well Plates were blocked with 200 µL/well Blocking Buffer for approximately 1 to 4 hours at room temperature. Plates were then washed 3 times with ~300 µL/well of MSD wash buffer. After the washing step, the plates were coated at 50 µL/well with 2 µg/mL biotinylated anti-drug antibody, clone AB0470011, prepared in Assay Buffer (Capture Solution) and incubated for 30 minutes ± 5 minutes with shaking at approximately 400 rpm at room temperature. Plates were washed 3 times with ~300 µL/well of MSD wash buffer after incubation. After washing, 30 µL/well of standards, controls, and/or samples prepared at the minimum required dilution of 1:20 were added to the wells. Plates were incubated for 1 hour ± 10 minutes, with shaking at approximately 400 rpm at room temperature. Unbound materials were removed after approximately 1 hour of incubation by washing 3 times with ~300 µL/well of MSD wash buffer. Ruthenylated mouse anti-human IgG Fc, (anti-TM clone A8) at 1 µg/mL prepared in Assay Buffer was added (30 µL/well) and incubated for approximately 1 hour ± 10 minutes at room temperature in the dark. Excess ruthenylated reagent was removed by washing 3 times with ~300 µL/well of MSD wash buffer after incubation and 150 µL/well of 1X MSD Read Buffer T was added. ECL signal for each plate well was measured by an MSD Sector Imager within 15 minutes

Materials used for calibration curve & concentration	Durvalumab in human serum at final concentrations (incorporating dilutions) of 1.25, 2.50, 5.00, 10.0, 20.0, 40.0, 80.0, 160 ng/mL, and 320 ng/mL (calibration points of 1.25 and 320 ng/mL were used as anchor points).		
Validated assay range	50.0 to 3200 ng/mL in undiluted human serum		
Material used for QCs & concentration	Durvalumab in human serum at 50, 100, 400, 2000, 3200 ng/mL prior to dilution (2.50, 5.00, 20.0, 100, and 160 ng/mL following minimum required dilution)		
Minimum required dilutions (MRDs)	1:20		
Source & lot of reagents (LBA)	Durvalumab (MedImmune) Lot: WRS4736-1 Biotinylated anti-durvalumab capture antibody clone AB0470011 Lot: RP17APR18SK02 Ruthenylated anti-TM detection antibody (b) (4) Lot: RP14APR18SK02 Human Serum (b) (4) Lot: (b) (4) 1494941 (pool)		
Regression model & weighting	5 parameter logistic curve with $1/Y^2$ weighting		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0 to 4.3%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.4%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs: 50 (LLOQ-QC), 100 (LQC), 400 (MQC), 2000 (HQC), and 3200 (ULOQ-QC) ng/mL	-9.0 to 2.6%	Yes
	Inter-batch %CV QCs: 50 (LLOQ-QC), 100 (LQC), 400 (MQC), 2000 (HQC), and 3200 (ULOQ-QC) ng/mL	≤8.6%	Yes
	Total Error (TE) QCs: 50 (LLOQ-QC), 100 (LQC), 400 (MQC), 2000 (HQC), and 3200 (ULOQ-QC) ng/mL	≤ 17.3%	Yes
Selectivity & matrix effect	The assay demonstrated selectivity for durvalumab in normal human serum at the high spiked concentration of 2000 ng/mL in 10 of 10 (100%) human serum samples and at the LLOQ spiked concentration of 50 ng/mL in 10 of 10 (100%) human serum samples, where recoveries ranged from 101.8% to 118.4% of the spiked concentration with CVs between 0.1% to 7.9%. The assay also demonstrated selectivity for durvalumab in disease states with 92% of the unspiked values below the LLOQ, a 96% pass rate for the high spike, and 80% pass rate for the LLOQ spikes.		Yes

Interference & specificity	Interference of tremelimumab: The assay demonstrated specificity for durvalumab as all samples spiked with tremelimumab within the quantifiable range of the assay had recoveries between 100.6% and 112.5% with %CVs of 0.1% to 8.2%. No interference from tremelimumab was detected in the assay	Yes
Hemolysis effect	Two of the three 100 % hemolyzed samples under recovered at both the high spike and the LLOQ. This could be due to a possible suppression of ECL signal from the high amounts of free hemoglobin. The visually hemolyzed samples (50% diluted) recovered within 82.0% to 92.3% and are more representative of serum samples. the assay shows suitable recovery in visually hemolyzed samples, but not in 100% hemolyzed samples.	Yes
Lipemic effect	Lipemic matrices recovered within 78.8% to 95.2%. The assay showed suitable recovery in lipemic samples	Yes
Dilution linearity & hook effect	Dilutional linearity and prozone effect were assessed by spiking 4 individual lots of neat human serum with 1.01 mg/mL of drug product (above the highest calibrator concentration). Each spiked sample was diluted in pooled human serum at seven dilutions. Each dilution of each lot of human serum was diluted 20-fold in Assay Buffer prior to analysis and was run in replicates of 5 in one run. Linearity was observed within the quantitation range at dilutions of serum up to 129280-fold, with recoveries ranging from 80.6% to 118.7% and %CVs between 0.7% to 7.8% across all dilutions. The data do not suggest that there is a prozone (hook) effect in the assay, as no decrease in signal was detected with increasing drug concentrations.	Yes
Bench-top/process stability	24 hours 15 minutes in human serum at room temperature	Yes
Freeze-Thaw stability	6 cycles frozen at -80°C ± 15°C and thawed to room temperature	Yes
Long-term storage	Ongoing	Yes
Parallelism	Not assessed	Yes
Carry over	Not assessed	Yes
Method performance in study D419MC00004 (POSEIDON)		
Assay passing rate	5 of 7 (71%), including incurred sample reanalysis	Yes
Standard curve performance	• Cumulative bias range: -1.8 to 6.2% • Cumulative precision: ≤ 4.7% CV	Yes
QC performance	• Cumulative bias range: -5.4 to -1.0% • Cumulative precision: ≤ 11.1% CV • TE: ≤ 12.9% [a]	Yes

Method reproducibility	Incurred Sample Reanalysis (ISR) was requested and performed according to current SOPs at the conclusion of sample analysis. The results from the evaluation will be reported separately in a bioanalytical validation report and not in the clinical study report as stated in section 5.4.1.2 of the clinical protocol.	Yes
Study sample analysis/ stability	Two samples were tested, but not reported, which were outside of the established stability of 885 days at 70°C ± 10°C	Yes

Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
[FDA will complete this section.]

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Melissa Pegues, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___X Authored X Approved
	Signature: Melissa A. Pegues -S Digitally signed by Melissa A. Pegues -S Date: 2022.11.07 17:03:33 -05'00'			
Acting Nonclinical Supervisor	Claudia P. Miller, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___X Authored ___X Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2022.11.07 21:07:11 -05'00'			
Nonclinical Team Division Director N/A (NME only)	John K. Leighton, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___ Authored X Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.11.07 17:13:28 -05'00'			
Clinical Pharmacology Reviewer	Yue Xiang, PhD	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** x___ Authored ___ Approved
	Signature: Yue Xiang -S Digitally signed by Yue Xiang -S Date: 2022.11.08 10:41:34 -05'00'			
Clinical Pharmacology Team Leader	Hong Zhao, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** x Authored x___ Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2022.11.08 10:36:52 -05'00'			
Division of Pharmacometrics (DPM) Reviewer	Ye Yuan, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x___ Authored ___ Approved
	Signature: Ye Yuan -S Digitally signed by Ye Yuan -S Date: 2022.11.07 21:22:53 -05'00'			

Division of Pharmacometrics (DPM) Team Leader	Liang Li, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored X Approved
	Signature: Liang Li -S Digitally signed by Liang Li -S Date: 2022.11.07 23:24:59 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCP II	Sections: 6	**Select one:** ___ Authored X__ Approved
	Signature: Nam A. Rahman -S		Digitally signed by Nam A. Rahman -S Date: 2022.11.08 11:44:22 -05'00'	
Clinical Reviewer	Erica Nakajima, MD	CDER/OOD/DO2	Sections: BRA, 8, Summary and Conclusions	**Select one:** _X_ Authored ___ Approved
	Signature: Erica C. Nakajima -S		Digitally signed by Erica C. Nakajima -S Date: 2022.11.08 14:56:44 -05'00'	

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Nicole Drezner, MD	CDER/OOD/DO2	Sections: see CTDL	**Select one:** ___ Authored ___ Approved
	Signature: see CDTL signature			
Statistical Reviewer	Arup Sinha, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature: Arup K. Sinha -S Digitally signed by Arup K. Sinha -S Date: 2022.11.08 14:07:40 -05'00'			
Statistical Team Leader	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** _X_ Authored _X_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2022.11.08 14:12:58 -05'00'			
Division Director (OB/DBV)	Yuan-Li Shen, PhD (Proxy: Shenghui Tang, PhD)	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2022.11.08 14:32:52 -05'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Section: 11	**Select one:** ___x Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2022.11.07 21:13:01 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Nicole Drezner, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___x Authored ___ x Approved
	Signature: Nicole L. Drezner -S Digitally signed by Nicole L. Drezner -S Date: 2022.11.08 15:27:04 -05'00'			
Division Director (Clinical)	Harpreet Singh, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored _X_ Approved

Signature:

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/s/

NICOLE L DREZNER
11/10/2022 11:36:42 AM

BONNIE HARPREET MOORE
11/10/2022 11:43:15 AM