EMA/20881/2026
Humans Medicines Division

Type II variation assessment report

Imfinzi & Imjudo

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Imfinzi	durvalumab	EMEA/H/C/004771/WS2543/0062
IMJUDO	tremelimumab	EMEA/H/C/006016/WS2543/0003

Procedure no: EMEA/H/C/WS2543

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	11 Sep 2023	11 Sep 2023	☐
☐	CHMP Rapporteur Assessment Report	16 Oct 2023	23 Oct 2023	☐
☐	CHMP members comments	27 Oct 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	31 Oct 2023	31 Oct 2023	☐
☐	Start of written procedure	07 Nov 2023	07 Nov 2023	☐
☐	RSI adopted	09 Nov 2023	09 Nov 2023	☐
☐	Response submitted	14 Nov 2023	14 Nov 2023	☐
☐	Restart date	15 Nov 2023	15 Nov 2023	☐
☐	CHMP Rapporteur AR	29 Nov 2023	28 Nov 2023	☐
☐	Comments from CHMP	4 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur AR	7 Dec 2023	6 Dec 2023	☐
☐	Start of written procedure	12 Dec 2023	12 Dec 2023	☐
☒	Opinion	14 Dec 2023	14 Dec 2023	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 24 August 2023 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include paediatric information based on final results from study D419EC00001 "Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies". In addition, the MAH took this opportunity to introduce editorial changes.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

The application included EMA Decisions P/0301/2023 and P/0302/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIPs P/0301/2023 and P/0302/2023 were completed.

The PDCO issued an opinion on compliance for the PIPs P/0301/2023 and P/0302/2023.

2. Overall conclusion and impact on the benefit/risk balance

This variation concerns an update of the Imfinzi and Imjudo Products information (PI) based on the results from study D419EC00001, to include pharmacokinetics, efficacy and safety paediatric data.

Study D419EC00001 was a phase I/II, open-label, multicenter study to evaluate the safety, tolerability, and preliminary efficacy of durvalumab monotherapy or durvalumab in combination with tremelimumab in paediatric patients with advanced solid tumours and haematological malignancies".

Pharmacokinetic

The paediatric PK studies were based on fully validated methods. The trial design, dose selection and reported data corresponds to the ICH guidelines on PK studies in paediatric population, paediatric extrapolation.

Overall, in the study D419EC00001, the paediatric durvalumab systemic exposures, in combination with tremelimumab for paediatric patients < 35 kg were lower relative to adult systemic exposures at a durvalumab dose of 20 mg/kg every 4 weeks but were generally similar to adult systemic exposures at a dose of 30 mg/kg every 4 weeks.

Population PK modelling and simulation data showed that systemic exposures in paediatric patients ≥ 35 kg were generally similar to adult systemic exposures at a durvalumab dose of 20 mg/kg every 4 weeks, but higher compared to adult systemic exposures (approximately 1.5-fold) at a durvalumab

dose of 30 mg/kg every 4 weeks. Tremelimumab systemic exposures, in combination with durvalumab, were generally similar to adult systemic exposures at a tremelimumab dose of 1 mg/kg every 4 weeks for paediatric patients ≥ 35 kg but were lower relative to adult systemic exposures for paediatric patients < 35 kg.

There is no indication for durvalumab or tremelimumab, and the combination of both in paediatric population. Therefore, no posology recommendation can be made. The Applicant´s summary of available information in section 4.2 reflects the data available.

Pharmacology

The combination of durvalumab and tremelimumab results in enhanced circulating quantities of proliferating CD4 T cells, as evident by an increase in CD4+Ki67+ T -cells, is consistent with the proposed mechanisms of action of both immune checkpoint inhibitors. This result is comparable to that observed for adult NSCLC patients also receiving this combination.

Efficacy

No formal efficacy analysis was performed for patients in the dose-finding phase; however, based on Investigator assessment of overall RECIST responses, 2 patients in the dose-finding phase, one at each dose level, with osteosarcoma and papillary type renal carcinoma, respectively, had a PR for over one year.

In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set, and 4.8% (1/21 patients) in the FAS. No response was observed in the 11 patients initially enrolled in the SARCOMA cohort in the first stage of the Simon 2-stage design, leading to cohort discontinuation. In the STO cohort, an ORR of 11.1% (1/9 patients) was reported in the evaluable for response analysis set, and 10.0% (1/10 patients) in the FAS, as one patient with chordoma had a confirmed response of PR 1.8 months after the first dose of study treatment, with a DoR of 10.8 months.

In the evaluable for response analysis set, DCR was 9.1% (1/11 patients) in the SARCOMA cohort and 11.1% (1/9 patients) in the STO cohort at both Week 16 and Week 24. Similar results were observed for sensitivity analyses performed on the FAS. The median PFS in the SARCOMA and STO cohorts was 1.7 months (90% CI: 1.58, 1.91) and 1.7 months (90% CI: 0.89, 2.76), respectively, and all patients in the dose-expansion phase of the study had progression events (PD or death). In the SARCOMA cohort, the median OS was 6.6 months (90% CI: 1.87, 15.77), with a survival rate of 25.6% at 12 months. In the STO cohort, the median OS was 6.9 months (90% CI: 1.61, NR), with a survival rate of 40.0% at 12 months and 30.0% at 24 months.

Overall, the study is negative efficacy-wise, and no paediatric indication is sought. The SmPC reflects the data available.

Safety

Assessment of safety was a primary objective for the dose-finding phase of this study. The safety profile was as expected for this patient population and consistent with the known safety profile of durvalumab administered as monotherapy or in combination with tremelimumab in adults.

No new safety concerns were identified.

No treatment-emergent ADA against durvalumab or tremelimumab were detected, thus no assessment of the potential impact of ADA on safety could be made.

The safety data collected in Study D419EC00001 belongs to a paediatric development for an indication neither approved in children nor in adults. Thus, the safety data are presented together with the

results of the paediatric clinical study in section 5.1 instead of section 4.8, in order to avoid confusions or off-label use in the paediatric population.

The full PIP compliance check opinions for the durvalumab PIP (EMEA-002028-PIP01-16-M04) and the tremelimumab PIP (EMEA-002029-PIP01-16-M04) has been submitted with the response to the RSI. PDCO adopted a positive opinion for both procedures on 13 October 2023.

The benefit-risk balance of Imfinzi and Imjudo, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include paediatric information based on final results from study D419EC00001 "Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies". In addition, the MAH took this opportunity to introduce editorial changes.

☒is recommended for approval

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I are recommended.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plans EMEA-C-002028-PIP01-16-M04 and EMEA-C-002029-PIP01-16-M04 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Based on the results from study D419EC00001 in children and adolescents, sections 4.2, 5.1, and 5.2 have been updated. The efficacy and safety of durvalumab in combination with tremelimumab in children were assessed but not established. Currently available data are reported in the SmPC. In the

dose-expansion phase, an Overall Response Rate of 5.0% (1/20 patients) was reported in the evaluable for response analysis set. No new safety signals were observed relative to the known safety profiles of durvalumab and tremelimumab in adults.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Imfinzi (durvalumab) is a human monoclonal antibody that binds to the PD L1 protein and blocks the interaction of PD-L1 with the PD-1 and CD80 proteins, countering the tumour's immune-evading tactics and releasing the inhibition of immune responses.

Tremelimumab is a human mAb that targets the activity of cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Tremelimumab blocks the activity of CTLA-4, contributing to T-cell activation, priming the immune response to cancer and fostering cancer cell death.

Durvalumab is being developed as monotherapy, and in combination with tremelimumab and other anticancer agents, as a potential immunotherapy treatment across various tumour types, stages of disease, and lines of treatment. Durvalumab is approved:

- As a monotherapy treatment for adults with unresectable, stage III non-small cell lung cancer (NSCLC) in patients whose disease has not progressed after chemoradiation therapy based on the PACIFIC Phase III study.

- 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) in the US, European Union (EU), Japan, China, and many other countries around the world based on the CASPIAN Phase III study.

- In combination with tremelimumab and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor mutation or anaplastic lymphoma kinase anaplastic lymphoma kinase genomic tumour aberrations (based on the pivotal Phase III POSEIDON study [D419MC00004]).

- In combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer (based on the pivotal Phase III TOPAZ-1 study [D933AC00001]).

- In combination with tremelimumab for adult patients with unresectable hepatocellular carcinoma (based on the pivotal Phase III HIMALAYA study [D419CC00002]).

Imjudo (tremelimumab) is currently only approved for use in combination with durvalumab as stated above.

With this submission the MAH is proposing an update to the paediatric information included in the product labelling for Imjudo and Imfinzi.

The MAH has included the final Clinical Study Report for Study D419EC00001, titled 'Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies.'

Study D419EC00001 is listed in the EU PIPs (EMEA-002028-PIP01-16-M04 and EMEA-002029-PIP01-16-M04) as Study 2. The study evaluated the combination of durvalumab and tremelimumab in 50 paediatric patients with relapsed or refractory malignant solid tumours (except primary central nervous system tumours). This submission of paediatric study results is performed in compliance with these paediatric investigation plans (PIP) which do not support a paediatric indication.

Please note that the same Type II update to the Tremelimumab AstraZeneca MAA has been submitted separately as this license is to withdraw as per notification to EMA 29 September 2023. In spite of this a separate report is circulated (Tremelimumab AstraZeneca II/002).

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

Population PK models

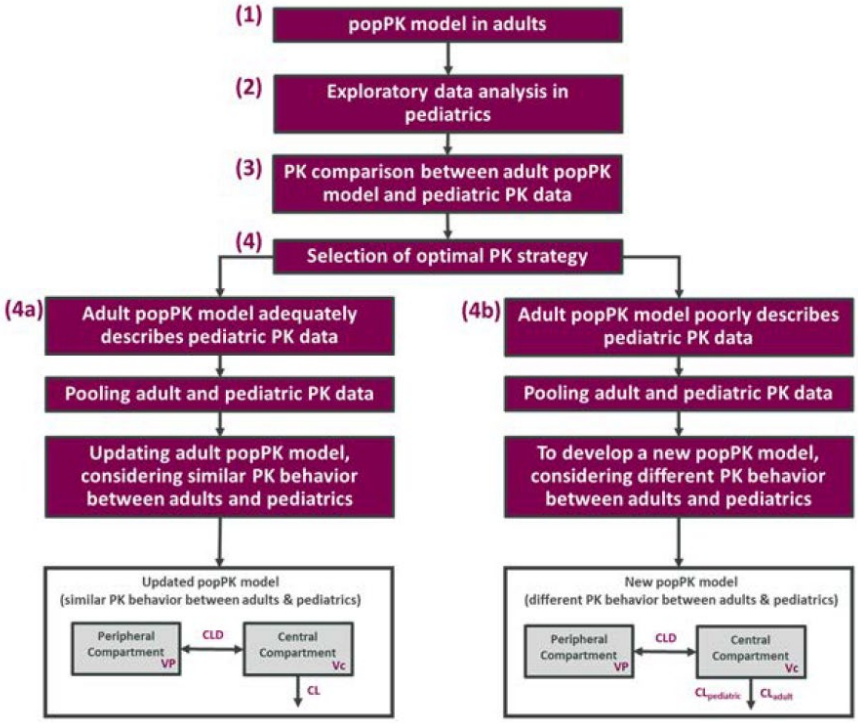
To evaluate if the pharmacokinetic behaviour of durvalumab and tremelimumab is similar between adults and paediatric patients, the pharmacokinetics of durvalumab and tremelimumab after IV administration in paediatric population with advanced solid malignancies were assessed in a phase I/II study (D419EC00001 2023). In the current analysis, previously developed population pharmacokinetic (PopPK) models for durvalumab and tremelimumab were updated by integrating the paediatric sparse PK data to describe the serum concentration-time profile of durvalumab and tremelimumab in paediatric and adult patients with various tumour types. Typical population mean parameters and associated inter- and intra-individual variability, as well as the influence of covariates on the PopPK parameters of durvalumab and tremelimumab were assessed.

Several PopPK models have been developed for durvalumab and the most recent one (D419CC00002 2021) was developed using 7 phase I/II/III clinical studies (1108, ATLANTIC, PACIFIC, CASPIAN, POSEIDON, Study 22, and HIMALAYA). Durvalumab PK was characterized using a 2-compartment model with a time dependent clearance. Albumin levels (ALB), creatinine CL, ECOG status, LDH, sex, body weight (WT), tumour types and combination therapy were statistically significant covariates on clearance. WT and sex had a statistically significant impact on central volume of distribution. However, none of the covariates were considered as clinically relevant (impact on CL and V1 were less than or about 30%).

Two PopPK models have been developed for tremelimumab and the most recent one (D419CC00002 2021) was developed using 8 phase I/II/III clinical studies (D4190C00002, D4190C00006, D4190C00010, D4880C00003 (DETERMINE), D4884C00001, POSEIDON, Study 22 and HIMALAYA). The model was described by a 2-compartmental distribution model with both linear and time-dependent elimination (for monotherapy, elimination was linear only). WT, ALB, sex, combination therapy and primary indication had a statistically significant impact on clearance. WT and sex had a statistically significant impact on central volume of distribution. However, none of the covariates were considered as clinically relevant (impact on CL and V1 were less than or about 30%).

A summary of the applied approach used to evaluate if the pharmacokinetic behaviour of durvalumab and tremelimumab is similar between adults and paediatrics can be seen in Figure 1.

Figure 1 Overview of Pharmacometrics Analysis



Firstly, Durvalumab and tremelimumab concentrations versus time profiles were explored graphically to isolate patterns and features in the pharmacokinetic behaviour of the different subjects and/or populations included in this PopPK analysis. Due to the different study designs of the studies included in this analysis, the graphical evaluation was performed using time after last dose instead of chronological time and also normalizing drug levels by dose level when appropriate.

Secondly, an external evaluation by means of VPC methodology was used to evaluate if the pharmacokinetic behaviour of durvalumab and tremelimumab is similar between adults and paediatrics. A graphical way of evaluating the performance of the established adult PopPK model was to simulate the same design properties of the external dataset (data from paediatrics) using the final parameter estimates of the established population PK model (adult PopPK model), and then, compare the distributions between simulations and observations. A plot of the time course of the paediatric durvalumab and tremelimumab observations along with the 90% prediction intervals for the simulated values from the PopPK model in adults provided a VPC. Similar PK behaviour between populations (adults and paediatrics) was concluded if the observations from paediatric mostly laid within the 90% prediction intervals and they are randomly distributed throughout the simulated typical PK profile derived from the adult PopPK model.

Results of this external evaluation determined the population approach that was implemented to adequately estimate pharmacokinetics of durvalumab and tremelimumab in paediatrics:

- Updating adult PopPK model: if adult PopPK model adequately described paediatric PK data
- To develop a new PopPK model: if adult PopPK model poorly described paediatric PK data

If similar PK behaviour of durvalumab or tremelimumab was concluded between both populations (adults and paediatrics) during the external evaluation, the adult PopPK model was updated including the paediatric PK data. Thus, the adult PopPK model was rerun adding the PK samples from paediatric study, and the new parameter estimates were considered as the final PopPK parameters for both populations (adults + paediatrics). This new PopPK model (adults + paediatrics) has the same

structure than that of adults. If deemed necessary, some arrangements in this new PopPK model (adult + paediatrics) were allowed to improve model fit.

Durvalumab Population PK model

Table 1 provides a stratification of the data used in the population PK analysis per study. There were 50 paediatric patients and 4050 patients from previous dataset, resulting a total 4100 patients in the dataset. A total of 221 below the lower limit of quantification (LLOQ) samples (1.46%) were excluded from current analysis and 5 of them were from paediatric study. In addition, 13 samples from paediatric study were also excluded from the analysis due to incorrect PK sample time. Eventually, 15166 serum PK samples from 4100 patients treated with durvalumab were available in the final dataset for analysis.

Table 1 Durvalumab Population PK Analysis - Summary of the Data

Study	Number of subjects	Total number of obs.	Number (%) of excluded obs.	Number (%) of obs. below the LLOQ (total)
CD-ON-MEDIA-4736-1108	1001	6090	4 (0.0657)	26 (0.427)
D419QC00001 (Caspian)	260	665	16 (2.41)	19 (2.86)
D4191C00001 (Pacific)	473	1760	0 (0)	24 (1.36)
D4191C00003 (Atlantic)	444	1405	0 (0)	17 (1.21)
D419MC00004 (Poseidon)	649	1761	1 (0.0568)	47 (2.67)
D4190C00022 (Study22)	295	963	20 (2.08)	15 (1.56)
D419CC00002 (Himalaya)	928	2245	37 (1.65)	68 (3.03)
D419EC00001 (Pediatrics)	50	277	18 (6.50)	5 (1.81)
Total	4100	15166	96 (0.633)	221 (1.46)

A summary the continuous characteristics of the population in the PopPK analysis dataset, stratified by paediatric and previous studies can be seen in Table 2. sPD-L1 was not available in several studies (including paediatric study) and had 58.9% of missing values overall. No ADA positive subjects were found in paediatric population.

Table 2 Summary of Continuous Covariates

	Total	Previous Studies	Pediatrics
Individuals			
N	4100	4050	50
Individuals by study			
Previous Studies	4050 (98.8%)	--	--
Pediatrics	50 (1.22%)	--	--
Age (years)			
Mean (SD)	61.6 (12.0)	62.2 (10.7)	11.5 (4.30)
Median (IQR)	63.0 (56.0-69.0)	63.0 (56.0-69.0)	11.5 (8.00-15.0)
Min-max	1.00-96.0	18.0-96.0	1.00-17.0
Missing	0 (0%)	0 (0%)	0 (0%)
Bodyweight (kg)			
Mean (SD)	70.7 (16.8)	71.0 (16.4)	43.9 (23.4)
Median (IQR)	69.0 (59.0-80.1)	69.1 (59.0-80.4)	39.0 (27.3-59.0)
Min-max	10.0-175	31.0-175	10.0-116
Missing	4 (0.0976%)	4 (0.0988%)	0 (0%)
Creatinine clearance (mL/min)			
Mean (SD)	90.9 (32.2)	90.5 (31.5)	133 (55.1)
Median (IQR)	85.8 (68.4-107)	85.6 (68.3-106)	125 (91.5-166)
Min-max	25.7-317	25.7-279	58.4-317
Missing	70 (1.71%)	65 (1.60%)	5 (10.0%)
Albumin (g/L)			
Mean (SD)	38.4 (5.19)	38.4 (5.19)	41.7 (4.65)
Median (IQR)	39.0 (35.0-42.0)	39.0 (35.0-42.0)	42.0 (39.8-44.9)
Min-max	4.10-57.1	4.10-57.1	31.0-52.0
Missing	79 (1.93%)	73 (1.80%)	6 (12.0%)
Lactate Dehydrogenase (IU/L)			
Mean (SD)	337 (428)	337 (429)	365 (395)
Median (IQR)	239 (186-361)	239 (186-361)	264 (210-365)
Min-max	18.0-15800	18.0-15800	130-2650
Missing	142 (3.46%)	137 (3.38%)	5 (10.0%)

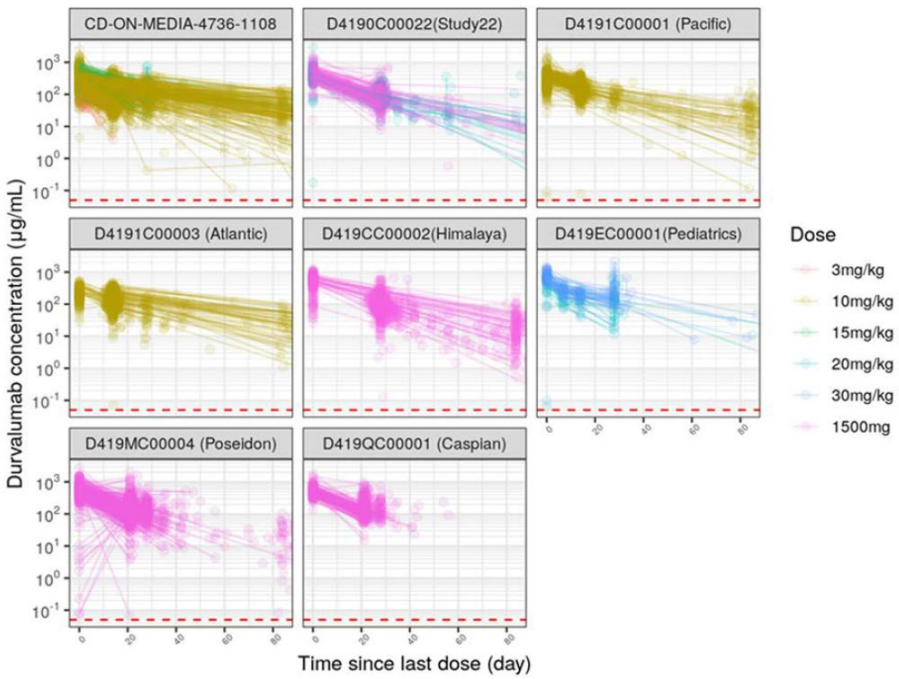
	Total	Previous Studies	Pediatrics
Neutrophil-to-Lymphocyte Ratio			
Mean (SD)	3.98 (6.28)	3.99 (6.33)	3.62 (3.38)
Median (IQR)	3.12 (2.17-4.62)	3.13 (2.19-4.62)	2.52 (1.54-3.93)
Min-max	0.00300-253	0.00300-253	0.452-18.0
Missing	2040 (49.8%)	2037 (50.3%)	3 (6.00%)
s-PDL1 (pg/mL)			
Mean (SD)	138 (103)	138 (103)	NA (NA)
Median (IQR)	125 (95.1-161)	125 (95.1-161)	NA (NA-NA)
Min-max	67.1-3470	67.1-3470	--
Missing	2416 (58.9%)	2366 (58.4%)	50 (100%)

IQR = inter-quartile range; NA = not available; SD = standard deviation; sPD-L1 = soluble programmed cell death ligand 1; -- = not applicable

A correlation plot illustrating correlations between continuous covariates indicated that CrCL was correlated with age and WT. Otherwise, no relevant correlations were observed. No important dependencies between categorical-continuous covariate pairs were observed.

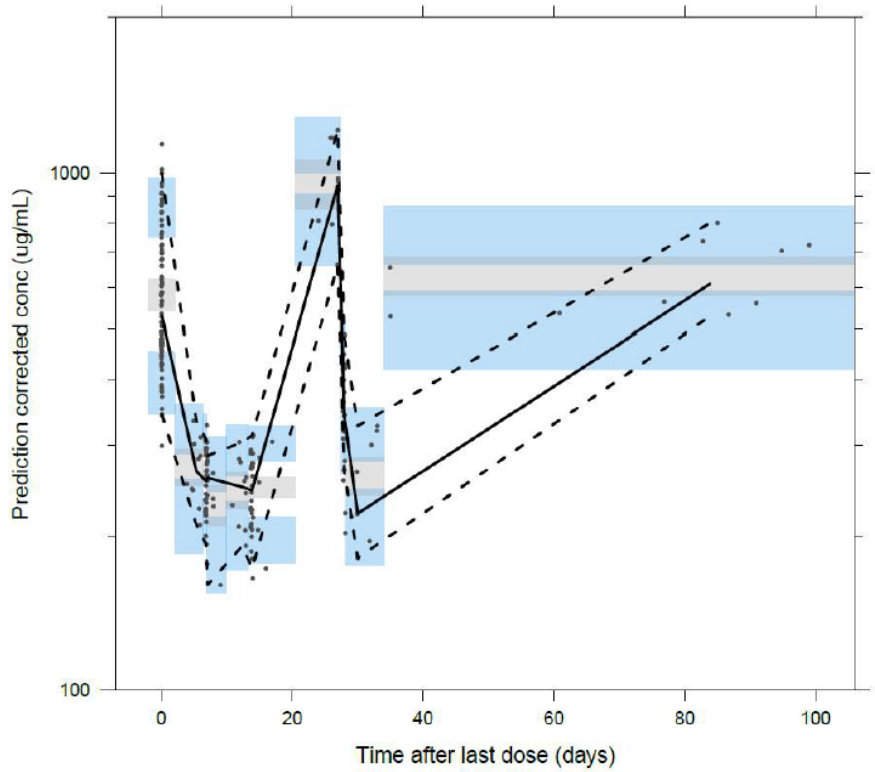
Figure 2 shows concentrations vs time since last dose (TSLD) by study and dose. There were no signs of evident differences in the systemic exposure of durvalumab between the paediatric group and adults.

Figure 2 Durvalumab Concentration vs Time Since Last Dose by Study



An external evaluation by means of pc-VPC methodology was used to evaluate if the previous adult PopPK model was able to predict the new paediatric PK data (see Figure 3). Due to most of the paediatric observations are within the prediction intervals of adult PopPK model, a similar PK behaviour between the two populations (adults and paediatrics) could be concluded.

Figure 3 Prediction-Corrected Visual Predictive Check Plot of the External Dataset (paediatric PK data) for the Previously Established Adult popPK Model of Durvalumab



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations; the shaded;
Grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model
CI = confidence interval; pcVPC = prediction-corrected visual predictive check

Based on these results, the full covariate model was re-evaluated based on the current data (paediatric + adult) and previous developed model structure (adult PopPK model). The covariate analysis was then conducted in three steps:

- Covariates included in the full covariate model were removed one by one to assess their impact to obtain a starting model for the following step.
- Graphical inspected all covariate effects and covariates of interest were tested to assess their impact on the full covariate model.
- In addition, the relevance of inter-individual variability and residual variability was also evaluated.

Additionally, the few covariates of interest (paediatric vs. adult population, and age) were tested on CL and V1. These analyses confirmed that age was a significant covariate for durvalumab on CL and V1.

The following durvalumab model was chosen as final model:

- Two-compartmental distribution model with time-dependent clearance.
- Inter-subject variability (IIV) was characterised on clearance (CL), central volume (V1), peripheral volume (V2) and the maximum change for time-dependent clearance
- A combination of proportional and additive residual error model
- Albumin levels (ALB), creatinine CL, ECOG status, LDH, sex, body weight (WT), combination therapy, tumour type and age as statistically significant covariates on CL

- WT, sex and age had a statistically significant impact on V1.

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

$$CL_{cat.cov} = 1_{comb=0} \cdot (1 - 0.0438_{comb=1}) \cdot (1 - 0.0358_{comb=2}) \cdot 1_{ECOGbin=0} \cdot (1 - 0.0484_{ECOGbin=1}) \cdot 1_{male} \cdot (1 - 0.137_{female}) \cdot 1_{tumtyp=0} \cdot (1 - 0.0381_{tumtyp=1}) \cdot (1 + 0.0724_{tumtyp=2}) \cdot (1 + 0.0465_{tumtyp=3})$$

$$CL_{cont.cov} = \left(\frac{alb_i}{39}\right)^{-0.635} \cdot \left(\frac{CrCL_i}{85.66}\right)^{0.147} \cdot \left(\frac{LDH_i}{247}\right)^{0.0447} \cdot \left(\frac{WT_i}{69.4}\right)^{0.395} \cdot \left(\frac{AGE_i}{63}\right)^{0.140}$$

$$CL_{T,i} = 0.286 \cdot CL_{cat.cov} \cdot CL_{cont.cov} \cdot exp\left(\frac{T_{max} \cdot t}{TC_{50} + t}\right) \cdot \exp(\eta_i)$$

$$V_{c,i} = 3.45 \cdot \left(\frac{WT_i}{69.4}\right)^{0.525} \cdot \left(\frac{AGE_i}{63}\right)^{0.094} \cdot 1_{male} \cdot (1 - 0.134_{female})$$

where CLcat.cov, CLcont.cov and CLT,i represent the impact of categorical and continuous covariates and the individual total CL including the time-dependent decrease of CL, respectively.

The parameter estimates for the final updated model are reported in Table 3. Parameters were well estimated and the typical parameter estimates CL, V1 and V2 are 0.286 L/day, 3.45 L and 2.08 L, which are close to what have been reported previously, 0.277 L/day, 3.45 L and 2.13 L respectively (D419CC00002 2021). All parameter estimates were reported with 95% confidence intervals, as a measure of estimation uncertainty, estimated using the standard error of the estimates obtained from the minimization routine. The paediatric population presents a reduction of the mean age and mean total body weight (11.5 years and 43.9 kg) compared with mean adult population (62.3 years and 71.0 kg) of -81% and -38%, respectively. Thus, as expected from the covariate effect of age and weight on PK parameters, the mean individual post-hoc parameters CL, V1 and V2 for paediatric population (0.171 L/day, 2.04 L and 1.71 L, respectively) were -39%, -39% and -19 % lower than the mean individual post-hoc PK parameters in adults (0.280 L/day, 3.35 L and 2.11 L, respectively).

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

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.286	2.16	[0.274; 0.298]	-	L/day
$V_{central}$	3.45	0.802	[3.39; 3.50]	-	L
$V_{peripheral}$	2.08	2.74	[1.97; 2.19]	-	L
$Q_{intercompartmental}$	0.474	5.78	[0.420; 0.527]	-	L/day
T_{max} change CL	-0.346	4.52	[-0.376; -0.315]	-	L/day
TC_{50} change CL	42.9	13.0	[31.9; 53.8]	-	day
LAM change CL	1.00	-	-	-	-
Covariate					
Albumin on CL	-0.635	2.99	[-0.672; -0.598]	-	-
Creatinine clearance on CL	0.147	14.9	[0.104; 0.190]	-	-
ECOG status on CL	-0.0484	21.8	[-0.0691; -0.0277]	-	-
LDH on CL	0.0447	23.0	[0.0245; 0.0649]	-	-
Sex on CL	-0.137	8.46	[-0.160; -0.114]	-	-
COMB1 on CL	-0.0438	28.2	[-0.0680; -0.0195]	-	-
COMB2 on CL	-0.0358	50.6	[-0.0712; -0.000333]	-	-
Bodyweight on CL	0.395	7.82	[0.335; 0.456]	-	-
Tumor type 1 on CL	-0.0381	47.7	[-0.0737; -0.00251]	-	-
Tumor type 2 on CL	0.0724	49.4	[0.00223; 0.143]	-	-
Tumor type 3 on CL	0.0465	46.6	[0.00403; 0.0889]	-	-
Age on CL	0.140	19.2	[0.0873; 0.192]	-	-
Sex on Vc	-0.134	7.75	[-0.155; -0.114]	-	-
Bodyweight on Vc	0.525	4.42	[0.479; 0.570]	-	-
Age on Vc	0.0942	19.2	[0.0588; 0.130]	-	-
Interindividual Variability					

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
ETA CL	0.0880	2.92	[0.0830; 0.0931]	15.8	-
Cov CL-V1	0.0366	5.61	[0.0326; 0.0406]	-	-
ETA Vc	0.0517	3.26	[0.0484; 0.0550]	29.2	-
ETA T_{max}	0.0226	18.8	[0.0143; 0.0309]	70.0	-
ETA Vp	0.209	9.06	[0.172; 0.247]	57.4	-
Residual Variability					
Proportional component	0.246	0.511	[0.243; 0.248]	17.5	-
Additive component	3.22	8.79	[2.67; 3.78]	17.5	µg/mL

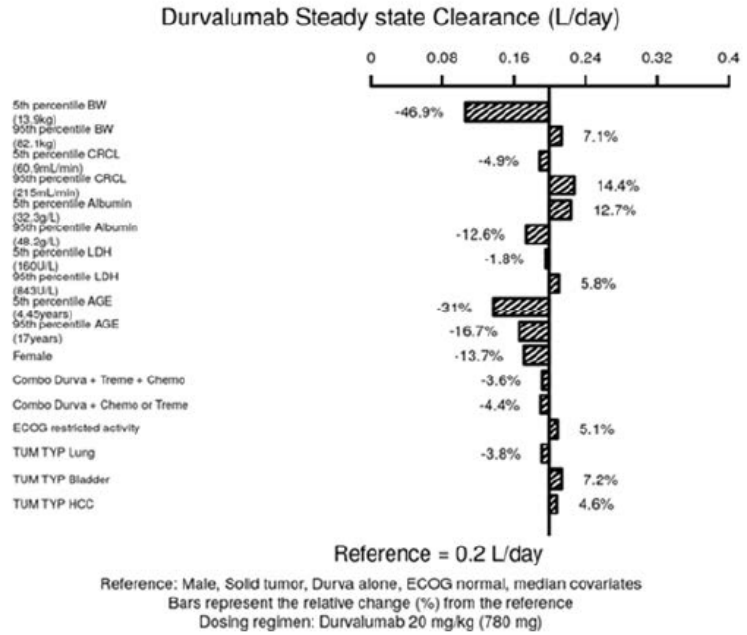
Abbreviations: CI=confidence interval, CL=clearance, COMB1=durvalumab + SOC or tremelimumab, COMB2=durvalumab + tremelimumab + SOC, Cov=Covariance, ECOG=Eastern Cooperative Oncology Group, ETA=random effect, LAM=Hill factor, LDH=lactate dehydrogenase, PK=pharmacokinetics, Q=inter-compartmental clearance, RSE=relative standard error, Tmax=maximum change of CL over time, TC50: time to 50% change of CL over time; Tumor type 1= NSCLC, Tumor type 2= bladder cancer, Tumor type 3 = HCC, V1=central volume of distribution, V2=peripheral volume of distribution.

Standard GOF plots showed good agreement between the model prediction and the durvalumab serum concentration when pooling all data. The other VPCs including stratification for each study, for age-

group and for weight-groups showed adequate model performance in the paediatric population. The large degree of overlap between the observed and model derived concentrations in subjects with age lower than 18 years and in subjects with weight lower than 35 kg indicated that the current model could adequately describe durvalumab pharmacokinetics in paediatric subjects.

The impact of the selected covariates on clearance at steady-state (CL,ss) and V1 based on a univariate assessment are presented as tornado plots in Figure 4 and Figure 5, using paediatric covariate range relative to adult reference after administration of 20 mg/kg (that corresponds to a total dose of 780 mg for a paediatric subject of 39 kg (median of paediatric population)).

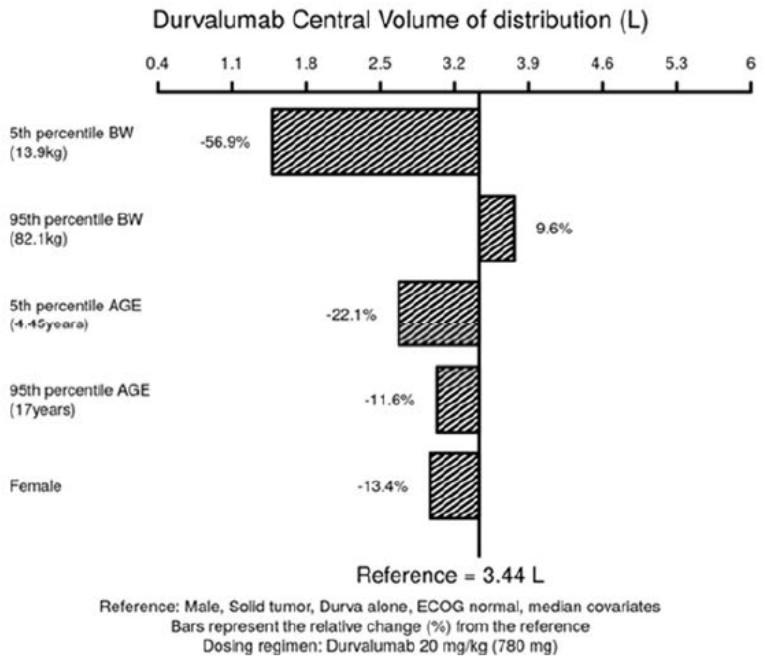
Figure 4 Impact of Paediatric Covariates on Durvalumab Clearance at Steady State -Tornado Plot



Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates)

Chemo = chemotherapy; CRCL = creatinine clearance; Durva = durvalumab; ECOG = Eastern Cooperative Oncology Group, LDH=lactate dehydrogenase, NSCLC=non-small cell lung cancer, Treme = tremelimumab

Figure 5 Impact of Paediatric Covariates on Durvalumab Central Volume - Tornado Plot

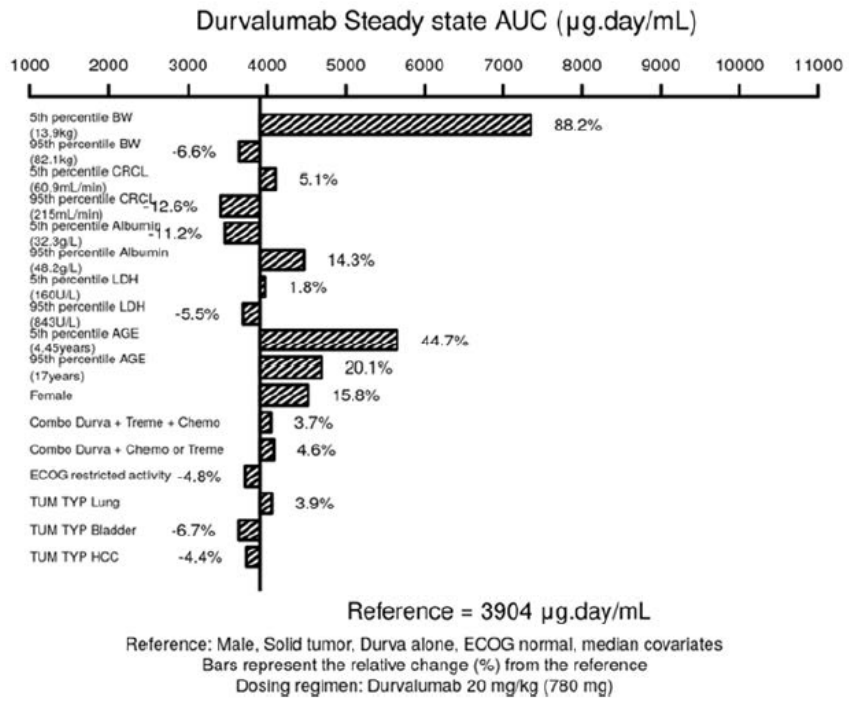


Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates)

Durva = durvalumab; ECOG = Eastern Cooperative Oncology Group

Only bodyweight showed a significant impact on model parameters CLss and V1, with a maximum change of -46.9% on CLss and -56.9% on V1 for the 5th percentile of observed paediatric WT values, predicting a significant increase of AUCss +88.2% (see Figure 6) in paediatric patients with lower bodyweight. For all other tested covariates, no covariate showed a significant impact on model parameters CLss and V1. AGE had the most pronounced impact on CLss and V1, with a maximum change of -31% in CLss and -22% [V1] for the 5th percentile of observed AGE in the paediatric population.

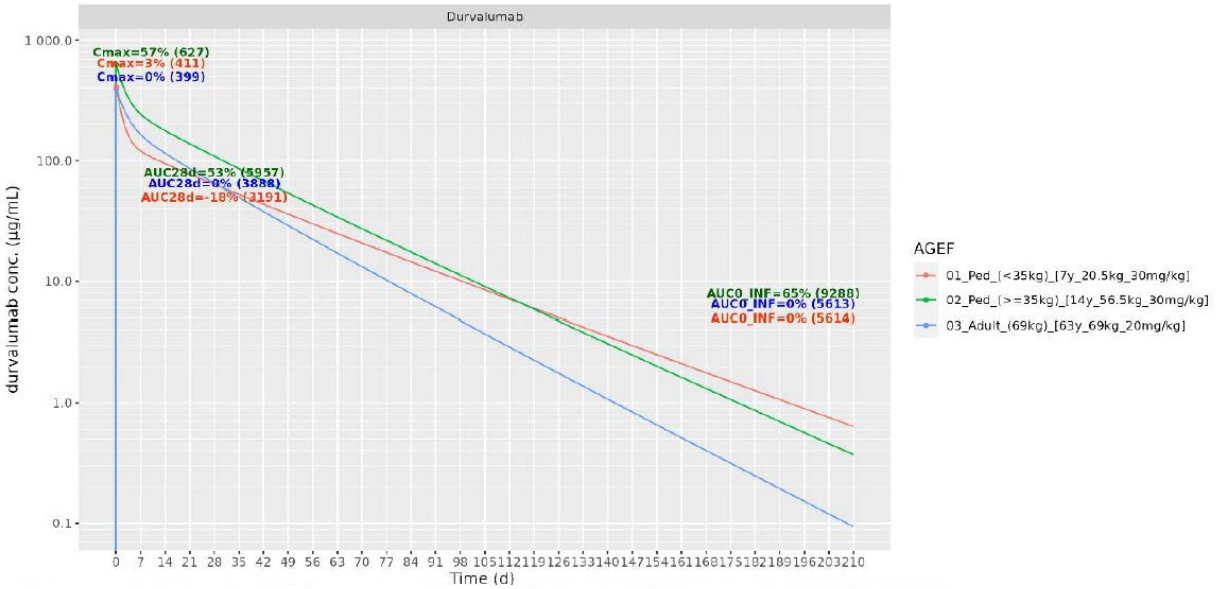
Figure 6 Impact of Paediatric Covariates on Durvalumab AUC at Steady State - Tornado Plot



Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates).
Durva = durvalumab; ECOG = Eastern Cooperative Oncology Group

Figure 7 depicts the simulated PK profiles that allow an evaluation of whether the drug exposure of paediatric patients after durvalumab administration at the dose of 30 mg/kg is similar than that for adults after administration of 20 mg/kg. In this case, the same paediatric population with WT < 35 kg and with WT ≥ 35 kg were modelled to receive a dose normalized by weight of 30 mg/kg, that corresponds to a total dose of 615 mg and 1695 mg, respectively. On the other hand, the adult reference patient of 69 kg, was modelled to receive a durvalumab dose of 20 mg/kg (total dose of 1380 mg). The predicted drug exposure at 28 days (AUC0-28) in paediatric patients with WT < 35 kg at 30 mg/kg (3191 day*µg/mL) is similar to that in adults at 20 mg/kg (3888 day*µg/mL) with a reduction of -18%, being both higher than the reference (2105 day*µg/mL). Additionally, a higher drug exposure at Day 28 (increase of +53%) is predicted for paediatric patients with WT ≥ 35 kg at 30 mg/kg (5957 day*µg/mL) compared with drug exposure predicted in adults at the dose of 20 mg/kg (3888 day*µg/mL).

Figure 7 Influence of Age (AGE) and Weight (WT) on Durvalumab PK Behaviour in Paediatric Population at a Dose of 30 mg/kg Compared with Adult Exposure at 20 mg/kg.



Tremelimumab population PK model

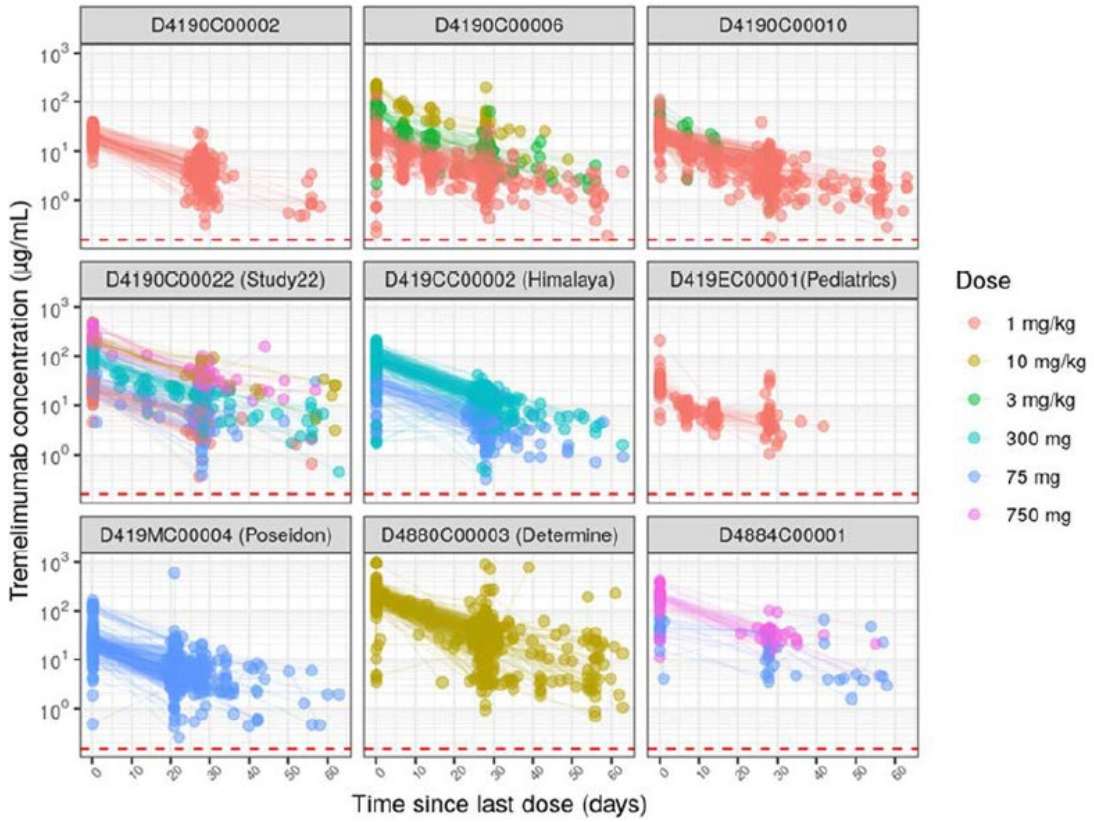
Table 4 provides a stratification of the data used in the population PK analysis per study. Eight out of 50 paediatric patients included in paediatric study D419EC00001 2023 were not included in this analysis due to the lack of tremelimumab PK data in these subjects. Thus, the tremelimumab dataset consisted of 42 paediatric patients and 2406 patients from previous dataset, resulting a total 2448 patients in the dataset. A total of 286 below the lower limit of quantification (LLOQ) samples (3.76%) were excluded from current analysis and 6 of them were from paediatric study. In addition, 2 samples from paediatric study were also excluded from the analysis due to incorrect PK sample time. Eventually, 7611 serum PK samples from 2448 patients treated with tremelimumab were available in the final dataset for analysis.

Table 4 Tremelimumab Population PK Analysis - Summary of the Data

Study	Number of subjects	Total number of obs.	Number (%) of obs. below the LLOQ (total)
D4190C00002 (Japan Study 02)	122	691	6 (0.8683)
D4190C00006 (Study 06)	350	1262	36 (2.853)
D4190C00010 (Study 10)	372	1073	92 (8.574)
D4190C00022 (Study22)	262	803.0	45 (5.604)
D419CC00002 (HIMALAYA)	539	1154	57 (4.939)
D419EC00001 (Pediatrics)	42	199	6 (3.015)
D419MC00004 (POSEIDON)	326	919.0	29 (3.156)
D4880C00003 (DETERMINE)	374	1325	13 (0.9811)
D4884C00001	61	185	2 (1.081)
Total	2448	7611	286 (3.758)

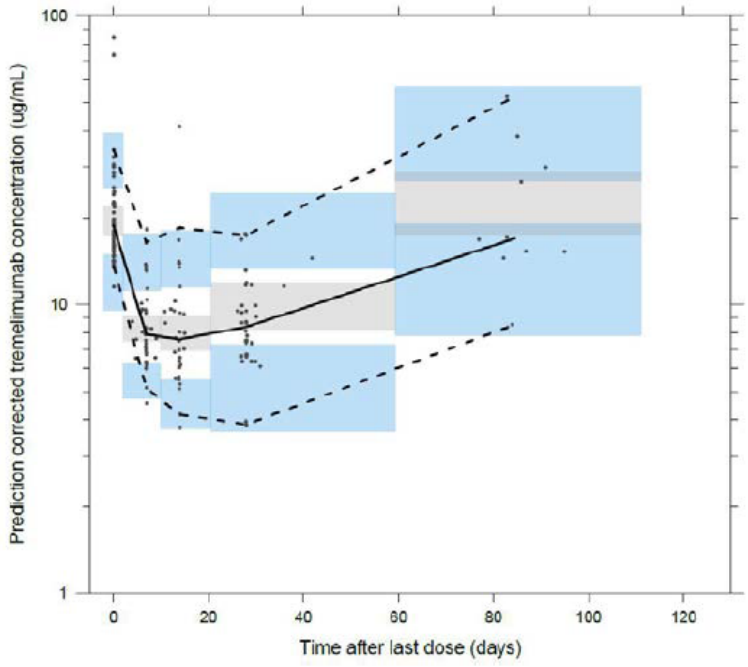
Figure 8 shows concentrations vs time since last dose (TSLD) by study and dose. There were no signs of evident differences in the systemic exposure of tremelimumab between the paediatric group and adults. None of the evaluated paediatric patients for tremelimumab were found ADA positive therefore, the influence of ADA on paediatric tremelimumab pharmacokinetics could not be evaluated.

Figure 8 Tremelimumab Concentration vs Time Since Last Dose by Study



The first step of model development consists of evaluating the feasibility to reproduce the same PopPK results than that obtained in the previous well-established adult PopPK (D419CC00002 2021). Thus, an external evaluation by means of pc-VPC methodology was used to evaluate if the previous adult PopPK model was able to predict the new paediatric PK data (see Figure 9). Due to most of the paediatric observations were within the prediction intervals of adult PopPK model, a similar PK behaviour between the two populations (adults and paediatrics) could be concluded.

Figure 9 Prediction-Corrected Visual Predictive Check Plot of the External Dataset (paediatric PK data) for the Previously Established Adult popPK Model of Tremelimumab



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations;

Shaded grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model

CI = confidence interval; pcVPC = prediction-corrected visual predictive check

Based on these results, the full covariate model was re-evaluated based on the current data (paediatric + adult) and previous developed model structure (adult PopPK model). The covariate analysis was then conducted in three steps:

- Covariates included in the full covariate model were removed one by one to assess their impact to obtain a starting model for the following step.
- Graphical inspected all covariate effects and covariates of interest were tested to assess their impact on the full covariate model.
- In addition, the relevance of inter-individual variability and residual variability was also evaluated.

Additionally, a few covariates of interest (paediatric vs. adult population, and age) were tested on CL and V1. The paediatric or adult effect on V1 and CL was barely made significant (14.2 and 15.6>10.83), but both models failed. In addition, these analyses confirmed that age was a not a significant covariate for tremelimumab on V1 and CL, and therefore, the following was considered as the final model:

- Two-compartmental distribution model with both linear and time-dependent elimination (for monotherapy, elimination was linear only).
- Inter-subject variability (IIV) was characterized on clearance (CL), central volume (V1), peripheral volume (V2) and the maximum change for time-dependent clearance. Correlations between CL, V1, and V2 were estimated via and omega block.
- A combination of proportional and additive residual error model

- Weight (WT), Albumin levels (ALB), sex, combination therapy and primary indication had a statistically significant impact on CL
- Weight (WT) and sex had a statistically significant impact on V1

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

$$CL_{cat.cov} = 1_{male} \cdot \left(1 - 0.0927_{female}\right) \cdot 1_{other\ indications} \cdot \left(1 - 0.131_{BTC/EC}\right) \cdot 1_{no\ chemotherapy}\left(1 - 0.111_{SoC\ chemotherapy}\right)$$

$$CL_{cont.cov} = \left(\frac{ALB_i}{39}\right)^{-0.793} \cdot \left(\frac{WT_i}{70.2}\right)^{0.489}$$

$$CL_{T,i} = 0.288 \cdot CL_{cat.cov} \cdot CL_{cont.cov} \cdot exp\left(\frac{T_{max} \cdot \exp(\eta_{Tmaxi}) \cdot t}{TC_{50} + t}\right) \cdot \exp(\eta_{CLi})$$

$$CL_i = 0.288 \cdot CL_{cat.cov} \cdot CL_{cont.cov} \cdot \exp(\eta_{CLi})$$

$$V_{c,i} = 3.57 \cdot \left(\frac{WT_i}{70.2}\right)^{0.534} \cdot 1_{male} \cdot \left(1 - 0.117_{female}\right) \cdot \exp(\eta_{V1i})$$

where CLcat.cov, CLcont.cov and CLT,i represent the impact of categorical and continuous covariates and the individual total CL including the time-dependent decrease of CL (for durvalumab + tremelimumab combinations), and CLi shows the respective CL term without time-dependency (for tremelimumab monotherapy).

The parameter estimates for the final updated model are reported in Table 5. Parameters were well estimated and the typical parameter estimates CL, V1 and V2 are 0.288 L/day, 3.57 L and 2.51 L, which are close to what have been reported previously, 0.295 L/day, 3.59 L and 2.69 L respectively (D419CC00002 2021). All parameter estimates were reported with 95% confidence intervals, as a measure of estimation uncertainty, estimated using the standard error of the estimates obtained from the minimization routine. The paediatric population presents a reduction of the mean total body weight compared with mean adult population (44.3 and 71.4 kg, respectively) of -38%. Thus, as expected from the covariate effect of weight on PK parameters, the mean individual post-hoc parameters CL, V1 and V2 for paediatric population (0.193 L/day, 2.03 L and 1.70 L, respectively) were -28%, -43% and -35% lower than the mean individual post-hoc PK parameters in adults (0.269 L/day, 3.54 L and 2.60 L, respectively).

Table 5 Population PK Model Parameter Estimates

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.288	1.23	[0.281 ; 0.295]	--	L/day
$V_{central}$	3.57	1.06	[3.50 ; 3.65]	--	L
$Q_{intercompartmental}$	0.425	1.03	[0.416 ; 0.433]	--	L/day
$V_{peripheral}$	2.51	2.59	[2.38 ; 2.63]	--	L
T_{max} change CL	-0.145	14.7	[-0.187 ; -0.103]	--	L/day
TC_{50} change CL	68.0	9.16	[55.7 ; 80.2]	--	days
Covariate					
Bodyweight on Vc	0.534	5.41	[0.477 ; 0.591]	--	--
Sex on Vc	-0.117	14.0	[-0.149 ; -0.0849]	--	--
Bodyweight on CL	0.489	7.09	[0.421 ; 0.557]	--	--
Albumin on CL	-0.793	5.61	[-0.880 ; -0.706]	--	--
Sex on CL	-0.0927	19.4	[-0.128 ; -0.0574]	--	--
Comb0 on CL	0	--	--	--	--
Comb2 on CL	-0.111	16.7	[-0.147 ; -0.0747]	--	--
Primary tumor 6-7 on CL	-0.131	19.4	[-0.181 ; -0.0813]	--	--
Interindividual Variability					
ETA CL	0.110	3.60	[0.102 ; 0.118]	20.4	--
Covariance CL-Vc	0.0654	3.65	[0.0607 ; 0.0701]	--	--
ETA $V_{central}$	0.0660	1.68	[0.0639 ; 0.0682]	22.4	--
Covariance CL-Vp	0.0905	9.35	[0.0739 ; 0.107]	--	--
Covariance Vc-Vp	0.117	7.10	[0.101 ; 0.134]	--	--
ETA $V_{peripheral}$	0.224	11.4	[0.174 ; 0.274]	27.1	--
ETA T_{max}	1.35	10.5	[1.07 ; 1.63]	65.0	--
Residual Variability					
Proportional component	0.283	0.788	[0.279 ; 0.287]	18.5	--
Additive component	0.370	0.923	[0.363 ; 0.376]	18.5	µg/mL

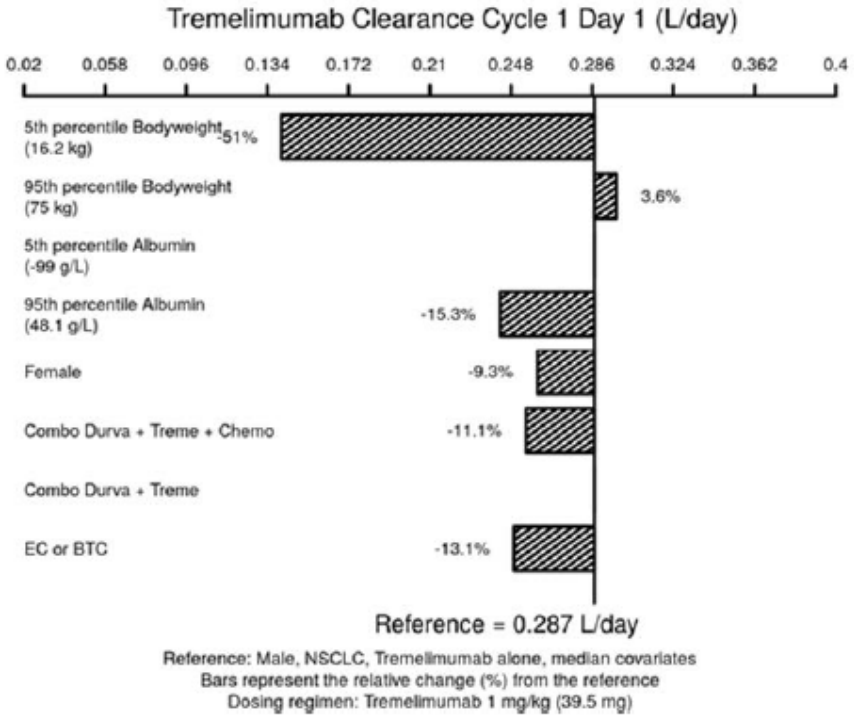
CI = confidence interval; CL = clearance; Comb2 = durvalumab, tremelimumab and chemotherapy (standard of care), as compared to treatment arms without chemotherapy; ETA = random effect; IIV = interindividual variability; PK = pharmacokinetics; Primary indication 6 = biliary tract carcinoma; Primary indication 7 = esophagus carcinoma; Q = inter-compartmental clearance; RSE = relative standard error; TC50 = time to 50% clearance reduction; Tmax = maximum change of CL over time; V1 = central volume of distribution; V2 = peripheral volume of distribution; -- = not applicable

Standard GOF plots showed good agreement between the model prediction and the tremelimumab serum concentration when pooling all data.

The impact of the selected covariates on clearance of cycle 1 (CL) and V1 based on a univariate assessment are presented as tornado plots in Figure 10 and Figure 11. The effect of each paediatric

covariate relative to adult reference was calculated one at a time, with all other covariates fixed to their typical paediatric values (as estimated for the reference paediatric patient) after administration of 1 mg/kg (that corresponds to a total dose of 39.5 mg for a paediatric subject of 39.5 kg [median of paediatric population]).

Figure 10 Impact of Paediatric Covariates on Tremelimumab Clearance at Cycle 1 - Tornado Plot

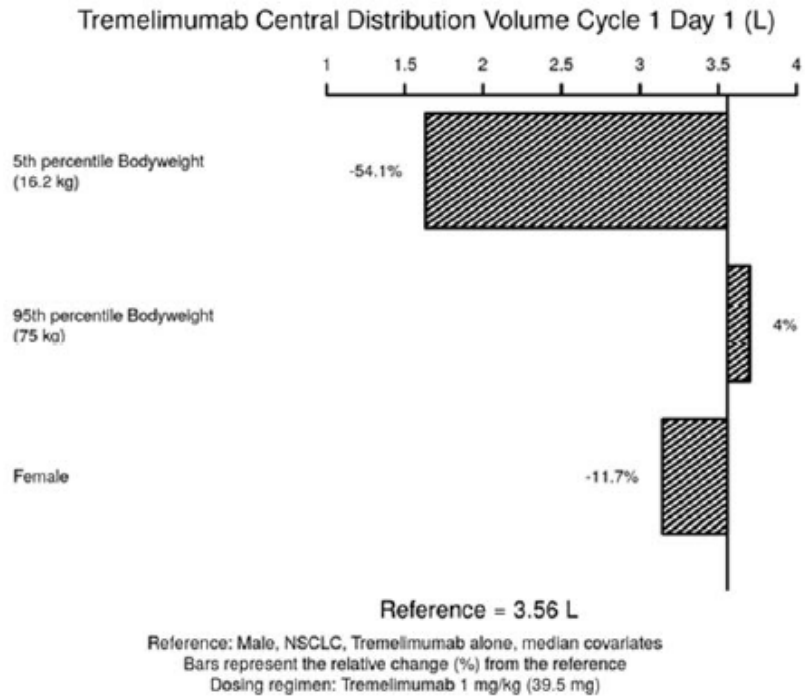


Covariate effects were expressed as a percentage change from the typical value of the reference patient

For continuous covariates, bars = the range of individual clearance values between the 5th and 95th percentiles, respectively, of the median observed covariate values

BTC = biliary tract carcinoma; Chemo = chemotherapy; Durva = durvalumab; EC = esophagus carcinoma; NSCLC = non-small cell lung cancer; Treme = tremelimumab

Figure 11 Impact of Paediatric Covariates on Tremelimumab Central Volume - Tornado Plot



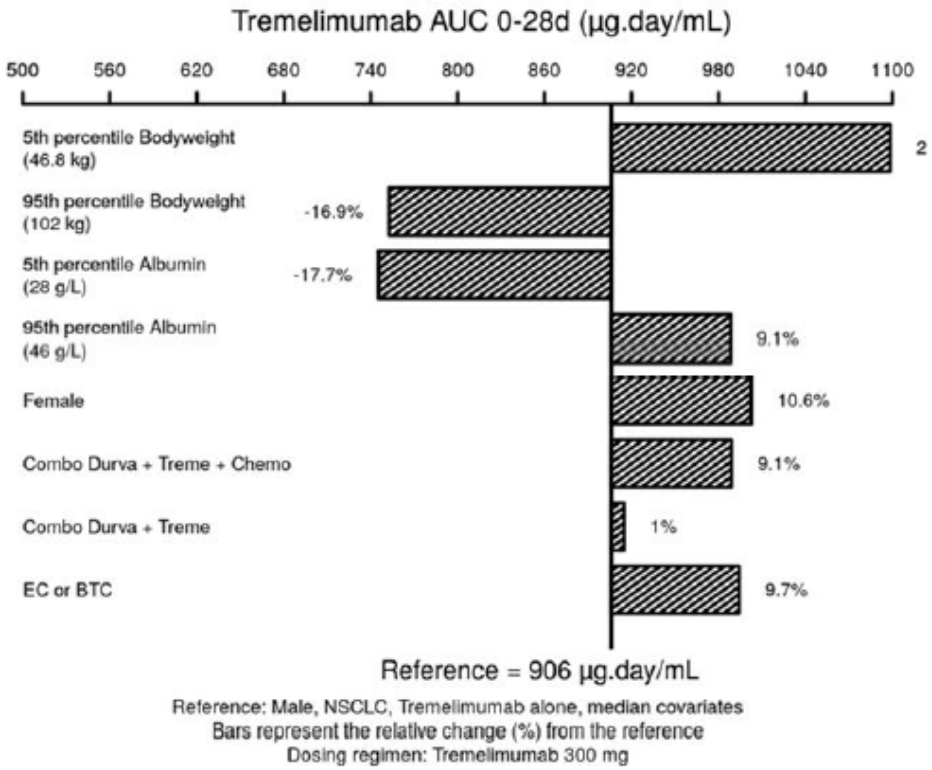
Covariate effects were expressed as a percentage change from the typical value of the reference patient

For continuous covariates, bars = the range of individual central volumes of distribution between the 5th and 95th percentiles, respectively of median observed covariate values

NSCLC = non-small cell lung cancer

Only bodyweight showed a significant impact on model parameters CL and V1, with a maximum change of -51% in CL and -54.1% on V1 for the 5th percentile of observed paediatric WT values, predicting a significant increase of +100.6% AUC0-28d (see Figure 12) in paediatric patients with lower bodyweight. The impact of all other tested covariates on CL and V1 was minimal (<30%) with a maximum change of -15.3% for the 95th percentile of observed ALB in the paediatric population.

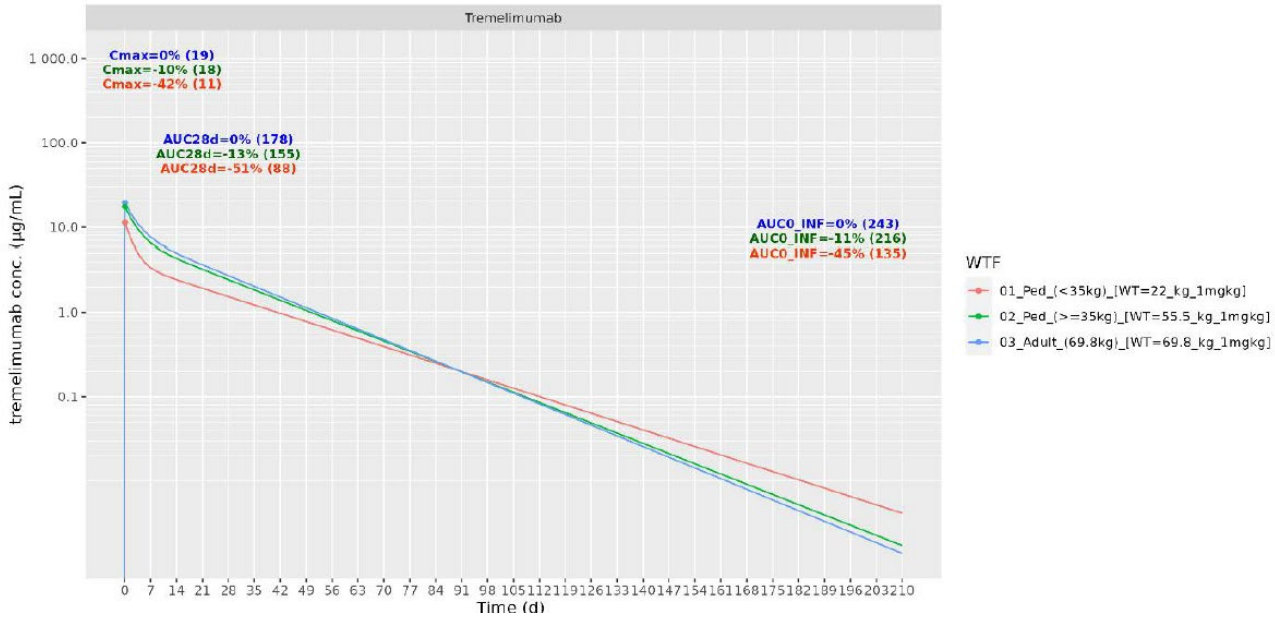
Figure 12 Impact of Adult Covariates on Tremelimumab AUC0-28d at Cycle 1 - Tornado Plot



Covariate effects were expressed as a percentage change from the typical value of the reference patient
For continuous covariates, bars = the range of individual clearance values between the 5th and 95th percentiles, respectively, of the median observed covariate values
Chemo = chemotherapy; BTC = biliary tract carcinoma; Durva = durvalumab; EC = esophagus carcinoma; NSCLC = non-small cell lung cancer; Treme = tremelimumab

In order to explore the influence of weight on paediatric population, it was decided to perform a new model simulation, where the dose was normalized by weight (D= 1 mg/kg) and subjects were grouped 3 different populations: paediatric patients with WT < 35 kg (median of 7 years and 22 kg), paediatric patients with WT ≥ 35kg (median of 15 years and 55.5 kg), and adults (median of 63 years and 69.8 kg). Each group were modelled to receive a dose normalized by weight of 1 mg/kg, that corresponds to a total dose of 22, 55.5, and 69.8 mg, respectively (Figure 13). A similar drug exposure (AUC0-INF) was predicted between paediatrics of WT ≥ 35kg and adults, observing a very slight decrease of drug exposure in paediatrics with WT ≥ 35kg (-11%). On the other hand, a greater reduction of AUC0-INF (-45%) was observed in paediatric subjects with WT < 35 kg. Considering that the minimum acceptable AUC0-28 for this paediatric population was established to be 119.5 day*µg/mL for tremelimumab, the simulated values of AUC0-28 were lower than 119.5 day*µg/mL for paediatric patients with WT < 35 kg (88 day*µg/mL) and higher for patients with WT ≥ 35 kg (155 day*µg/mL), that corresponds to a reduction of -26% and increase of +30% with respect to reference, respectively.

Figure 13 Influence of Weight (WT) on Tremelimumab PK Behaviour in Paediatric Population at a Dose of 1 mg/kg



6.2. Results

Pharmacodynamics

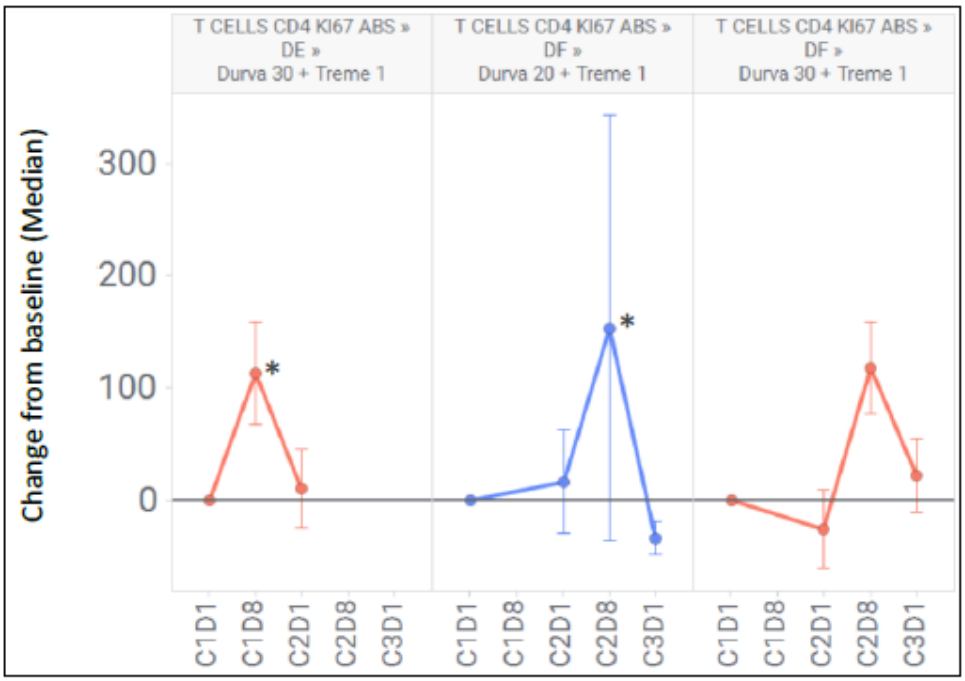
In study D419EC00001, no patient received a routine vaccination during the study; therefore, no data were available for reporting the impact of treatment on vaccine antibody titer measurements before and after planned routine immunization administered during the study.

The effects of durvalumab and tremelimumab on circulating quantities of T, B, and NK cells (TBNK) as well as effects on CD4 and CD8 T-cell activation were evaluated in patients enrolled in the initial dose-finding phase and the subsequent dose-expansion phase. Treatment in the dose-finding phase consisted of a single durvalumab cycle followed by 4 cycles of the combination regimen; regimens consisting of durvalumab 20 mg/kg and 30 mg/kg – both combined with tremelimumab 1 mg/kg, were evaluated. Results from this study are analysed and compared with flow cytometry data reported in adults from a chosen comparator study, Study D4190C00006.

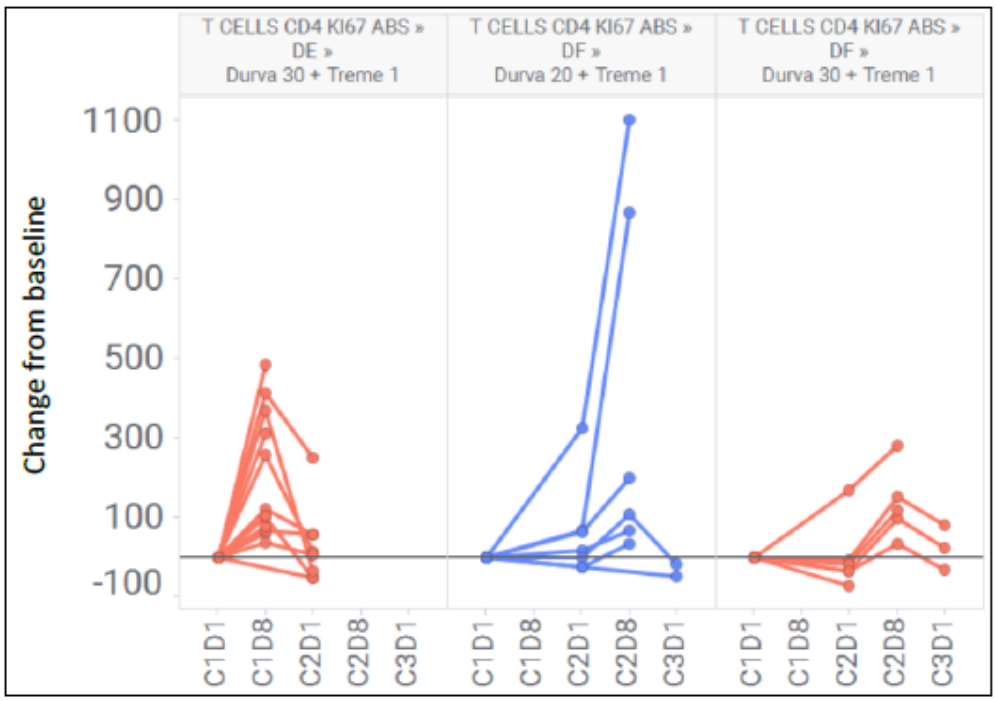
An increase in CD4+Ki67+ T-cells was observed in all evaluable patients within the dose-finding phase, specifically at day 8 following the combination of durvalumab and tremelimumab (Cycle 2 Day 8) but only demonstrated significance in the patients receiving the 20 mg/kg durvalumab and 1 mg/kg tremelimumab regimen ($p < 0.05$ by Wilcoxon method). Of significance, results in this study indicated that CD4+ Ki67+ T-cell quantities were elevated on day 8 (Cycle 1 Day 8) in 100% of patients in the dose-expansion phase receiving the durvalumab 30 mg/kg and tremelimumab 1 mg/kg regimen ($p < 0.01$) (Figure 14). These data are similar to findings from the adult NSCLC population in Study D4190C00006, specifically reported for the cohorts of patients receiving durvalumab as 10, 15, and 20 mg/kg in combination with a tremelimumab dose of 1 mg/kg. In the adult study, the magnitude of the increase in CD4+Ki67+ T-cells was correlated with the tremelimumab dose; however, only a single dose level of tremelimumab (1 mg/kg) was evaluated in this study.

Figure 14 CD4+Ki67+ T-cell absolute count (cells/mm3) percent changes from baseline over time in evaluable patients

Median change from baseline



Individual changes from baseline



Tremelimumab and durvalumab doses in mg/kg and dosing schedule (dose expansion or dose finding) indicated in the plots: Dose finding was a single cycle of durvalumab administration at the indicated dose followed by coadministration of both durvalumab and tremelimumab at the doses starting on Cycle 2 Day 1 following a q4w schedule. Dose expansion was coadministration of both durvalumab and tremelimumab starting on Cycle 1 Day 1 following a q4w schedule. Samples were collected prior to dosing on dose administration days. Black lines denote baseline value (0 for change from baseline evaluations). Median with standard error shown.

Value significantly different median RV value ($p < 0.05$) by pairwise comparison using the Wilcoxon Signed-Rank test. No "" indicates Wilcoxon Signed-Rank test $p > 0.050$.

ABS = absolute count values; C = Cycle; CD = cluster of differentiation; D = day; DE = dose expansion; DF = dose finding; Durva = durvalumab; q4w = every 4 weeks; RV = range of variability; Treme = tremelimumab.

Immunogenicity

Assessment of immunogenicity was a secondary objective for the dose-finding and dose-expansion phases of this study. Of patients who were evaluable for ADA, 2 patients had detectable ADA against durvalumab at baseline, one each in the dose-finding and dose-expansion phases, and no post-baseline ADA against durvalumab was observed. For tremelimumab, no ADA response was observed at either baseline or post baseline in patients who were evaluable for ADA. Since there was no treatment-emergent ADA against durvalumab or tremelimumab, an assessment of the potential impact of ADA on PK or safety could not be performed.

6.3. Discussion

In the population PK analyses, pooled data of durvalumab or tremelimumab concentrations versus time profiles were explored graphically stratified by study to isolate patterns and features in the pharmacokinetic behaviour of the adult vs. paediatric populations. Thereafter, an external evaluation by means of pcVPCs was used to evaluate if the pharmacokinetic behaviour of durvalumab or tremelimumab was similar between adults and paediatrics. It is agreed that the pcVPCs (stratified by study, age and weight groups) indicates that the existing durvalumab and tremelimumab population PK models are sufficient to describe PK characteristics in the paediatric population of Study D419EC00001. The full covariate model was re-evaluated based on the pooled data (paediatric + adult) and previous developed model structure (adult population PK model structure). Additionally, the paediatric/adult population effect was tested as a categorical covariate and age was tested as a continuous covariate on clearance and central volume of distribution. Age was found to be statistically significant on CL and V1 in the durvalumab model and included in the final model. The paediatric/adult effect was found to be marginally statistically significant on CL and V1 in the tremelimumab model but both models failed. Therefore, the paediatric/adult effect on CL and V1 was not included in the final tremelimumab model and the model fails to capture any tremelimumab age-related effect on CL and V1 that may have been present in Study D419EC00001. Using the univariate approach, WT was the only covariate in the durvalumab model that had a clinically meaningful impact on CL and V1, with a maximum change -46.9% on CL and -56.9% change on V1 for the 5th percentile of the paediatric WT distribution. Simulations indicated that exposure in paediatric patients ≥ 35kg were generally similar to adult exposures at durvalumab doses of 20 mg/kg every 4 weeks, but higher compared to adult systemic exposures at durvalumab doses of 30 mg/kg every 4 weeks. For the tremelimumab model, WT was also highly influential on CL and V1 when testing the impact of covariates using the univariate approach. WT exerted a maximum change of -51% and -54.1% on CL and V1, respectively, at the 5th percentile of the paediatric WT distribution. Tremelimumab model simulations, showed that systemic exposures in paediatric patients ≥ 35kg receiving tremelimumab 1 mg/kg every 4 weeks were similar to exposures in adults receiving 1 mg/kg every 4 weeks, whereas in paediatric patients < 35kg,

exposure was lower relative to adults. The additional text in section 5.2 of the SmPC is considered appropriate.

The combination of durvalumab and tremelimumab results in enhanced circulating quantities of proliferating CD4 T cells, as evident by an increase in CD4+Ki67+ T -cells, is consistent with the proposed mechanisms of action of both immune checkpoint inhibitors. This result is comparable to that observed for adult NSCLC patients also receiving this combination. However, no similar increases were seen for the CD8 Ki67+ CD8+ T-cells, which were increased in selected cohorts within Study D4190C00006 but were not observed in this study, suggesting a difference in activation patterns for this subset of immune cells. This could reflect a biologic difference between the adult and paediatric populations or could be a result of the small sample size within the current study.

6.4. Pharmacokinetics

The Applicant submitted updated clinical pharmacology data supporting the intended label updates for IMFINZI® (durvalumab) and IMJUDO® (tremelimumab). Data included PK, and immunogenicity data from study D419EC00001, an open-label, non-randomized, international, multicentre study investigating durvalumab in combination with tremelimumab (every 4 weeks for 4 cycles) followed by durvalumab monotherapy (every 4 weeks) in paediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumours. The study was conducted in 2 sequential phases: a dose-finding phase (Phase I), followed by a dose-expansion phase (Phase II).

The clinical pharmacological data are derived from one main study (D419EC00001) and 12 supportive studies, of which 10 provide supportive data for durvalumab and 8 provide supportive data for tremelimumab. These supportive studies were described in a previous submission to the agency.

Methods – analysis of data submitted

The primary objective was to identify the adult equivalent dose to be taken forward and to determine the safety profile and preliminary antitumor activity of durvalumab in combination with tremelimumab in solid malignant tumours, using disease specific response criteria. Table 6 shows D419EC00001 study population and dosing regimen.

Table 6 D419EC00001 Study Population and Dosing Regimen

Study Phase	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg (DL1)	Durvalumab 30 mg/kg + Tremelimumab 1 mg/kg (DL2)
Dose-finding (n=29)[a]	10	19
Dose-expansion (n=21)[b]		21

[a] all subjects received durvalumab monotherapy treatment at C1D1 and durvalumab and tremelimumab combination treatment starting at C2D1

[b] all subjects received durvalumab and tremelimumab combination therapy starting at C1D1

Further objectives were to assess the 1) PK and 2) immunogenicity of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumours.

Results

Analytical methods:

Durvalumab concentrations in human serum samples were analysed based on a validated quantitative electro-chemiluminescent (ECL) immunoassay using MSD technology, while tremelimumab concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA).

The bioanalytical methods used for the determination of durvalumab (MEDI4736) and tremelimumab (MEDI1123) serum concentration, the detection of ADA, and the detection of NAb against durvalumab in human serum in the D419EC00001 study are listed in Table 7 and Table 8, respectively. The corresponding bioanalytical methods used in the supportive studies have been described in HIMALAYA study (D419CC00002).

Table 7 Bioanalytical Methods Used in D419EC00001

Drug product	Measurement	Laboratory	Validation report	Method number
Durvalumab	Concentration	BioAgilytix	BAL-17-078-230-REP	BAL-17-078-230
	ADA	PPD	RAVC2	ICDIM 166
	nAb	PPD	RJRG2	ICDIM 324

ADA, anti-drug antibody; nAb, neutralizing antibody.

Table 8 Bioanalytical Methods for Tremelimumab Used in D419EC00001

Drug product	Measurement	Laboratory	Validation Report	Method Number
Tremelimumab	Concentration	PPD Intertek AstraZeneca	RPXJ2 AR4785 CTVR-0150	ICD 899 IC-P-1354 CT-051173
	ADA	PPD	EWZ2	ICDIM 153
	nAb	PPD	RCQK2	ICDIM 189

See Appendix 4.3.1 for method life cycle information.
ADA, anti-drug antibody; nAb, neutralizing antibody.

Analytical methods for determination of durvalumab:

Validation and performance parameter for method BAL-17-078-230 are summarized in Table 9.

Table 9 Summary Method Performance of a Bioanalytical Method to Measure Durvalumab in Human Serum (BioAgilytix Labs Method BAL-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 BAL-17-078-230-REP – Main Validation Report BAL-17-078-230.01-REP – Long-Term Stability Report BAL-17-078-230.02-REP – Incurred Sample Reanalysis
Method description	Meso Scale Discovery 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 (Eurofins) Lot: RP14APR18SK02 Human Serum (BioIVT) Lot: BRH1494941 (pool)
Regression model & weighting	5 parameter logistic curve with $1/Y^2$ weighting

Validation parameters	Method validation summary		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	See Table 5 of Report BAL-17-078-230-REP
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0 to 4.3%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.4%	
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%	See Table 7 of Report BAL-17-078-230-REP
	Inter-batch %CV QCs: 50 (LLOQ-QC), 100 (LQC), 400 (MQC), 2000 (HQC), and 3200 (ULOQ-QC) ng/mL	≤8.6%	
	Total Error QCs: 50 (LLOQ-QC), 100 (LQC), 400 (MQC), 2000 (HQC), and 3200 (ULOQ-QC) ng/mL	≤ 17.3%	
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%.		See Table 9 of Report BAL-17-078-230-REP
	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.		See Table 10 of Report BAL-17-078-230-REP
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		See Table 11 of Report BAL-17-078-230-REP
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.		See Table 12 of Report BAL-17-078-230-REP
Lipemic effect	Lipemic matrices recovered within 78.8% to 95.2%. The assay showed suitable recovery in lipemic samples		

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 7 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.	See Table 13 of Report BAL-17-078-230-REP See Figure 2 of Report BAL-17-078-230-REP
Bench-top/process stability	24 hours 15 minutes in human serum at room temperature	See Table 14 of Report BAL-17-078-230-REP
Freeze-Thaw stability	6 cycles frozen at -80°C ± 15°C and thawed to room temperature	See Table 15 of Report BAL-17-078-230-REP
Long-term storage	1430 days at -20°C ± 10°C 1430 days at -80°C (-65°C to -90°C)	See Table 12 of Report BAL-17-078-230.01-REP
Parallelism	Not assessed	Not applicable
Carry over	Not assessed	Not applicable
Method performance in Study D419EC00001 Bioanalytical Report: BAL-20-223-182-REP		
Assay passing rate	12 of 13 (92%), including incurred sample reanalysis	See Table 10 of Report BAL-20-223-182-REP
Standard curve performance	• Cumulative bias range: -1.8 to 5.1% • Cumulative precision: ≤ 7.8% CV	See Table 12 of Report BAL-20-223-182-REP
QC performance	• Cumulative bias range: 3.7 to 9.2% • Cumulative precision: ≤ 11.0% CV • TE: ≤ 15.5%	See Table 13 of Report BAL-20-223-182-REP

Method reproducibility	Acceptable reproducibility of the method was demonstrated through Incurred Sample Reanalysis performed across various durvalumab studies. The results can be found in Validation Report Addendum BAL-17-078-230.02-REP. Separate ISR was performed according to BioAgilytix Document Number 513919 throughout this study and will be reported within an addendum to the validation report in the future.	See Validation Report Addendum BAL-17-078-230.02-REP Will be reported separately
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 1430 days at -70°C ± 10°C.	See Table 14 of Report BAL-20-223-182-REP
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 7 Performance during accuracy and precision runs: Not applicable	

Analysis of durvalumab antidrug antibodies (ADA):

Method ICDIM 166 (validation report RAVC2) is a validated ECL immunoassay. Relevant parameters are described in Table 10.

Table 10 Summary of Anti-Durvalumab Antibody Assay Parameters in the D419EC00001 Study -PPD

Method number	ICDIM 166
Screening assay cut point [a]	1.59
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL) [d]	8.22
Assay detectable range (ng/mL)	8.22 to 100000
Assay drug tolerance	Assay can detect ≥ 82.3 ng/mL positive control in the presence of ≤ 100 µg/mL of durvalumab [e]
Inter-assay precision (%CV)	15.6 to 27.0 [b]
Intra-assay precision (%CV)	1.94 to 3.80
Confirmatory assay cut point (% inhibition) [c]	29.4
Confirmatory assay false-positive rate (%)	0.1
Validation report number	See Module 5.3.1.4 Main Validation: RAVC2 Addendum 1: RAVC4
Synopsis of amendment history	Addendum 1: Additional Stability

Cut point was established in each validation study by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

[a] The overall precision of the raw response for each positive control level (high positive control, low positive control), and re-adjusted low positive control was ≤ 23.0% and met the target criterion of ≤ 25.0%. The overall precision of the raw response for negative control was 27.0%, which was greater than the target criterion of ≤ 25.0%. High negative control response was observed in 2 runs. The runs were performed on the same day and met the final acceptance criteria of cut point factor (1.59 signal to background ratio) < low positive control signal to noise. All other runs demonstrated comparable negative control response; therefore, overall precision of the raw response for negative control was found to be acceptable.

[b] Confirmatory cut point was established for each disease state matrix by statistical analysis of the percent inhibition levels of the responses of individual naïve samples from patients with cancer tested, both with and without drug. A 0.1% false-positive rate was used for mesothelioma and other cancer indications.

[c] Represents screening assay sensitivity.

[d] Additional drug tolerance evaluation was performed at the AstraZeneca South San Francisco bioanalytical laboratory. According to the report G-IM-0143, the assay can detect ≥ 100 ng/mL positive control in the presence of ≤ 161 µg/mL of durvalumab (≤ 182 µg/mL in the screening tier).

%CV, percent coefficient of variation; LOD, limit of detection, also referred to as assay sensitivity; RLU, relative light unit; SN, signal/negative control ratio.

Analysis of anti-durvalumab neutralizing antibodies (NAb):

Method ICDIM 324 (validation report RJRG2) is a validated ECL immunoassay. Relevant parameters are summarized in Table 11.

Table 11 Summary of Anti-Durvalumab Neutralizing Antibody Assay Parameters in the D419EC00001 Study - PPD

Method number	ICDIM 324
Assay cut point [a]	1.20
Assay false-positive rate (%)	1
Assay LOD (ng/mL) [b]	220.69
Assay drug tolerance	Assay can detect ≥ 2000 ng/mL of positive control in the presence of 1000 ng/mL of durvalumab in 100% serum
Inter-assay precision (%CV) range	7.91 to 18.3 (Based on signal to noise ratio)
Intra-assay precision (%CV) range	2.3 to 10.3
Validation report number	See Module 5.3.1.4 Main Validation: RJRG2
Synopsis of amendment history	N/A

[a] Cut point was established by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

[b] Represents assay sensitivity.

%CV, percent coefficient of variation; LOD, limit of detection, also referred to as assay sensitivity; N/A, not applicable; RLU, relative light unit; SN, signal/negative control ratio.

Analytical methods for determination of tremelimumab

Validation and performance parameter for method IC-P-1354 are summarized in Table 12.

Table 12 Summary Method Performance of a Bioanalytical Method to Measure Tremelimumab in Human Serum (Intertek Pharmaceutical Services Method IC-P-1354; Report AR4785)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of the Quantitative ELISA Assay for Measurement of MEDI-1123 Concentrations in Human Serum (see 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 (see 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 (see 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: BRH673682 Selectivity in human serum from patients with solid tumors from Report AR4785 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: BRH1222126
Regression model & weighting	Data were fit using a linear adjusted variance weighted five-parameter logistic function.

Validation parameters	Method validation summary		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	6	See Table 10-2 of Report AR4785
	Cumulative accuracy (%bias) from LLOQ to ULOQ [a]	-2.4 to 0.5%	
	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%	See Table 10-5 of Report AR4785
	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%	
	Total Error QCs:156.0 (LLOQ-QC), 300.0 (LQC), 1000.0 (MQC), 4000.0 (HQC), and 5000.0 (ULOQ-QC) ng/mL	≤ 21.7%	
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.		See Section 5.1 and Table 10-9 of Report AR4785
	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.		See Table 6 of Report VR4785 Amendment 4

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.	See Table 10-11 of Report AR4785
Hemolysis effect	Not applicable	Not applicable
Lipemic effect	Not applicable	Not applicable
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 = 20000)	See Table 10-7 of Report AR4785
Bench-top/process stability	24 hours in human serum at room temperature	See Table 10-10 of Report AR4785
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	See Section 3.2 of Report CTVR-0150 See Conclusion of AR4785 Addendum 2
Parallelism	Not applicable	Not applicable
Carry over	Not applicable	Not applicable
[a] Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated from Table 10-2 of Report AR4785, using the equation: (Observed Concentration – Nominal Concentration)/Nominal Concentration*100%.		
Method performance in Study D419EC00001 Bioanalytical Method: Report 119-C1113-18-0184		
Assay passing rate	10 out of 10 (100%)	See Table 1 of Report 119-C1113-18-0184
Standard curve performance	• Cumulative bias range: -0.8 to 2.1% (from LLOQ to ULOQ) [a] • Cumulative precision: ≤ 9.4% CV (from LLOQ to ULOQ)	See Table 4 of Report 119-C1113-18-0184
QC performance	• Cumulative bias range: -3.7 to 1.7% [b] • Cumulative precision: ≤ 13.0% CV • TE: ≤ 16.7% [c]	See Table 5 of Report 119-C1113-18-0184
Method reproducibility	Incurred sample reanalysis was not performed for this study	

Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 2170 days at -70°C ± 10°C.	See Table 2 of Report 119-C1113-18-0184
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 6 Performance during accuracy and precision runs: Not applicable	

[a] Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated from Table 4 of Report 119C1113-18-0184, using the equation of (Observed Concentration – Nominal Concentration)/Nominal Concentration*100%.
[b] Cumulative accuracy (%bias) in QCs calculated from See Table 5 of Report 119-C1113-18-0184, using the equation of (Observed Concentration – Nominal Concentration)/ Nominal Concentration*100%.
[c] Total error calculated from Table 5 of Report 119-C1113-18-018, using the equation of %TE= %CV + |%RE|.

Summary of the cross-validation results for method IC-P-1354 (validation report AR4785 Addendum 3) is shown in Table 13.

Table 13 Summary of Method Modifications and Cross-Validation Results for Tremelimumab in Human Serum (Intertek Pharmaceutical Services Method IC-P-1354; Report AR4785 Addendum 3)

Bioanalytical method validation report name and hyperlink	Method Transfer: Building Transfer of the Quantitative Determination of MEDI-1123 in Human Serum Using an ELISA (Report AR4785 Addendum 3).		
Changes in method	Intertek Pharmaceutical Services moved from 3985 Sorrento Valley Blvd. Suite C, San Diego, CA 92121 to 10420 Wateridge Circle, San Diego, CA 92121 in November 2014. There were no changes to the method; additional precision and accuracy testing was performed to validate IC-P-1354, "Quantitative Determination of MEDI-1123 in Human Serum Using an ELISA," at the new location as described below.		
New validated assay range if any	No change		
Validation parameters	**Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-3.5 to 1.3%	See Table 1 of Report AR4785 Addendum 3 *
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.4%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-10.3 to 7.3%	See Table 2 of Report AR4785 Addendum 3
	Inter-batch %CV	≤ 7.0%	
	Percent TE	≤ 15.1%	
Cross-validation	Intertek Pharmaceutical Services moved from 3985 Sorrento Valley Blvd. Suite C, San Diego, CA 92121 to 10420 Wateridge Circle, San Diego, CA 92121 in November 2014. Additional precision and accuracy testing was performed to validate IC-P-1354, "Quantitative Determination of MEDI-1123 in Human Serum Using an ELISA," at the new location. A total of 4 runs across 2 days, 2 analysts, and 2 instruments were performed. Each run consisted of 2 sets of qualified QCs at the LLOQ, Low QC, Mid QC, High QC, and ULOQ. One run consisted of a total of 6 sets of QCs for intra-assay evaluation.	Not applicable	See Addendum Notes Report AR4785 Addendum 3
List other parameters	Not applicable	Not applicable	Not applicable

* Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ calculated from Table 10-2 of Report AR4785, using the equation:(Observed Concentration – Nominal Concentration)/Nominal Concentration*100%.

Summaries of validation parameter of method CT-051173 (validation report CTVR-0150) and bioanalysis report (report CTBR-0271) are shown in Table 14.

Table 14 Summary Method Performance of a Bioanalytical Method to Measure Tremelimumab in Human Serum (AstraZeneca, Gaithersburg Method CT-051173; Report CTVR-0150)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of the Quantitative ELISA Assay for Measurement of MED11123 Concentrations in Human Serum (See Report CTVR-0150).		
Method description	In this assay, MEDI1123 is captured by the recombinant CTLA4 (human CD152 murine IgG2a fusion antibody) coated on a microtiter plate. A mouse monoclonal antibody against human IgG2 that carries a biotin label is used for detection of MEDI1123 bound to the plate. Bound biotin molecules are detected by addition of streptavidin-horseradish peroxidase (SA-HRP) conjugate. Tetramethylbenzidine (TMB) enzyme substrate is added to generate a colorimetric reaction that is measured at a wavelength of 450 nm with wavelength correction set to 650 nm. The MEDI1123 concentration in a sample is determined by interpolation from a standard curve using a five-parameter curve fit with 1/Y weighting relating the color intensity to the concentration of MEDI1123.		
Materials used for calibration curve & concentration	Tremelimumab in human serum at final concentrations (in 5% human serum) of 3.05, 4.88, 7.81, 12.50, 20.00, 32.00, 51.20, 81.92, 131.07, 209.72, and 335.54 ng/mL		
Validated assay range	156.25 ng/mL to 2621.44 ng/mL in 100% human serum		
Material used for QCs & concentration	Tremelimumab in 100% human serum at concentrations of 156.25 (LLOQ-QC), 300.00 (LQC), 500.00 (MQC), 2000.00 (HQC), and 2621.44 (ULOQ-QC) ng/mL		
Minimum required dilutions (MRDs)	1:20		
Source & lot of reagents (LBA)	Tremelimumab Lot: PS01 CD152-mulg (Coat) Lot: 240101 Biotinylated Mouse Monoclonal Antibody IgG2 Lot: QK221423 Streptavidin-HRP Conjugate Lot: 1711896 Pooled Human Serum Lot: BRH1106170		
Regression model & weighting	Data were fit using a linear adjusted variance weighted five-parameter logistic function.		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	See Table 11-4 of Report CTVR-0150
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.9 to 1.4%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 3.1%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs:156.25 (LLOQ-QC), 300.00 (LQC), 500.00 (MQC), 2000.00 (HQC), and 2621.44 (ULOQ-QC) ng/mL	-8.6 to 12.3%	See Table 11-7 of Report CTVR-0150

	Inter-batch %CV QCs:156.25 (LLOQ-QC), 300.00 (LQC), 500.00 (MQC), 2000.00 (HQC), and 2621.44 (ULOQ-QC) ng/mL	≤ 6.7%	
	TE QCs:156.25 (LLOQ-QC), 300.00 (LQC), 500.00 (MQC), 2000.00 (HQC), and 2621.44 (ULOQ-QC) ng/mL	≤ 16.6%	
Selectivity & matrix effect	Selectivity in Serum from Patients with Various Types of Cancer: Selectivity in disease state matrix was evaluated using 24 serum samples from patients diagnosed with various types of cancer. The individual samples were analysed in an assay together with 3 replicate spikes of a normal human serum matrix pool. The individual samples and the 3 pool samples were tested both unspiked and spiked with 250 ng/mL MEDI1123. Each sample was tested in duplicate. The method was considered to be selective for measuring MEDI1123 in human serum from patients with solid tumors if 100% of the unspiked samples measured below the expected LLOQ (156.25 ng/mL) of the assay and if at least 80% of the spiked samples measured within 25% of the mean value of the 3 spiked samples of pooled normal human serum. One hundred percent (100%) of the unspiked serum samples and the unspiked normal human serum pool samples returned values below the LLOQ. All of the spiked serum samples measured between -6.9% and 16.8% of the mean value of the spiked pooled normal human serum samples. The results demonstrate that the method is selective for measuring MEDI1123 in human serum from patients with solid tumors.		See Section 6.6 and Table 11-11 of Report CTVR-0150
Interference & specificity	Specificity of tremelimumab measurement was tested in the presence of durvalumab and LY3022855 in prepared QCs. The assay was found to be specific to the measurement of tremelimumab.		See Table 11-12 and 11-13 of Report CTVR-0150
Hemolysis effect	Not applicable		Not applicable
Lipemic effect	Not applicable		Not applicable
Dilution linearity & hook effect	Dilution linearity tested and passed at 750 µg/mL (dilution factor = 1000), 75.0 µg/mL (dilution factor = 100), and 7.50 µg/mL (dilution factor = 10)		See Table 11-9 of Report CTVR-0150
Bench-top/process stability	24 hours in human serum at room temperature		See Table 10-10 of Report AR4785
Freeze-Thaw stability	5 cycles in human serum at -70°C		

Long-term storage	Tremelimumab is stable in human serum for 2190 days at -70°C ± 10°C Tremelimumab is stable in human serum for 121 days at -20°C ± 5°C	See Section 3.2 of Report CTVR-0150 See Conclusion of AR4785 Addendum 2
Parallelism	Not applicable	Not applicable
Carry over	Not applicable	Not applicable
Method performance in Study D419EC00001 Bioanalytical Report: Report CTBR-0271		
Assay passing rate	7 out of 7 (100%)	See Table 4 of Report CTBR-0271
Standard curve performance	• Cumulative bias range: -0.4 to 0.7% (from LLOQ to ULOQ) • Cumulative precision: ≤ 3.0% CV (from LLOQ to ULOQ)	See Table 3 of Report CTBR-0271
QC performance	• Cumulative bias range: -0.6 to 4.7% • Cumulative precision: ≤ 10.5% CV • TE: ≤ 15.2% [a]	See Table 4 of Report CTBR-0271
Method reproducibility	Incurred sample reanalysis was not performed for this study	Not Applicable
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 2170 days at -70°C ± 10°C.	See Table 6 of Report CTBR-0271
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 7 Performance during accuracy and precision runs: Not applicable	

[a] Total error calculated from Table 4 of Report CTBR-0271, using the equation of %TE= %CV + |%RE|.

Summary of the method modifications and cross-validation results for method CT-051173 (validation report CTVR-0150) is shown in Table 15.

Table 15 Summary of Method Modifications and Cross-Validation Results for the Determination of Tremelimumab Concentrations in Human Serum (AstraZeneca, Gaithersburg Method CT-051173; Report CTVR-0150)

Bioanalytical method validation report name and hyperlink	Validation of the Quantitative ELISA Assay for Measurement of MED11123 Concentrations in Human Serum (See Report CTVR-0150).		
Changes in method	There were no changes to the method.		
New validated assay range if any	No Change: 156.25 ng/mL to 2621.44 ng/mL in 100% human serum		
Validation parameters	**Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	Not applicable	Not applicable
	Cumulative precision (%CV) from LLOQ to ULOQ	Not applicable	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	Not applicable	Not applicable
	Inter-batch %CV	Not applicable	
	Percent total error	Not applicable	
Cross-validation	Evaluation of inter-laboratory accuracy was performed using samples prepared and measured by Intertek Pharmaceutical Services and analysed as unknowns by MedImmune. Intertek provided MedImmune with 30 serum samples containing MEDI1123 at various concentrations. These samples were shipped on dry ice and were stored at -80°C f 10°C until thawed prior to analysis for MEDI1123 using MedImmune using the standard operating procedure CT-051173. Results generated by MedImmune were compared to the values measured by Intertek. At least 66.7°/a of MedImmune and Intertek measured sample values were expected to agree within 30% relative difference. Out of 30 samples, 26 were evaluable for this comparison. Four samples prepared at Intertek could not tested without an additional dilution due to the narrower dynamic range of the MedImmune assay (156.25 ng/mL to 2621.44 ng/mL at MedImmune vs. 156.25 ng/mL to 5000.00 ng/mL at Intertek). Results shown in Table 11-17 demonstrate 100% agreement between the evaluable results generated by Intertek and MedImmune.	Not applicable	See Section 6.13 of Report CTVR-0150
List other parameters	Not applicable	Not applicable	Not applicable

Summaries of validation parameter of method ICD 899 (validation report RPXJ2) and bioanalysis report (report RVQT) are shown in Table 16.

Table 16 Summary Method Performance of a Bioanalytical Method to Measure Tremelimumab in Human Serum (PPD, Richmond, Method ICD 899; Report RPXJ2)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an ELISA Method for the Quantitation of MEDI1123 (Tremelimumab) in Human Serum (See Report RPXJ2).		
Method description	MEDI1123 is quantitatively measured from human serum using ELISA. In this assay, 96-well assay plates are coated with the recombinant CTLA4 capture reagent overnight, washed with PBS-T Wash Buffer and blocked with SuperBlock™ T20 (PBS) Blocking Buffer. The wash step is repeated, and standards, controls and test samples are then loaded to the plate. After incubation, unbound material is washed away, and biotinylated mouse anti-human IgG2 monoclonal antibody is added to all wells. Following further incubation and wash steps, a conjugated HRP-streptavidin detection reagent is added. A final wash step is employed, TMB peroxidase substrate is added, the color development is stopped, and the intensity of the color is measured at 450 nm with wavelength correction set to 650 nm on a colorimetric absorbance plate reader. The signal is directly proportional to the concentration of MEDI1123.		
Materials used for calibration curve & concentration	Tremelimumab in human serum at final concentrations (in 100% human serum) of 100, 156, 225, 337, 506, 759, 1139, 1708, 2563, 3844, and 5766 ng/mL		
Validated assay range	156 ng/mL to 2563 ng/mL in 100% human serum		
Material used for QCs & concentration	Tremelimumab in 100% human serum at concentrations of 156 (LLOQ-QC), 225 (Back-up LLOQ), 375 (LQC), 620 (MQC), 1900 (HQC), 2250 (Back-up ULOQ) and 2563 (ULOQ-QC) ng/mL		
Minimum required dilutions (MRDs)	1:20		
Source & lot of reagents (LBA)	Tremelimumab Lot: PS01 (AstraZeneca) CD152-mulg (Coat) Lot: 274504 (Ancell) Biotinylated Mouse Monoclonal Antibody IgG2 Lot: UL295383, VF301769 (Invitrogen) Streptavidin-HRP Conjugate Lot: 2145534, 2207541 (Thermo Fisher Scientific) Pooled Human Serum Lot: NB23428-18-01 (PPD)		
Regression model & weighting	Data were fit using a linear adjusted variance weighted five-parameter logistic function.		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	See Table 3A of Report RPXJ2
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.59 to 1.76%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.48%	

QCs performance during accuracy & precision	Cumulative accuracy (%bias) QCs:156 (LLOQ-QC), 225 (Back-up LLOQ), 375 (LQC), 620 (MQC), 1900 (HQC), 2250 (Back-up ULOQ) and 2563 (ULOQ-QC) ng/mL	-4.43 to 4.19%	See Method Validation Summary of Report RPXJ2
	Inter-batch %CV QCs:156 (LLOQ-QC), 225 (Back-up LLOQ), 375 (LQC), 620 (MQC), 1900 (HQC), 2250 (Back-up ULOQ) and 2563 (ULOQ-QC) ng/mL	≤ 7.70%	
	Total Error QCs:156 (LLOQ-QC), 225 (Back-up LLOQ), 375 (LQC), 620 (MQC), 1900 (HQC), 2250 (Back-up ULOQ) and 2563 (ULOQ-QC) ng/mL	≤ 12.1%	
Selectivity & matrix effect	Twenty out of 20 unfortified individual healthy normal donors met the acceptance criteria. Twenty out of 20 individual healthy normal donors fortified at the LLOQ level, and 20 out of 20 individual healthy normal donors fortified at the high level, met the acceptance criteria. Twenty-three out of 24 unfortified individual disease state donors met the acceptance criteria. Twenty-four out of 24 individual disease state donors fortified at the LLOQ level, and 24 out of 24 individual disease state donors fortified at the high level, met the acceptance criteria.		See Method Validation Summary of Report RPXJ2
Interference & specificity	No effect from 600 µg/mL MEDI4736 on the quantitation of MEDI1123. No effect from 100 ng/mL CTLA-4 on the quantitation of MEDI1123.		See Method Validation Summary of Report RPXJ2
Hemolysis effect	No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of MEDI1123.		See Method Validation Summary of Report RPXJ2
Lipemic effect	No effect from lipemia (> 300 mg/dL triglycerides) on the quantitation of MEDI1123.		See Method Validation Summary of Report RPXJ2
Dilution linearity & hook effect	Dilution linearity tested and passed at 980,000 ng/mL diluted Dil 500, Dil 1500, and Dil 3000.		See Method Validation Summary of Report RPXJ2
Bench-top/process stability	25 hours in human serum at room temperature		See Method Validation Summary of Report RPXJ2
Freeze-Thaw stability	5 cycles in human serum frozen at -70°C and thawed at room temperature		

Long-term storage	Tremelimumab is stable in human serum for 2190 days at -70°C ± 10°C Tremelimumab is stable in human serum for 121 days at -20°C ± 5°C	See Section 3.2 of Report CTVR-0150 See Conclusion of AR4785 Addendum 2
Parallelism	Not applicable	Not applicable
Carry over	Not applicable	Not applicable
Method performance in Study D419EC00001 Bioanalytical Report: Report RVQT		
Assay passing rate	9 out of 10 (90.0%)	See Page 9 of Report RVQT
Standard curve performance	• Cumulative bias range: -2.7 to 2.8% (from LLOQ to ULOQ) • Cumulative precision: ≤ 4.8% CV (from LLOQ to ULOQ)	See Table 6 of Report RVQT
QC performance	• Cumulative bias range: -1.1 to 4.5% • Cumulative precision: ≤ 9.1% CV • TE: ≤ 13.6%	See Table 7 of Report RVQT
Method reproducibility	100.0% of incurred sample reanalysis agreed within 30% of the original reported results for study D419EC00001	See Table 8 of Report RVQT
Study sample analysis/ stability	All standards, QCs, and study samples were analyzed within the established stability of 2170 days at -70°C ± 10°C.	See Page 6 of Report RVQT
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 8 Performance during accuracy and precision runs: Not applicable	

[a] Total error calculated from Table 7 of Report RVQT, using the equation of %TE= %CV + |%RE|.

Summary of the method modifications and cross-validation results for method ICD 899 (validation report RPXJ2)) is shown in Table 17.

Table 17 Summary of Method Modifications and Cross-Validation Results for the Determination of Tremelimumab Concentrations in Human Serum (PPD, Richmond, Method ICD 899; Report RPXJ2)

Bioanalytical method validation report name and hyperlink	Validation of an ELISA Method for the Quantitation of MEDI1123 (Tremelimumab) in Human Serum (See Report RPXJ2).		
Changes in method	There were no changes to the method.		
New validated assay range if any	No Change: 156 ng/mL to 2563 ng/mL in 100% human serum		
Validation parameters	**Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	Not applicable	Not applicable
	Cumulative precision (%CV) from LLOQ to ULOQ	Not applicable	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	Not applicable	Not applicable
	Inter-batch %CV	Not applicable	
	Percent total error	Not applicable	
Cross-validation	AstraZeneca provided PPD with 30 samples containing MEDI1123 at concentrations unknown to PPD. These samples were shipped on dry ice, stored at -80°C, thawed at room temperature prior to analysis. Results from the samples were sent to AstraZeneca, where the PPD results were compared to AstraZeneca values. 100% of the PPD- and AstraZeneca-measured sample values agreed within 30.0% relative difference. Therefore, the acceptance criteria for cross-laboratory performance were met	Not applicable	See Cross-Laboratory Performance Section of Report RPXJ2
List other parameters	Not applicable	Not applicable	Not applicable

Analysis of tremelimumab antidrug antibodies (ADA):

Summary of the validation parameter of method ICDIM 153 (validation report EWZ2) is shown in Table 18.

Table 18 Summary of Anti-Tremelimumab Antibody Assay Parameters in the D419EC00001 Study -PPD

Method number	ICDIM 153
Screening assay cut point [a]	1.24
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL) [b]	6.61
Assay detectable range (ng/mL)	6.61-100000
Assay drug tolerance	Assay can detect 125 ng/mL positive control antibody in the presence of 100 µg/mL of tremelimumab
Inter-assay precision (%CV)	≤ 23.6
Confirmatory assay cut point (% inhibition) [c] Mesothelioma Other cancer (NSCLC, lung cancer, and solid tumor)	 23.8 [c] 20.1
Confirmatory assay false-positive rate (%)	0.1
Validation report numbers	See Module 5.3.1.4 Main Validation: EWZ2 Addendum 1: EWZ5 Addendum 2: EWZ7
Synopsis of amendment history	Addendum 1: Disease state Cut Point Evaluation Addendum 2: Co-medication Interference Addendum 3: Additional Confirmatory Assay Validation and New Instrument Qualification Addendum 4: Pediatric Selectivity

[a] Cut point was established in each validation study by statistical analysis of SN ratios of RLU responses of the individual samples without drug normalized relative to the pooled serum matrix blank RLU signal.

[b] Represents screening assay sensitivity.

[c] Confirmatory cut point was established for each disease state matrix by statistical analysis of the percent inhibition levels of the responses of individual samples tested, both with and without drug. The confirmatory cut point of 20.1% was used for cancer patient samples. A 0.1% false-positive rate was used for mesothelioma and other cancer indications.

[d] CV validation criteria (25%) was met.

LOD, limit of detection; NSCLC, non-small cell lung cancer; RLU, relative light unit; SN, signal/negative control ratio; %CV, percent coefficient of variation.

Analysis of anti-tremelimumab neutralizing antibodies (NAb):

Summary of the validation parameter of method ICDIM 198 (validation report RCQK2) is shown in Table 19.

Table 19 Summary of Anti-Tremelimumab Neutralizing Antibody Assay Parameters in the D419EC00001 Study - PPD

Method number	ICDIM 189
Assay cut point [a]	Mesothelioma 0.84 Other cancers [b] 0.81
Assay false-positive rate (%)	1
Assay LOD (ng/mL) [c]	750
Assay drug tolerance	Antibody level of 1250 ng/mL was detectable in the presence of 0.250 µg/mL of tremelimumab; antibody level of 2500 ng/mL was detectable in the presence of 0.500 to 1.25 µg/mL of tremelimumab; antibody level of 5000 ng/mL was detectable in the presence of 2.5 µg/mL of tremelimumab.
Inter-assay precision (%CV) range	21.1 to 26.0
Intra-assay precision (%CV) range	1.9 to 9.1
Validation report numbers	See Module 5.3.1.4 Main Validation: RCQK2 Addendum 1: RCQK2
Synopsis of amendment history	Addendum 1: Additional Freeze/Thaw Stability

[a] Cut point was established by statistical analysis of SN ratios of RLU responses of the individual samples without drug normalized relative to the pooled serum matrix blank RLU signal.
[b] Includes NSCLC, lung cancer, and other solid tumor cancers.
[c] Represents assay sensitivity.
%CV, percent coefficient of variation; LOD, limit of detection; NSCLC, non-small cell lung cancer; RLU, relative light units; SN, signal/negative control ratio.

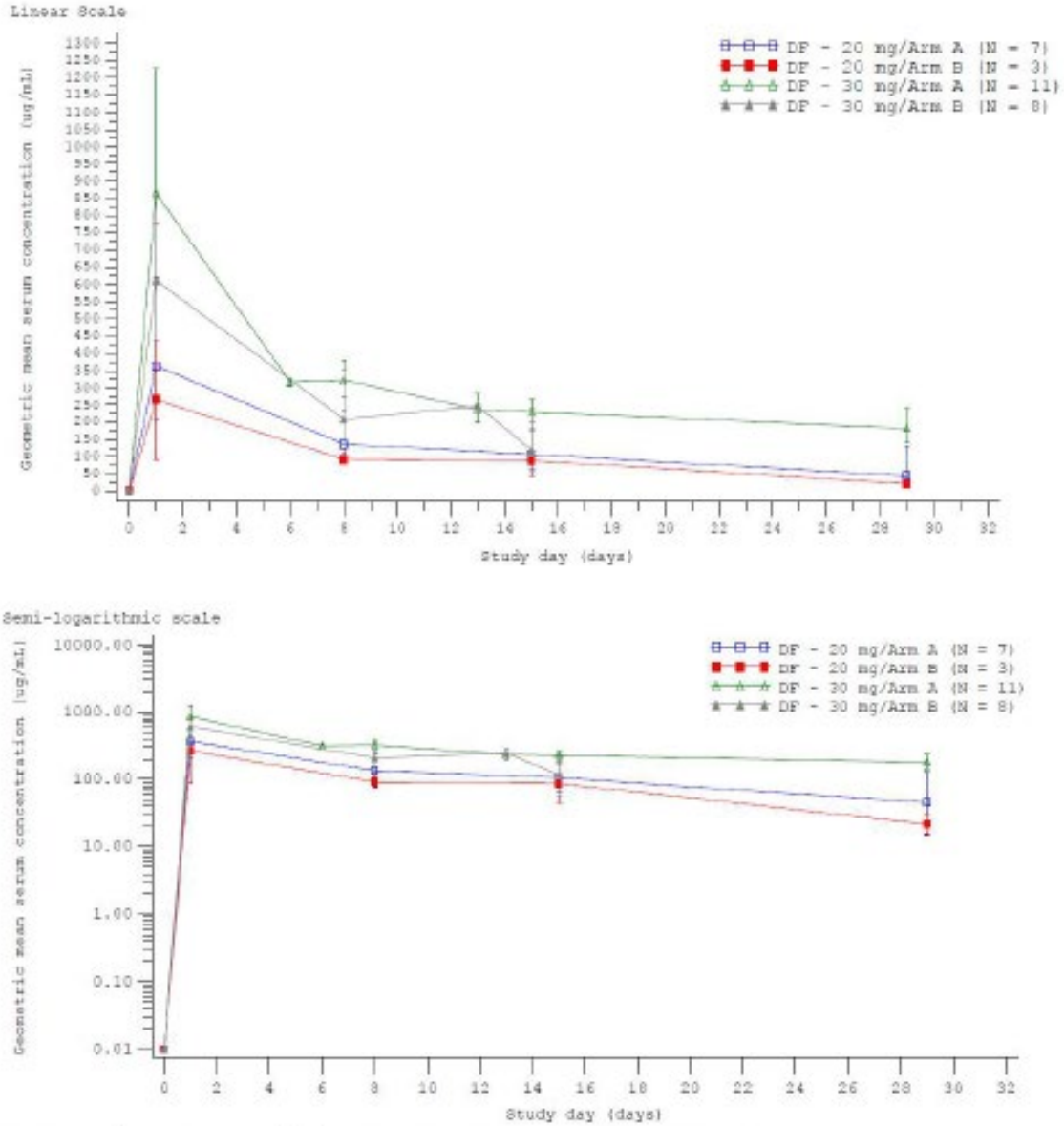
Pharmacokinetic results

Dose-finding phase:

Pharmacokinetic results were grouped by treatment and body weight (≥ 35 kg [Arm A] versus < 35 kg [Arm B]) for the dose-finding phase in the study D419EC00001. Arm A and Arm B, each contained a dosing group with durvalumab 20 mg/kg + tremelimumab 1 mg/kg (D20+T1) and durvalumab 30 mg/kg + tremelimumab 1 mg/kg (D30+T1).

Geometric mean serum durvalumab concentrations are summarized for C1 in Figure 15, with tremelimumab concentrations from C2 (the first administration) summarized in Figure 16. Pharmacokinetic results are summarized in Table 20 and Table 21 for durvalumab and tremelimumab, respectively.

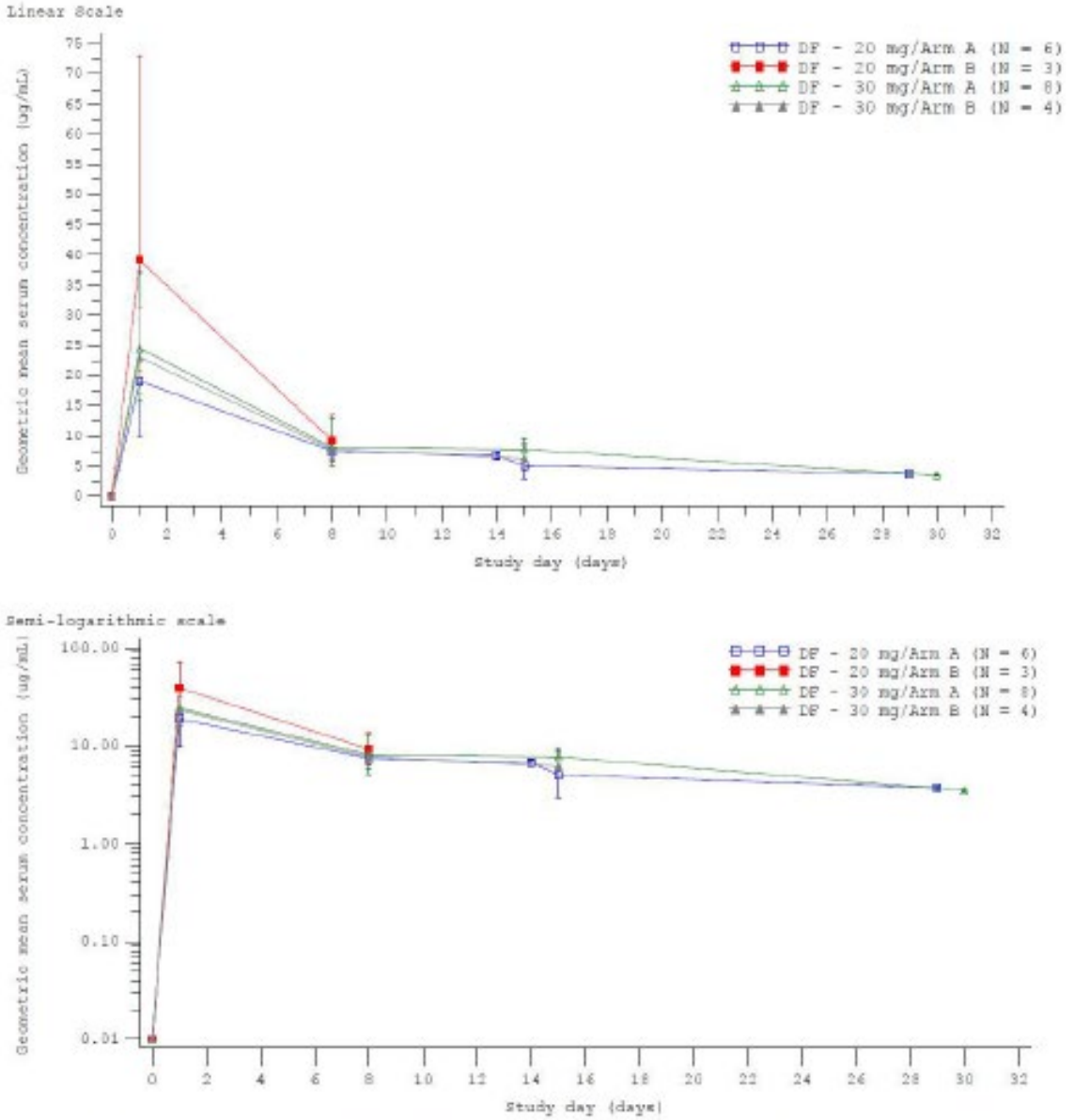
Figure 15 Geometric Mean (# gSD) Serum Concentrations (ug/mL) of Durvalumab versus Time (PK Analysis Set) - Dose-Finding



For graph display purposes, initial pre-dose values are presented above study day 0 and post-dose values are presented above study day 1, even if both pre-dose and post-dose assessments occurred on study day 1. Only first cycle of treatment is displayed.
Arm A = >= 35kg, Arm B = < 35kg, DF - 20mg = Dose-finding Durvalumab 20 mg/kg + Tremelimumab 1mg/kg.
DF - 30mg = Dose-finding Durvalumab 30mg/kg + Tremelimumab 1mg/kg.
[Source: ASTRAZENECA\MEDI4736\TYA24559\BIOSTATISTICS\PRODUCTION\FIGURES\PSC\PC300E_DF.SAS] IQVIA 08AUG2023

Note: For figure presentation, time is presented with the day of dose administration assigned a value of 1 day.
gSD = geometric standard deviation; PK = pharmacokinetic(s).

Figure 16 Geometric Mean (± gSD) Serum Concentrations (ug/mL) of Tremelimumab versus Time (PK Analysis Set) - Dose-Finding



Note: For figure presentation, time is presented with the day of dose administration assigned a value of 1 day.
gSD, geometric standard deviation; PK, pharmacokinetic(s).

Table 20 Summary of PK parameters of Durvalumab (PK Analysis Set) - Dose-Finding

PK parameter (Units)	Statistic	Arm A: ≥ 35 kg		Arm B: < 35 kg	
		Durva 20 mg/kg + Treme 1 mg/kg (N = 7)	Durva 30 mg/kg + Treme 1 mg/kg (N = 11)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)
AUC (0-14) (day*µg/mL)	Geomean (CV%)	2650 (61.5)	5660 (17.7)	1830 (54.7)	3720 (46.9)
	Min - Max	1270 - 6790	4620 - 8170	1030 - 2760	2280 - 7900
	n	7	9	3	6
AUC (0-28) (day*µg/mL)	Geomean (CV%)	3290 (50.1)	8790 (13.5)	2500 (55.4)	6380 (40.1)
	Min - Max	1650 - 6370	7220 - 11400	1420 – 3920	4600 - 10700
	n	6	8	3	4
C_{max} (µg/mL)	Geomean (CV%)	363 (58.0)	865 (36.0)	275 (135)	612 (34.2)
	Min - Max	200 - 338	491 - 1440	88.6 - 632	415 - 1050
	n	7	11	3	8
C_{min} (µg/mL)	Geomean (CV%)	48.6 (104)	169 (28.5)	21.7 (34.6)	118 (45.4)
	Min - Max	11.9 - 135	114 – 295	16.1 – 31.3	73.4 - 176
	n	6	8	3	4
t_{max} (day)	Median	0.094	0.087	0.088	0.087
	Min - Max	0.09 - 0.10	0.00 - 0.14	0.09 - 6.94	0.08 - 0.09
	n	7	11	3	8
t½λz (day)	Geomean (CV%)	16.7 (47.1)	25.3 (56.5)	8.26 (NC)	15.6 (23.3)
	Min - Max	8.03 - 25.2	18.0 - 73.0	8.26 - 8.26	13.2 - 18.3
	n	6	6	1	2
AUC (0-14)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	132 (61.5)	189 (17.7)	91.6 (54.7)	124 (46.9)
	Min - Max	63.7 - 340	154 - 272	51.6 - 138	76.0 - 263
	n	7	9	3	6
AUC (0-28)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	164 (50.1)	293 (13.5)	125 (55.4)	213 (40.1)
	Min - Max	82.5 - 318	241 - 382	71.0 - 196	153 - 358
	n	6	8	3	4
C_{max}/dose administered (µg/mL)/(mg/kg)	Geomean (CV%)	18.1 (58.0)	28.8 (36.0)	13.7 (135)	20.4 (34.2)
	Min - Max	10.0 - 45.3	16.4 - 47.9	4.43 - 31.6	13.8 - 35.1
	n	7	11	3	8

Data represent single dose of durvalumab administered at Cycle 1.
AUC(0-t) = area under the serum concentration-time curve from time zero to time 't'; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV = geometric coefficient of variance (%); Durva = durvalumab; Geomean = geometric mean; Max = maximum; Min = minimum; N = number of patients in the PK analysis set; n = number of patients included in analysis; NC = not calculable; PK = pharmacokinetic(s); t½λz = apparent terminal elimination half-life associated with the terminal slope (λz) of the semi-logarithmic concentration-time curve, estimated as (ln2)/λz; t_{max} = time to maximum serum concentration; Treme = tremelimumab.

Table 21 Summary of PK parameters of Tremelimumab (PK Analysis Set) - Dose-Finding

PK Parameter (Units)	Statistic	Arm A: ≥ 35 kg		Arm B: < 35 kg	
		Durva 20 mg/kg + Treme 1 mg/kg (N = 6)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 4)
AUC (0-14) (day*µg/mL)	Geomean (CV%)	127 (47.3)	160 (35.6)	165 (7.00)	149 (20.1)
	Min - Max	58.2 - 181	90.0 - 259	157 - 173	122 - 191
	n	5	7	2	4
AUC (0-28) (day*µg/mL)	Geomean (CV%)	235 (11.2)	205 (22.9)	NC	208 (14.8)
	Min - Max	217 - 254	150 - 246		178 - 239
	n	2	4		3
C_{max} (µg/mL)	Geomean (CV%)	19.1 (73.3)	24.5 (44.7)	39.2 (68.8)	23.0 (31.7)
	Min - Max	5.24 - 30.3	14.2 - 57.9	25.6 - 80.0	18.2 - 36.3
	n	6	8	3	4
C_{min} (µg/mL)	Geomean (CV%)	3.71 (3.75)	3.45 (29.2)	NC	3.03 (50.3)
	Min - Max	3.61 - 3.81	2.42 - 4.85		1.84 - 4.74
	n	2	4		3
t_{max} (day)	Median	0.046	0.051	0.040	0.046
	Min - Max	0.04 - 0.08	0.04 - 0.07	0.04 - 0.05	0.04 - 0.18
	n	6	8	3	4
$t_{½\lambda z}$ (day)	Geomean (CV%)	16.8 (5.27)	18.7 (20.5)	NC	31.6 (86.0)
	Min - Max	16.2 - 17.5	14.8 - 21.4		18.7 - 53.5
	n	2	3		2
AUC (0-14)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	127 (47.3)	160 (35.6)	165 (7.00)	149 (20.1)
	Min - Max	58.2 - 181	90.0 - 259	157 - 173	122 - 191
	n	5	7	2	4
AUC (0-28)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	235 (11.2)	205 (22.9)	NC	208 (14.8)
	Min - Max	217 - 254	150 - 246		178 - 239
	n	2	4		3
C_{max}/dose administered (µg/mL)/(mg/kg)	Geomean (CV%)	19.1 (73.3)	24.5 (44.7)	39.2 (68.8)	23.0 (31.7)
	Min - Max	5.24 - 30.3	14.2 - 57.9	25.6 - 80.0	18.2 - 36.3
	n	6	8	3	4

Data represent single dose of tremelimumab administered (with durvalumab) at Cycle 2.
AUC(0-t) = area under the serum concentration-time curve from time zero to time 't'; Cmax = maximum serum concentration; Cmin = minimum serum concentration; CV = geometric coefficient of variance (%); Durva = durvalumab; Geomean = geometric mean; Max = maximum; Min = minimum; N = number of patients in the PK analysis set; n = number of patients included in analysis; NC = not calculable; PK = pharmacokinetic(s); $t_{½\lambda z}$ = apparent terminal elimination half-life associated with the terminal slope (λz) of the semi-logarithmic concentration-time curve, estimated as (ln2)/λz; tmax = time to maximum serum concentration; Treme = tremelimumab.

Geometric mean durvalumab AUC0-28 was approximately 25% lower for patients < 35 kg compared to patients ≥ 35 kg at both DLs. Where comparisons could be made (noting that, AUC0-28 was not calculable for Arm B/D20+T1 cohort), geometric mean tremelimumab AUC0-28 was nearly the same between these groups.

Systemic exposure targets were established for the paediatric population that represented 50% of the adult AUC0-28 (study D4190C00006). For patients with calculable AUC0-28, 5 of 6 patients in the Arm A/D20+T1 cohort, and 2 of 3 patients in the Arm B/D20+T1 cohort achieved target durvalumab systemic exposure. All patients with calculable AUC0-28 receiving 30 mg/kg durvalumab achieved or

exceeded the target durvalumab systemic exposure. Target tremelimumab systemic exposures were achieved for all patients with reportable AUC0-28, regardless of body weight. On the basis of these results, the RP2D was determined to be 30 mg/kg durvalumab and 1 mg/kg tremelimumab.

Between the 20 mg/kg and 30 mg/kg dosages, durvalumab systemic exposure appeared to increase slightly more than proportionally, as AUC0-28 and Cmax increased by 2- to 3- fold and Cmin increased by 3- to 5- fold.

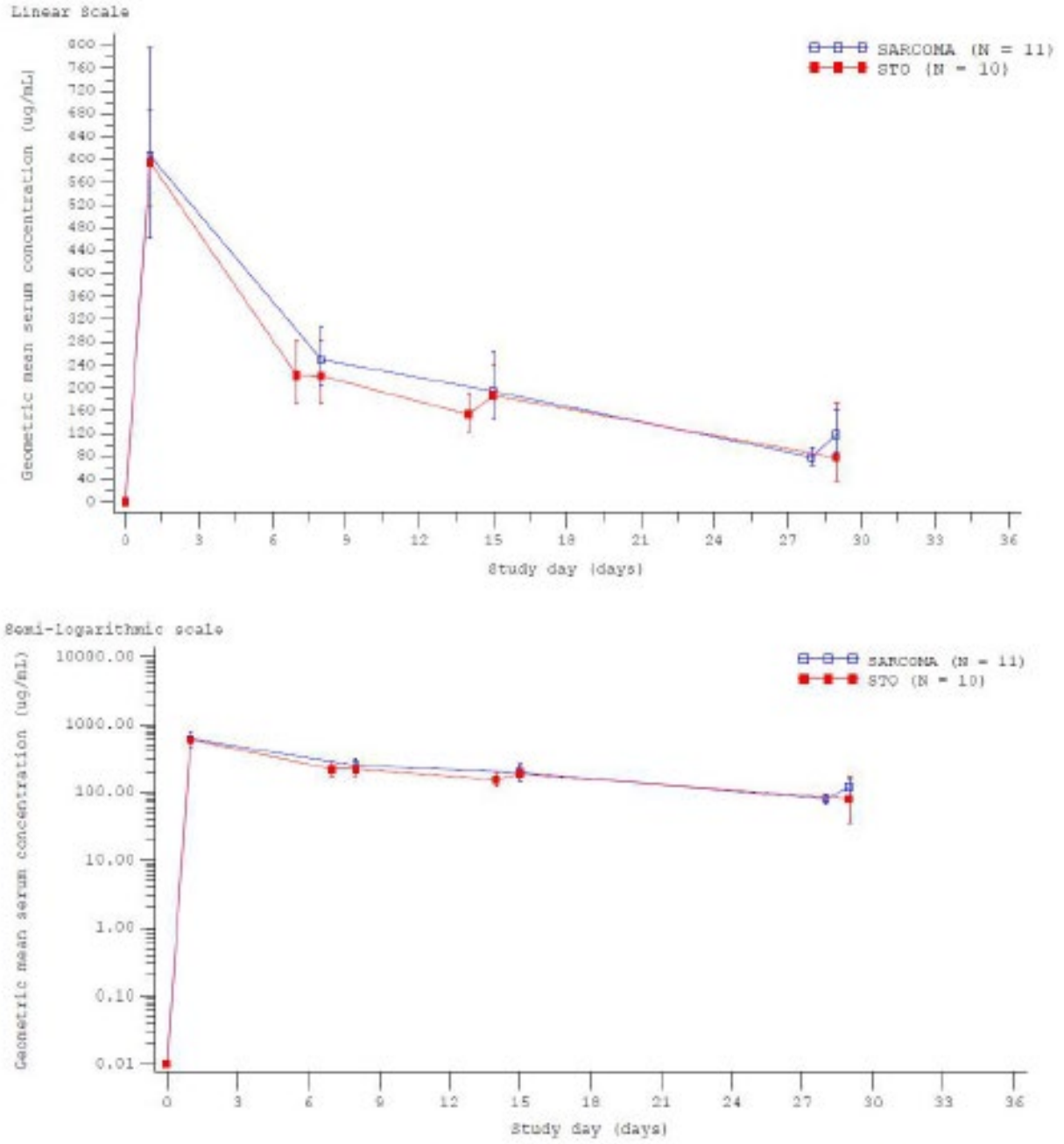
Geometric mean estimates of t½λz (terminal half-life, time required to divide the plasma concentration by two after reaching pseudo-equilibrium) ranged from 14.2 to 25.4 days for durvalumab (where n ≥ 2, geometric mean not discussed where n = 1) and from 15.6 to 31.6 days for tremelimumab; t½λz values were derived from a limited number of samples and should be interpreted cautiously. For both analytes, there was no evidence of any notable changes in PK following repeat administration; trough and end of infusion sampling demonstrated relatively stable serum concentrations, albeit from a small sampling of patients.

Systemic exposure for durvalumab at 20 mg/kg was found to not meet the criteria of adult equivalent exposure defined in the CSP for both weight groups. Systemic exposure was found to be generally similar to adult target systemic exposure with a dose of 30 mg/kg for participants < 35kg. Systemic exposure in participants receiving durvalumab at 30 mg/kg and that were ≥ 35 kg was found to be approximately 2-fold higher than the adult target systemic exposure. Tremelimumab systemic exposure was found to be generally similar to adult systemic exposure in all weight groups at 1 mg/kg.

Dose-finding phase:

Pharmacokinetic results were summarized by tumour type in the dose-expansion phase (SARCOMA [bone sarcomas: osteosarcoma, Ewing sarcoma; soft-tissue sarcomas: rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, other sarcomas] versus STO [other solid tumours]), where all patients received the same planned treatment of 30 mg/kg durvalumab and 1 mg/kg tremelimumab from the first cycle onward. Geometric mean serum durvalumab concentrations are summarized for C1 of the dose-expansion phase in Figure 17, with tremelimumab concentrations summarized in Figure 18. Pharmacokinetic results are summarized for durvalumab and tremelimumab in Table 22 and Table 23, respectively.

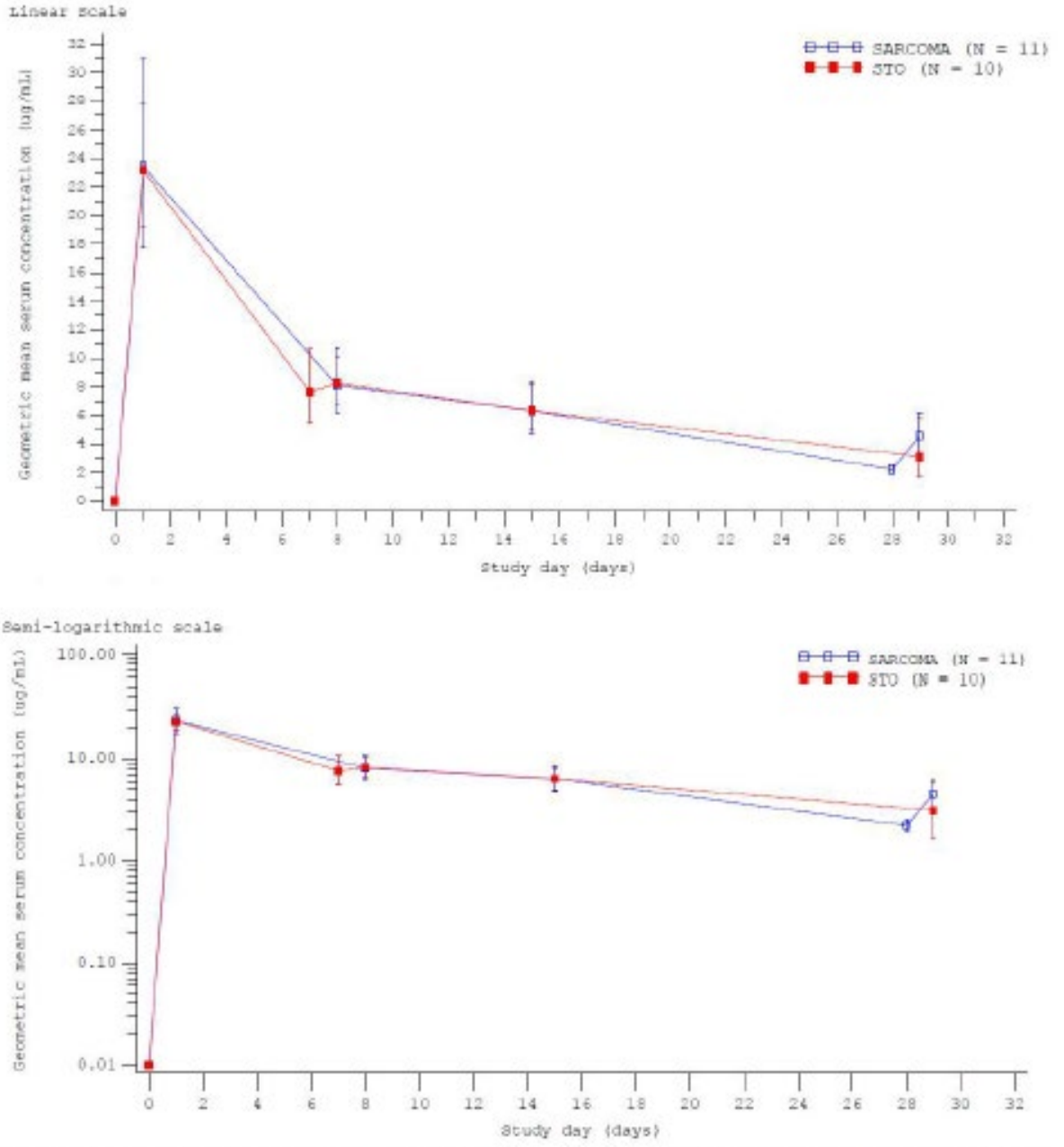
Figure 17 Geometric Mean (# gSD) Serum Concentrations (ug/mL) of Durvalumab versus Time (PK Analysis Set) - Dose-Expansion



For graph display purposes, initial pre-dose values are presented above study day 0 and post-dose values are presented above study day 1, even if both pre-dose and post-dose assessments occurred on study day 1. Only first cycle of treatment is displayed.
SARCOMA = Osteosarcoma, Ewing Sarcoma, Rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma or other sarcomas. STO = Other solid tumors.
[Source: ASTRAZENECA\MEDI4736\TYA24559\BIOSTATISTICS\PRODUCTION\FIGURES\PSC\PC300E_DE.SAS] IQVIA 09AUG2023

gSD = geometric standard deviation; PK = pharmacokinetic(s).

Figure 18 Geometric Mean (± gSD) Serum Concentrations (ug/mL) of Tremelimumab versus Time (Pk Analysis Set) - Dose-Expansion



For graph display purposes, initial pre-dose values are presented above study day 0 and post-dose values are presented above study day 1, even if both pre-dose and post-dose assessments occurred on study day 1.
Only first cycle of treatment is displayed.
SARCOMA = Osteosarcoma, Ewing Sarcoma, Rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma or other sarcomas. STO = Other solid tumors.
[Source: ASTRAZENECA\MEDI4736\TVA24558\BIOSTATISTICS\PRODUCTION\FIGURES\PSC\PC300F_DE.SAS] IQVIA 08AUG2023

gSD = geometric standard deviation; PK = pharmacokinetic(s).

Table 22 Summary of PK Parameters of Durvalumab (PK Analysis Set) - Dose-Expansion

PK Parameter (Units)	Statistic	Durva 30 mg/kg + Treme 1 mg/kg SARCOMA (N = 11)	Durva 30 mg/kg + Treme 1 mg/kg STO (N = 10)
AUC (0-14) (day*µg/mL)	Geomean (CV%)	4240 (23.2)	3900 (20.0)
	Min - Max	3250 - 6820	3030 - 5010
	n	10	9
AUC (0-28) (day*µg/mL)	Geomean (CV%)	6400 (23.7)	5880 (25.2)
	Min - Max	4560 - 10500	3870 - 7520
	n	9	5
C_{max} (µg/mL)	Geomean (CV%)	606 (27.7)	595 (14.2)
	Min - Max	403 - 1090	447 - 706
	n	11	10
C_{min} (µg/mL)	Geomean (CV%)	108 (29.6)	78.3 (94.1)
	Min - Max	69.1 - 198	19.3 - 130
	n	9	5
t_{max} (day)	Median	0.049	0.051
	Min - Max	0.04 - 0.09	0.04 - 0.08
	n	11	10
t½λz (day)	Geomean (CV%)	17.4 (26.2)	14.2 (48.6)
	Min - Max	12.5 - 25.2	6.67 - 23.0
	n	8	5
AUC (0-14)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	141 (23.2)	130 (20.0)
	Min - Max	108 - 227	101 - 167
	n	10	9
AUC (0-28)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	213 (23.7)	196 (25.2)
	Min - Max	152 - 349	129 - 251
	n	9	5
C_{max}/dose administered (µg/mL)/(mg/kg)	Geomean (CV%)	20.2 (27.7)	19.8 (14.2)
	Min - Max	13.4 - 36.3	447 - 706
	n	11	10

Data represent single dose of durvalumab administered with tremelimumab at Cycle 1.
AUC(0-t) = area under the serum concentration-time curve from time zero to time 't'; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV = geometric coefficient of variance (%); Durva = durvalumab; Geomean = geometric mean; Max = maximum; Min = minimum; N = number of patients in the PK analysis set; n = number of patients included in analysis; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors; PK = pharmacokinetic(s); t½λz = apparent terminal elimination half-life associated with the terminal slope (λz) of the semi-logarithmic concentration-time curve, estimated as (ln2)/λz; t_{max} = time to maximum serum concentration; Treme = tremelimumab.

Table 23 Summary of PK Parameters of Tremelimumab (PK Analysis Set) - Dose-Expansion

PK Parameter (Units)	Statistic	Durva 30 mg/kg + Treme 1 mg/kg SARCOMA (N = 11)	Durva 30 mg/kg + Treme 1 mg/kg STO (N = 10)
AUC (0-14) (day*µg/mL)	Geomean (CV%)	183 (65.9)	150 (11.8)
	Min - Max	112 - 892	126 - 173
	n	10	8
AUC (0-28) (day*µg/mL)	Geomean (CV%)	270 (58.1)	228 (12.4)
	Min - Max	154 - 1000	184 - 252
	n	9	6
C_{max} (µg/mL)	Geomean (CV%)	29.2 (86.0)	23.2 (18.8)
	Min - Max	16.8 - 212	19.2 - 32.6
	n	10	10
C_{min} (µg/mL)	Geomean (CV%)	3.91 (41.7)	3.40 (66.2)
	Min - Max	2.05 - 6.92	1.03 - 5.45
	n	9	6
t_{max} (day)	Median	0.049	0.052
	Min - Max	0.04 - 0.06	0.04 - 0.07
	n	10	10
$t_{½\lambda z}$ (day)	Geomean (CV%)	15.9 (26.2)	15.6 (40.4)
	Min - Max	12.6 - 24.4	7.58 - 22.1
	n	7	6
AUC (0-14)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	183 (65.9)	150 (11.8)
	Min - Max	112 - 892	126 - 173
	n	10	8
AUC (0-28)/dose administered (day*µg/mL)/(mg/kg)	Geomean (CV%)	270 (58.1)	228 (12.4)
	Min - Max	154 - 1000	184 - 252
	n	9	6
C_{max}/dose administered (µg/mL)/(mg/kg)	Geomean (CV%)	29.2 (86.0)	23.2 (18.8)
	Min - Max	16.8 - 212	19.2 - 32.6
	n	10	10

Data represent single dose of tremelimumab administered with durvalumab at Cycle 1.
AUC(0-t) = area under the serum concentration-time curve from time zero to time 't'; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV = geometric coefficient of variance (%); Durva = durvalumab; Geomean = geometric mean; Max = maximum; Min = minimum; N = number of patients in the PK analysis set; n = number of patients included in analysis; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors; PK = pharmacokinetic(s); $t_{½\lambda z}$ = apparent terminal elimination half-life associated with the terminal slope (λz) of the semi-logarithmic concentration-time curve, estimated as $(\ln 2)/\lambda z$; t_{max} = time to maximum serum concentration; Treme = tremelimumab.

Prior to C1 dosing, durvalumab concentrations were quantified at low concentrations (< 1% Cmax) for 7 patients (2 in SARCOMA cohort, 5 in STO cohort). No pre-dose concentration of durvalumab was detected for the remaining patients (9 in SARCOMA cohort, 5 in STO cohort). There was no impact on single dose PK results and no data handling was deemed necessary. Following the first dose, serum durvalumab peaked at the end of the infusion for all patients, declining thereafter through 28 days post-dose, where levels were quantifiable for all patients evaluated; geometric Cmin was 108 and 78.3 µg/mL for SARCOMA and STO cohorts, respectively. Geometric mean concentration-time profiles were very similar for SARCOMA and STO cohorts, with no notable difference in PK results. Geometric mean

values for t½λz were 17.4 and 14.2 days for the SARCOMA and STO cohorts, respectively. Interpatient variability was generally in the range of 20% to 30%, with values ranging from 14.2% to 94.1%, in terms of geometric CV% for durvalumab AUC, Cmax, and Cmin parameters. The relatively high variability for Cmin (94.1%) appeared largely attributable to a low value for a single patient (19.2 µg/mL). Overall, durvalumab PK results in the dose-expansion phase were similar to the dose-finding phase, most closely matching the Arm B/D30+T1 cohort (< 35 kg).

Target durvalumab systemic exposures (i.e., AUC0-28 $\geq$ 2105 day*μg/mL) were achieved for all patients with an evaluable AUC in the dose-expansion phase. AUC0-28 was reported for 14 patients, with all results > 2105 day*µg/mL. Of 7 patients with no reported AUC0-28, the AUC0-14 was reportable and > 2105 day*µg/mL for 5 patients and was not calculable for 2 patients. Subsequent sampling at trough and end of infusion (EOI) was available for a limited number of patients; these results suggested durvalumab systemic exposure was relatively stable following repeat administration (28 day cycle).

Tremelimumab was BLQ prior to the first dose in all patients in C1. Following dosing, serum concentrations peaked at the end of the 1 hour-infusion before declining through the last sample at 28 days post-dose, where levels were quantifiable for all patients evaluated at a geometric Cmin of 3.91 or 3.40 µg/mL for SARCOMA and STO cohorts, respectively. Overall, tremelimumab concentrations were similar between cohorts in the dose-expansion phase; mean concentration-time profiles overlaid very well, with no notable differences in PK. Tremelimumab PK was similar between the dose-finding (D30+T1) and expansion phases

Estimates of t½λz were reported for 13 patients in the dose-expansion phase, with geometric means of approximately 16 days for both cohorts. Tremelimumab variability appeared higher in the SARCOMA cohort, where geometric CV% for AUC, Cmax, or Cmin ranged from 42% to 86%, compared to the STO cohort where variability ranged from 12% to 19% except for Cmin (66%).

Target tremelimumab exposures (i.e., AUC0-28 $\geq$ 119.5 day*μg/mL) were achieved for all 15 patients with calculable AUC0-28. Of 5 patients with no reportable AUC0-28 in the dose-expansion phase, 2 patients had no calculable AUC (< 3 samples), and the remaining 3 patients had AUC0-14 ranging from 113 to 127 day*µg/mL, with 2 of 3 values achieving the target exposure.

Subsequent sampling at trough and EOI was available for a limited number of patients and these results suggested tremelimumab exposure was also relatively stable following repeat administration (28-day cycle).

Immunogenicity results

Assessment of immunogenicity was a secondary objective for the dose-finding and dose-expansion phases of the study D419EC00001. Immunogenicity results were summarized for the ADA analysis set.

Anti-drug antibody evaluable patients were patients who received at least one dose of study treatment and who had a baseline ADA result and at least one post baseline result.

Dose-finding phase: Durvalumab: In the ADA analysis set, in Arm A of the D20+T1 group, of 4 patients who were ADA evaluable, ADA against durvalumab was detected for 1 patient, but only at baseline (median [range] of maximum titer: 1.0 [1, 1]). No other ADA evaluable patient in the dose-finding phase was ADA positive to durvalumab at any time during the study, D419EC00001. Tremelimumab: There were no ADA evaluable patients for tremelimumab in the dose-finding phase in the study D419EC00001.

Dose-expansion phase: Durvalumab: In the ADA analysis set, in the STO cohort, of 5 patients who were ADA evaluable, ADA against durvalumab was detected for 1 patient, but only at baseline (median

[range] of maximum titer: 1.0 [1, 1]). No other ADA evaluable patient in the dose-expansion phase was ADA positive to durvalumab at any time during the study, D419EC00001. Tremelimumab: No ADA evaluable patient was ADA positive to tremelimumab at any time during the study D419EC00001 in the dose-expansion phase.

Of patients who were evaluable for ADA, there were 2 baseline-positive patients, and no patients had treatment-emergent ADA response against durvalumab or tremelimumab; therefore, it is not feasible to analyse the potential impact of ADA on the PK of durvalumab.

Discussion

The durvalumab + tremelimumab combination therapy doses and regimen selected for the study, D419EC00001, was based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab in paediatrics that would yield similar systemic exposures to adults, have an acceptable safety profile, and demonstrate promising efficacy.

Durvalumab has been approved as monotherapy in Stage III NSCLC at 10 mg/kg Q2W. Dose regimens with less frequent Q4W dosing periods and fixed 1500 mg dosing approaches were proposed and subsequently approved. The fixed dose of durvalumab 1500 mg Q4W (equivalent to 20 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 10 mg/kg Q2W, based on PopPK simulations. Therefore, it is expected to demonstrate a similar efficacy and safety profile as the 10 mg/kg Q2W regimen. This dose regimen has also been approved for durvalumab in ES-SCLC (1500 mg Q3W in combination with etoposide and either carboplatin or cisplatin for 4 cycles followed by 1500 mg Q4W monotherapy), advanced biliary tract cancer (1500 mg Q3W in combination with gemcitabine/cisplatin chemotherapy for up to 8 cycles followed by 1500 mg Q4W monotherapy), and metastatic NSCLC (1500 mg in combination with tremelimumab 75 mg and platinum-based chemotherapy Q3W for 4 cycles, followed by 1500 mg Q4W as monotherapy and pemetrexed maintenance therapy Q4W).

In paediatric patients < 35 kg, durvalumab systemic exposures, in combination with tremelimumab, were lower relative to adult systemic exposures at a durvalumab dose of 20 mg/kg every 4 weeks but were generally similar to adult systemic exposures at a dose of 30 mg/kg every 4 weeks. However, population PK modelling and simulation data showed that systemic exposures in paediatric patients ≥ 35 kg were generally similar to adult systemic exposures at a durvalumab dose of 20 mg/kg every 4 weeks, but higher compared to adult systemic exposures (approximately 1.5-fold) at a durvalumab dose of 30 mg/kg every 4 weeks. Furthermore, the tremelimumab exposures, in combination with durvalumab, were generally similar to adult exposures at a tremelimumab dose of 1 mg/kg every 4 weeks for paediatric patients ≥ 35 kg but were lower relative to adult systemic exposures for paediatric patients < 35 kg. No clinically meaningful drug-drug interactions between durvalumab and tremelimumab are anticipated when given as combination.

Pharmacokinetic data from the 20 mg/kg Q4W dose-finding cohort in Study D419EC00001 revealed the geometric mean systemic exposure, regardless of weight, failed to achieve the equivalent adult exposure for durvalumab. Based on modelling, a regimen consisting of 30 mg/kg Q4W of durvalumab was predicted to achieve the equivalent target exposure and was initiated for the second cohort as the dose-level 2 regimen. This durvalumab regimen was confirmed to have met the criteria for adult systemic exposure and therefore, was declared as the RP2D to be evaluated in the dose-expansion phase. Population PK modelling and simulation of paediatric patients in both the dose-finding and dose-expansion cohorts showed that durvalumab drug systemic exposure was similar in adults receiving a dose of 20 mg/kg Q4W, paediatric patients ≥ 35 kg receiving a dose of 20 mg/kg Q4W, and

paediatric patients < 35 kg receiving a dose of 30 mg/kg Q4W. Similar to what was seen in the dose-finding phase, PopPK modelling also indicated that paediatric patients ≥ 35 kg have a higher systemic exposure than adults when given a dose of 30 mg/kg Q4W, approximately 1.5-fold higher.

Similarly, tremelimumab has been approved in combination with durvalumab and platinum-based chemotherapy for the treatment of metastatic non-small cell lung cancer at a dose of 75 mg Q3W for 4 cycles and a 5th dose is given on Week 16. This fixed dose is equivalent to the weight adjusted dose of 1 mg/kg.

Pharmacokinetic data from the 1 mg/kg Q4W cohort in the dose-finding phase of Study D419EC00001 revealed that the tremelimumab systemic exposure was similar to that of adults in both weight groups (<35 kg and ≥35 kg). Therefore, this regimen was confirmed to have met the criteria for adult systemic exposure and therefore, was declared as the RP2D of tremelimumab to be evaluated in the dose-expansion phase. Population PK modelling and simulation of paediatric patients in both the dose-finding and dose-expansion cohorts showed that tremelimumab systemic exposure at a dose of 1 mg/kg was similar between adults and paediatric patients ≥ 35 kg, but lower than adults for paediatric patients < 35 kg.

When the paediatric extrapolation strategy relies on matching adult exposures, the target exposure metric(s), range, and acceptance criteria should be prospectively specified and should be defined in the context of the disease, treatment regimen, route of administration, and formulation. The target exposure metric should be based on the exposure range associated with treatment response (efficacy and/or safety) and can be derived from established exposure-response relationships or observed data in the reference population. The selected target exposure metric(s) should be associated with the treatment response, and an adequate discussion and justification should be provided based on, but not limited to, the mechanism of action and the metrics previously established in the exposure-response relationships in the reference population. When exposure matching alone is insufficient to establish efficacy, biomarkers can be used as part of the extrapolation plan.

The sample size for a paediatric PK study should be sufficient to meet the objectives of the study and be based on quantitative methods (modelling and simulation and/or statistical approaches). Adequate representation of subgroups (e.g., body weight ranges, age ranges) should be considered and justified. The sample size justification and its feasibility in the targeted indication should include the following: the availability of patients in a specific body weight/age range, the adequacy of the sample size to demonstrate precision in key PK parameters in the 631 paediatric population such as clearance and volume of distribution, the adequacy of the sample size to match the pre-specified target exposure range (e.g., the interquartile range for the PK metric(s) in the reference population), and the methodology(ies) used to determine the sample size.

According to the Applicant, the overall immunogenicity results are consistent with the known immunogenicity profile of durvalumab and tremelimumab. Due to the limited number of patients and the low incidence of anti-drug antibodies, it was not feasible to analyse the impact of anti-drug antibodies on PK, efficacy and safety of durvalumab and/or tremelimumab. Ligand-binding immunoassays were employed to determine ADA levels at screening and confirmatory thresholds, and titer. Drug tolerance levels were given related to ADA levels, i.e. high concentrations of drug did not interfere with the assay, if ADA levels were high, too. The loss of assay sensitivity at mean Ctrough concentrations due to drug interference needs to be taken into consideration when evaluating samples that are ADA-positive at baseline.

The NAb bioanalysis reports for durvalumab and tremelimumab in study D419EC00001 outline samples that were confirmed as ADA positive. No further information was provided. In contrast, the summary of clinical pharmacology states, that no treatment-emergent ADAs against durvalumab were reported

in patients who were evaluable for ADA in the study. The Applicant is asked to 1) justify the lack of Nab testing after confirmation of ADA-positives (**OC**).

As for the proposed update to the SmPC the Applicant´s summary of available information in section 4.2, according to the SmPC guideline, the paediatric population is not part of the Special populations and, therefore, it should be at the same level as Special populations (i.e., underlined and with no Italic font).

Regarding the standard statement currently included in the "Paediatric population" sub-section, the proposed update is not considered completely acceptable. The appropriate standard statement(s) should be chosen according to the reason for the lack of indication in the corresponding subsets of the paediatric population and, also, in compliance with the Paediatric Investigation Plan (PIP) or Class Waiver (as appropriate). The proposed standard statements should be chosen based on the authorised indications [please refer to the Frequently asked questions on SmPC paediatric information (EMA/551202/2010 Rev 1)].

The proposed paediatric standard statement "The safety and efficacy of IMJUDO in children and adolescents below 18 years of age have not been established. Currently available data for IMJUDO in combination with durvalumab are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made." does not reflect the reasons for the lack of paediatric indication for the already authorised indications (in adults). In this respect, we consider that the most appropriate standard statement should be the following:

"The safety and efficacy of tremelimumab in the paediatric population have not been established with regard to HCC and NSCLC. No data are available."

This is also applicable for Imfinzi in its currently approved indications.

Additionally, the paediatric standard statement in section 4.2 has been updated in this case, as a consequence of the inclusion of the final results from the paediatric study D419EC00001. Although these results do not support granting a paediatric indication, a description of this study should be included in section 5.1. Moreover, when results of study(ies) in the paediatric population in an indication not authorised in any population (i.e. neither in children nor in adults) are presented e.g. in section 5.1, the information relating to an indication not authorised in any population could be summarised in section 4.2. Consequently, the following standard statement can be considered:

"Outside its authorised indications, (Product X) has been studied in children aged x to y years with (disease y), however the results of study(ies) did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in section <4.8><5.1><5.2>."

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

Assessment of preliminary antitumor activity was a primary objective for the dose-expansion phase of this study. Efficacy results were summarized using the FAS, with some analyses also summarized using the evaluable for response analysis set. Definitions of the analysis sets are described in Table 24.

Table 24 Analysis sets

Analysis set	Definition	Phase derived for
Full analysis set (FAS)	The FAS included all patients who were assigned to treatment and received at least one dose of study treatment. The FAS (or subset of the FAS specified below) was used for all efficacy analyses.	Dose-finding and dose-expansion

Evaluable for response analysis set	The subset of patients in the FAS who had:
	• measurable disease (per RECIST 1.1) at baseline
	  ° and had at least one follow-up scan measuring all required target lesions
	  ° and had been followed for at least 3 cycles (to allow for a confirmatory scan at 4 weeks after the first assessment scan)
	OR
	• measurable disease (per RECIST 1.1) at baseline
	  ° and progressed or died in the absence of a follow-up scan.
		Dose-expansion

Safety analysis set (SAS)	The SAS consisted of all patients who received any amount of study treatment. Safety data were summarized using the SAS according to the treatment received.	Dose-finding and dose-expansion
Dose-limiting toxicity (DLT) evaluable analysis set	The DLT evaluable analysis set was a subset of the SAS for the dose-finding phase of the study. It included all patients enrolled in the dose-finding phase of the study who received the protocol-assigned treatment with durvalumab + tremelimumab and completed the safety follow-up through the DLT evaluation period (Cycle 1 + Cycle 2) or experienced a DLT during the DLT evaluation period.	Dose-finding
PK analysis set	All patients who received at least one dose of study treatment per the CSP for whom any post-dose data were available and who did not violate or deviate from the CSP in ways that would significantly affect the PK analyses were included in the PK analysis set. The population was defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.	Dose-finding and dose-expansion
ADA analysis set	All patients who received at least one dose of study treatment per the CSP for whom baseline and any post-dose data were available were included in the ADA analysis set.	Dose-finding and dose-expansion

ADA = anti-drug antibody; CSP = clinical study protocol; DLT = dose-limiting toxicity; FAS = full analysis set; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAS = safety analysis set.

Efficacy analyses were performed for patients in the dose-expansion phase only. Tumour assessment details are listed by patient for the dose-expansion phase in Appendix 16.2.6.1.1.1. No formal efficacy analysis was performed for patients in the dose-finding phase; however, based on Investigator assessment of overall RECIST responses, 2 patients in the dose-finding phase, one at each dose level, with osteosarcoma and papillary type renal carcinoma, respectively, had a PR for over one year. One of these patients, in the D30+T1 group, continued to receive treatment as part of the post-trial access program.

7.2. Results

In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set, and 4.8% (1/21 patients) in the FAS.

• No response was observed in the 11 patients initially enrolled in the SARCOMA cohort; therefore, the cohort was not expanded further as per the Simon 2-stage design.

• In the STO cohort, an ORR of 11.1% (1/9 patients) was reported in the evaluable for response analysis set, and 10.0% (1/10 patients) in the FAS, as one patient with chordoma had a confirmed response of PR. No other patient reported additional confirmed or unconfirmed responses during the study.

In the SARCOMA cohort, all 11/11 (100%) patients in the FAS had no response (Table 25).

Table 25 Best objective response (full analysis set) - dose expansion

Response status	Best objective response	Number (%) of patients		
		SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Response	Total	0	1 (10.0)	1 (4.8)
	Complete response [a]	0	0	0
	Partial response [a]	0	1 (10.0)	1 (4.8)
Non-response	Total	11 (100.0)	9 (90.0)	20 (95.2)
	Unconfirmed complete or partial response [b]	0	0	0
	Stable disease ≥ 7 weeks	1 (9.1)	1 (10.0)	2 (9.5)
	Progression	9 (81.8)	7 (70.0)	16 (76.2)
	RECIST progression	6 (54.5)	6 (60.0)	12 (57.1)
	Death	3 (27.3)	1 (10.0)	4 (19.0)
	Not evaluable	1 (9.1)	1 (10.0)	2 (9.5)
	Stable disease < 7 weeks [c]	0	0	0
	Incomplete post-baseline assessments	1 (9.1)	1 (10.0)	2 (9.5)

[a] Response required confirmation scan at least 4 weeks later.

[b] Partial response or complete response achieved but either no confirmation assessment performed, or a confirmation assessment performed but response not confirmed.

[c] Stable disease assessment observed prior to Day 49 (8 weeks ± 1 week).

Percentages were calculated from number of patients in the full analysis set in each cohort.

RECIST version 1.1.

RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

The BOR was SD ≥ 7 weeks in 1/11 (9.1%) patient, PD in 9/11 (81.8%) patients, including RECIST progression in 6/11 (54.5%) patients and death in 3/11 (27.3%) patients, and NE due to incomplete post-baseline assessments in 1/11 (9.1%) patient. In the STO cohort, 1/10 (10.0%) patient in the FAS had a response, with a BOR of PR. For patients in the FAS with no objective response, the BOR was SD ≥ 7 weeks in 1/10 (10.0%) patient, PD in 7/10 (70.0%) patients, including RECIST progression in 6/10 (60.0%) patients and death in 1/10 (10.0%) patient, and NE due to incomplete post-baseline assessments in 1/10 (10.0%) patient.

In the evaluable for response analysis set, DCR was 9.1% (1/11 patients) in the SARCOMA cohort and 11.1% (1/9 patients) in the STO cohort at both Week 16 and Week 24 (Table 26). Similar results were observed for sensitivity analyses performed on the FAS, with a DCR of 9.1% (1/11 patients) in the SARCOMA cohort and 10.0% (1/10 patients) in the STO cohort at both Week 16 and Week 24.

Table 26 Disease control rate at 16 and 24 weeks (evaluable for response analysis set) - dose expansion

Time point	Cohort	N	Disease control rate, number (%) [a]	90% CI [b]
Week 16	SARCOMA	11	1 (9.1)	0.005, 0.364
	STO	9	1 (11.1)	0.006, 0.429
	Total	20	2 (10.0)	0.018, 0.283
Week 24	SARCOMA	11	1 (9.1)	0.005, 0.364
	STO	9	1 (11.1)	0.006, 0.429
	Total	20	2 (10.0)	0.018, 0.283

[a] Includes unconfirmed complete responses or partial responses, or those with stable disease, after the start of treatment for the time point of interest (without subsequent therapy).

[b] The confidence interval was estimated using Clopper-Pearson exact method.

Disease control rate was determined from the overall visit response using all data up until the first progression event.

RECIST version 1.1.

CI = confidence interval; N = number of patients in evaluable for response analysis set within each cohort; RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

In the SARCOMA cohort, the median PFS was 1.7 months (90% CI: 1.58, 1.91) (Table 27 and Figure 19). All 11/11 (100%) patients had progression events during the study, including RECIST progression in 8/11 (72.7%) patients and death in the absence of progression in 3/11 (27.3%) patients. In total, 7/11 (63.6%) patients were on treatment at the time of progression and 4/11 (36.4%) patients had discontinued treatment prior to progression (Table 28).

In the STO cohort, the median PFS was 1.7 months (90% CI: 0.89, 2.76) (Table 27 and Figure 19). All 10/10 (100%) patients had progression events during the study, including RECIST progression in 9/10 (90.0%) patients and death in the absence of progression in 1/10 (10.0%) patient. In total, 7/10 (70.0%) patients were on treatment at the time of progression and 3/10 (30.0%) patients had discontinued treatment prior to progression (Table 28).

Table 27 Progression status at time of PFS analysis (full analysis set) - dose expansion

Progression status	Type of event	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Progression [a]	Total events, n (%)	11 (100.0)	10 (100.0)	21 (100.0)
	RECIST progression	8 (72.7)	9 (90.0)	17 (81.0)
	Target lesions [b]	6 (54.5)	7 (70.0)	13 (61.9)
	Non-target lesions [b]	6 (54.5)	3 (30.0)	9 (42.9)
	New lesions [b]	2 (18.2)	7 (70.0)	9 (42.9)
	Death in the absence of progression	3 (27.3)	1 (10.0)	4 (19.0)
No progression	Censored patients, n (%)	0	0	0
	Median progression-free survival (months) [c]	1.7	1.7	1.7
	90% CI for median progression-free survival [c]	1.58, 1.91	0.89, 2.76	1.58, 1.87
	Progression-free survival rate at 12 months (%) [c]	9.1	10.0	9.5
	90% CI for progression-free survival rate at 12 months [c]	0.99, 28.74	1.07, 31.06	2.32, 23.02
	Progression-free survival rate at 18 months (%) [c]	9.1	NR	4.8
	90% CI for progression-free survival rate at 18 months [c]	0.99, 28.74	NR, NR	0.58, 16.58

[a] Only includes progression events that occurred within 2 visits of the last evaluable assessment.

[b] Target lesions, non-target lesions, and new lesions are not necessarily mutually exclusive categories.

[c] Calculated using Kaplan-Meier technique.

Progression was determined by RECIST.

One month was calculated as 30.4375 days.

RECIST version 1.1.

CI = confidence interval; N = number of patients in full analysis set within each cohort; NR = not reached; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

Table 28 Treatment status at progression (full analysis set) - dose expansion

	Number (%) of patients		
	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Patients who had progressed			
n	11	10	21
On treatment at time of progression	7 (63.6)	7 (70.0)	14 (66.7)
Combination therapy [a]	6 (54.5)	7 (70.0)	13 (61.9)
Monotherapy [a]	1 (9.1)	0	1 (4.8)
Discontinued treatment prior to progression	4 (36.4)	3 (30.0)	7 (33.3)
Patients who had not progressed (censored)			
n	0	0	0
On-treatment prior to censoring	0	0	0
Discontinued treatment prior to censoring	0	0	0

[a] Patients treated with durvalumab + tremelimumab combination therapy for Cycles 1 to 4 and durvalumab monotherapy from Cycle 5 onwards.

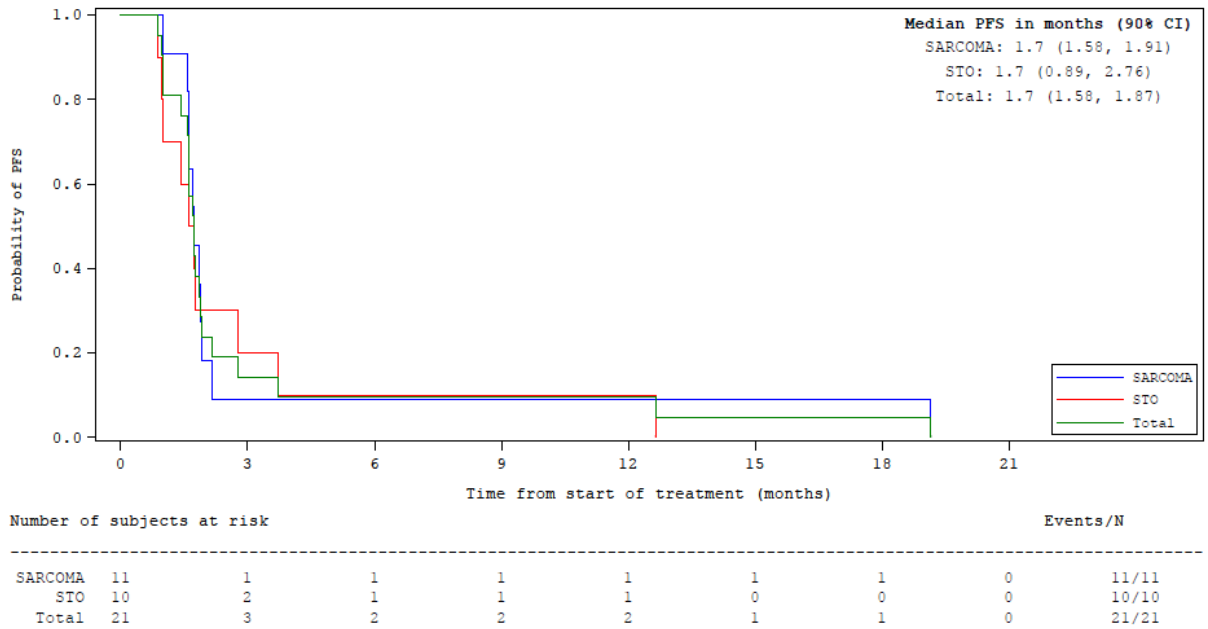
Percentages were calculated from the number of patients who had/had not progressed.

A window of 28 days was used to assess if patients were still on treatment at date of progression or date of censoring.

RECIST version 1.1.

N = number of patients in full analysis set within each cohort; n = number of patients included in analysis; RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

Figure 19 Progression-free survival, Kaplan-Meier plot (full analysis set) - dose expansion



Circle indicates a censored observation.

One month was calculated as 30.4375 days.

RECIST version 1.1.

CI = confidence interval; N = number of patients in full analysis set within each cohort; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

In the SARCOMA cohort, the median OS was 6.6 months (90% CI: 1.87, 15.77), with a survival rate of 25.6% at 12 months (Table 29 and Figure 20). In total, 8/11 (72.7%) patients died during the study, including survival follow-up beyond 90 days post the last dose of study treatment, and 3/11 (27.3%) patients were censored and terminated prior to death. Median (range) duration of follow-up in censored patients was 5.75 (1.9, 23.1) months.

In the STO cohort, the median OS was 6.9 months (90% CI: 1.61, NR), with a survival rate of 40.0% at 12 months and 30.0% at 24 months (Table 29 and Figure 20). In total, 7/10 (70.0%) patients died during the study, including survival follow-up beyond 90 days post the last dose of study treatment, and 3/10 (30.0%) patients were censored and terminated prior to death. Median (range) duration of follow-up in censored patients was 21.42 (13.4, 24.3) months.

Table 29 Overall survival (full analysis set) - dose expansion

	Number (%) of patients		
	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Death, n (%)	8 (72.7)	7 (70.0)	15 (71.4)
Censored patients, n (%)	3 (27.3)	3 (30.0)	6 (28.6)
Still in survival follow-up [a]	0	0	0
Terminated prior to death [b]	3 (27.3)	3 (30.0)	6 (28.6)
Lost to follow-up	0	0	0
Withdrawn consent	0	0	0
Other	3 (27.3)	3 (30.0)	6 (28.6)
25th percentile overall survival (months) [c]	2.2	3.2	2.3
Median overall survival (months) [c]	6.6	6.9	6.6
75th percentile overall survival (months) [c]	15.8	NR	15.8
Survival rate at 12 months (%) [c]	25.6	40.0	33.6
90% CI for survival rate at 12 months [c]	6.27, 51.10	15.94, 63.31	16.93, 51.21
Survival rate at 24 months (%) [c]	NR	30.0	21.0
90% CI for survival rate at 24 months [c]	NR, NR	9.74, 53.67	7.71, 38.67
Median (range) duration of follow-up in censored patients (months)	5.75 (1.9, 23.1)	21.42 (13.4, 24.3)	17.41 (1.9, 24.3)

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

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

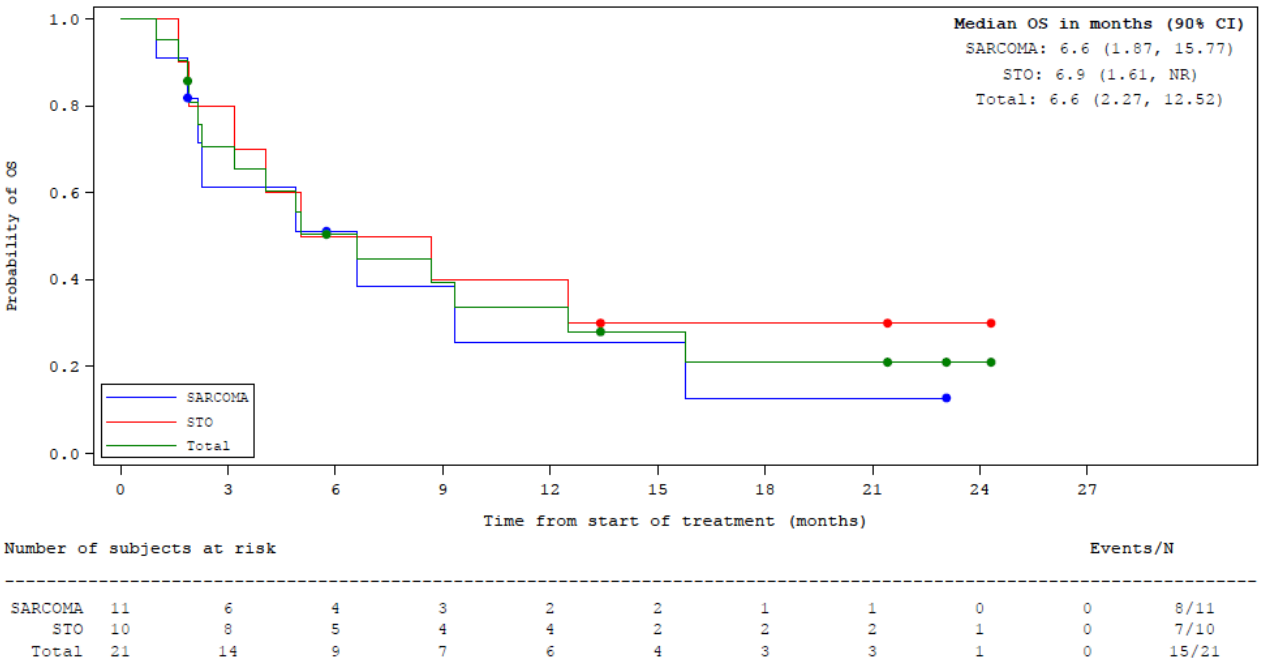
[c] Calculated using Kaplan-Meier technique.

Percentages were calculated from number of patients in the full analysis set in each cohort.

One month was calculated as 30.4375 days.

CI = confidence interval; N = number of patients in full analysis set within each cohort; NR not reached; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

Figure 20 Overall survival, Kaplan-Meier plot (full analysis set) - dose expansion



Circle indicates a censored observation.
One month was calculated as 30.4375 days.
CI = confidence interval; N = number of patients in full analysis set within each cohort; NR not reached; OS = overall survival; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

The best change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. In the dose expansion phase the median (range) best percentage change from baseline in target lesion size in the evaluable for response analysis set was 55.70% (-25.6% to 123.3%) in the SARCOMA cohort and 29.45% (-31.4% to 181.0%) in the STO cohort (Table 30 and Figure 21).

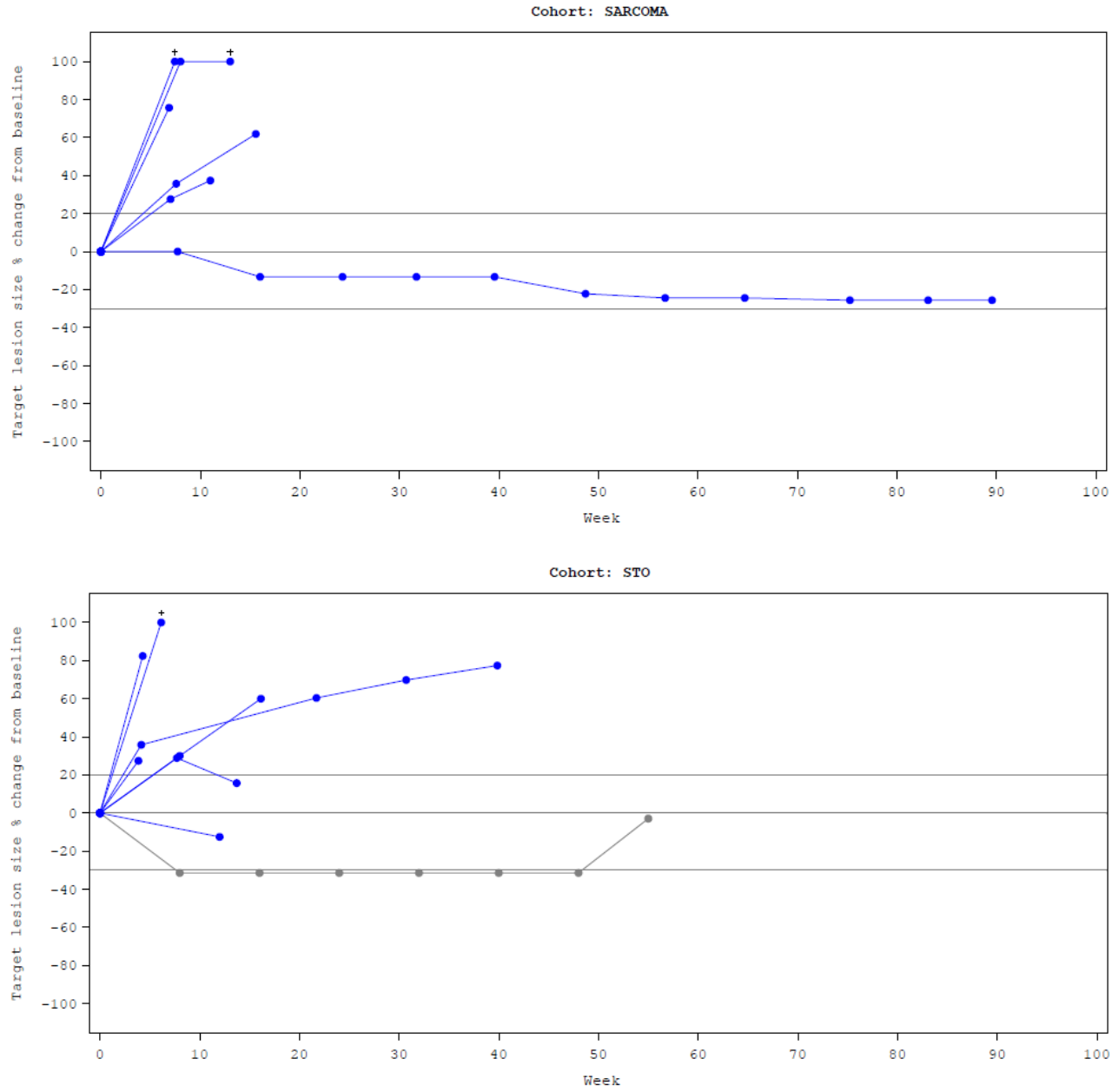
Table 30 Best percentage change from baseline in target lesion size (evaluable for response analysis set) - dose expansion

Table 31 Best percentage change from baseline in target lesion size (evaluable for response analysis set) - dose expansion

	Baseline (mm)			Best percentage change (%)		
Statistic	SARCOMA (N = 11)	STO (N = 9)	Total (N = 20)	SARCOMA (N = 11)	STO (N = 9)	Total (N = 20)
n	6	8	14	6	8	14
Mean	64.8	61.9	63.1	56.12	42.70	48.45
StD	54.09	37.92	43.61	54.278	65.328	58.980
Min	14	10	10	-25.6	-31.4	-31.4
Median	42.5	54.5	48.0	55.70	29.45	32.85
Max	163	124	163	123.3	181.0	181.0

Best change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
A negative change denotes a reduction in target lesion size.
RECIST version 1.1.
Max = maximum; Min = minimum; N = number of patients in evaluable for response analysis set within each cohort; n = number of patients with at least one post-baseline RECIST target lesion assessment scan; RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; StD = standard deviation; STO = other solid tumors.

Figure 21 Target lesion size, percentage change spider plot (evaluable for response analysis set) - dose expansion



Target lesion size is the sum of diameters of target lesions.
[+] Percentage change from baseline in tumor lesion size exceeds +100%. Spider plot truncated for the patient at this point.
Dotted reference lines at -30% and 20% indicate thresholds for partial response and potential progressive disease, respectively.
Grey lines represent patients who were responders.
RECIST version 1.1.
RECIST = Response Evaluation Criteria in Solid Tumours; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

7.3. Discussion

No formal efficacy analysis was performed for patients in the dose-finding phase; however, based on Investigator assessment of overall RECIST responses, 2 patients in the dose-finding phase, one at each dose level, with osteosarcoma and papillary type renal carcinoma, respectively, had a PR for over one year.

In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set, and 4.8% (1/21 patients) in the FAS. No response was observed in the 11 patients initially enrolled in the SARCOMA cohort in the first stage of the Simon 2-stage design, for which that cohort was stopped. In the STO cohort, an ORR of 11.1% (1/9 patients) was reported in the evaluable for response analysis set, and 10.0% (1/10 patients) in the FAS, as one patient with chordoma had a confirmed response of PR 1.8 months after the first dose of study treatment, with a DoR of 10.8 months.

In the evaluable for response analysis set, DCR was 9.1% (1/11 patients) in the SARCOMA cohort and 11.1% (1/9 patients) in the STO cohort at both Week 16 and Week 24. Similar results were observed for sensitivity analyses performed on the FAS. The median PFS in the SARCOMA and STO cohorts was 1.7 months (90% CI: 1.58, 1.91) and 1.7 months (90% CI: 0.89, 2.76), respectively, and all patients in the dose-expansion phase of the study had progression events (PD or death). In the SARCOMA cohort, the median OS was 6.6 months (90% CI: 1.87, 15.77), with a survival rate of 25.6% at 12 months. In the STO cohort, the median OS was 6.9 months (90% CI: 1.61, NR), with a survival rate of 40.0% at 12 months and 30.0% at 24 months.

Overall efficacy-wise a negative study, for which consequently no paediatric indication is sought.

Regarding the paragraph added in section 5.1, the description of the trial is outlined, but the preliminary results of efficacy in the expansion phase, already available, are omitted. In order to minimise the risk of off-label use of the combination of tremelimumab and durvalumab in the paediatric population, the MAH is requested to add a statement that summarises such efficacy results, e.g. "In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set" in section 5.1 of both products. As outlined in section 4.8, safety results should be summarised in section 5.1 as well. The preliminary efficacy and safety results on paediatric use of tremelimumab plus durvalumab preclude any potential encouragement to its off-label use. The reference to section 4.2 can be maintained: when there are data available but there is no authorised paediatric indication, data should be presented and a cross-reference should always be made to section 4.2, which summaries available information and recommendations in the paediatric population through the use of the standard statements.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

Safety analyses were performed on the SAS unless otherwise specified. Assessment of safety was a primary objective for the dose-finding phase of this study.

8.2. Results

Duration of exposure

Patients in the dose-finding phase were to receive durvalumab as monotherapy at Cycle 1 and from Cycle 6 onwards, and durvalumab + tremelimumab combination therapy from Cycle 2 through Cycle 5. Total treatment duration and actual treatment duration, i.e., total duration excluding duration of dose delays, for durvalumab administered as monotherapy or in combination with tremelimumab were comparable within each dose-level group, indicative of minimal dose delays (Table 31).

Table 31 Duration of exposure to durvalumab and tremelimumab (safety analysis set) - dose finding

Treatment duration (months)		Arm A: ≥ 35 kg		Arm B: < 35 kg		Total	
		Durva 20 mg/kg + Treme 1 mg/kg (N = 7)	Durva 30 mg/kg + Treme 1 mg/kg (N = 11)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)	Durva 20 mg/kg + Treme 1 mg/kg (N = 10)	Durva 30 mg/kg + Treme 1 mg/kg (N = 19)
Total durvalumab monotherapy treatment duration (months) [a]	n	7	11	3	8	10	19
	Mean	4.39	3.97	0.92	1.53	3.35	2.94
	StD	9.119	9.110	0.000	1.626	7.632	6.976
	Median	0.92	0.92	0.92	0.92	0.92	0.92
	Min	0.9	0.9	0.9	0.9	0.9	0.9
	Max	25.1	31.3	0.9	5.6	25.1	31.3
	Total treatment years	2.56	3.64	0.23	1.02	2.79	4.66
Actual durvalumab monotherapy treatment duration (months) [b]	n	7	11	3	8	10	19
	Mean	4.31	3.82	0.92	1.49	3.29	2.84
	StD	8.966	8.762	0.000	1.628	7.501	6.714
	Median	0.92	0.92	0.92	0.92	0.92	0.92
	Min	0.9	0.9	0.9	0.9	0.9	0.9
	Max	24.6	30.1	0.9	5.5	24.6	30.1
	Total treatment years	2.51	3.50	0.23	0.99	2.74	4.50
Total durvalumab + tremelimumab combination treatment duration (months) [c]	n	6	8	3	4	9	12
	Mean	1.69	1.86	0.92	1.90	1.43	1.87
	StD	1.223	1.234	0.000	1.293	1.040	1.194
	Median	0.92	1.38	0.92	1.51	0.92	1.38
	Min	0.9	0.9	0.9	0.9	0.9	0.9
	Max	3.7	3.8	0.9	3.6	3.7	3.8
	Total treatment years	0.84	1.24	0.23	0.63	1.07	1.87
Actual durvalumab + tremelimumab combination treatment duration (months) [b]	n	6	8	3	4	9	12
	Mean	1.69	1.71	0.92	1.82	1.43	1.75
	StD	1.223	1.005	0.000	1.270	1.040	1.042
	Median	0.92	1.38	0.92	1.38	0.92	1.38
	Min	0.9	0.9	0.9	0.9	0.9	0.9
	Max	3.7	3.6	0.9	3.6	3.7	3.6
	Total treatment years	0.84	1.14	0.23	0.61	1.07	1.75

[a] Total treatment duration = (min (date of last dose > 0 mg + 27 days, date of death, date of DCO) − first dose + 1)/(365.25/12). First and last dose refers to first or last dose of durvalumab monotherapy.

[b] Actual treatment duration = total treatment duration, excluding the duration of dose delays.

[c] Total treatment duration = (min (date of last dose > 0 mg + 27 days, date of death, date of DCO) − first dose + 1)/(365.25/12). First dose refers to first dose of tremelimumab and last dose refers to latest last dose of either durvalumab or tremelimumab.

At Cycle 1 and Cycle 6 onwards: only durvalumab monotherapy was given; from Cycle 2 to Cycle 5: combination of durvalumab + tremelimumab was given.

Planned number of dosing days were collected in the CRF.

CRF = Case Report Form; DCO = data cutoff; Durva = durvalumab; Max = maximum; Min = minimum; N = number of patients in safety analysis set within each dose level/cohort; n = number of patients included in analysis; StD = standard deviation; Treme = tremelimumab.

In the D20+T1 group, for the 10 patients who received durvalumab as monotherapy, the median (range) total treatment duration was 0.92 (0.9 to 25.1) months and actual treatment duration was 0.92 (0.9 to 24.6) months. For the 9 patients who also received durvalumab + tremelimumab combination therapy, the median (range) total treatment duration was 0.92 (0.9 to 3.7) months and

actual treatment duration was 0.92 (0.9 to 3.7) months. In the D30+T1 group, for the 19 patients who received durvalumab as monotherapy, the median (range) total treatment duration was 0.92 (0.9 to 31.3) months and actual treatment duration was 0.92 (0.9 to 30.1) months. For the 12 patients who also received durvalumab + tremelimumab combination therapy, the median (range) total treatment duration was 1.38 (0.9 to 3.8) months and actual treatment duration was 1.38 (0.9 to 3.6) months.

Patients in the dose-expansion phase were to receive durvalumab + tremelimumab combination therapy from Cycle 1 through Cycle 4, and durvalumab as monotherapy from Cycle 5 onwards. Total treatment duration and actual treatment duration, i.e., total duration excluding duration of dose delays, for durvalumab administered in combination with tremelimumab were comparable within each cohort, indicative of minimal dose delays (Table 32).

Table 32 Duration of exposure to durvalumab and tremelimumab (safety analysis set) - dose expansion

Treatment duration (months)		SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Total durvalumab + tremelimumab combination treatment duration (months) [a]	n	11	10	21
	Mean	2.25	1.82	2.04
	StD	1.041	1.065	1.050
	Median	1.84	1.72	1.84
	Min	0.9	0.9	0.9
	Max	3.8	3.7	3.8
	Total treatment years	2.06	1.51	3.58
Actual durvalumab + tremelimumab combination treatment duration (months) [b]	n	11	10	21
	Mean	2.23	1.81	2.03
	StD	1.005	1.058	1.027
	Median	1.84	1.72	1.84
	Min	0.9	0.9	0.9
	Max	3.6	3.7	3.7
	Total treatment years	2.04	1.51	3.55
Total durvalumab monotherapy treatment duration (months) [c]	n	1	1	2
	Mean	15.67	8.28	11.98
	StD	NC	NC	5.227
	Median	15.67	8.28	11.98
	Min	15.7	8.3	8.3
	Max	15.7	8.3	15.7
	Total treatment years	1.31	0.69	2.00

Treatment duration (months)		SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Actual durvalumab monotherapy treatment duration (months) [b]	n	1	1	2
	Mean	14.65	8.25	11.45
	StD	NC	NC	4.530
	Median	14.65	8.25	11.45
	Min	14.7	8.2	8.2
	Max	14.7	8.2	14.7
	Total treatment years	1.22	0.69	1.91

[a] Total treatment duration = (min (date of last dose > 0 mg + 27 days, date of death, date of DCO) − first dose + 1)/(365.25/12). First dose refers to first dose of tremelimumab and last dose refers to latest last dose of either durvalumab or tremelimumab.

[b] Actual treatment duration = total treatment duration, excluding the duration of dose delays.

[c] Total treatment duration = (min (date of last dose > 0 mg + 27 days, date of death, date of DCO) − first dose + 1)/(365.25/12). First and last dose refers to first or last dose of durvalumab monotherapy.

From Cycle 1 to Cycle 4: combination of durvalumab + tremelimumab was given; from Cycle 5 onwards: only durvalumab monotherapy was given.

Planned number of dosing days were collected in the CRF.

CRF = Case Report Form; DCO = data cutoff; Max = maximum; Min = minimum; N = number of patients in safety analysis set within each cohort; n = number of patients included in analysis; NC = not calculable; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; StD = standard deviation; STO = other solid tumors.

In the SARCOMA cohort, the median (range) durvalumab + tremelimumab total treatment duration was 1.84 (0.9 to 3.8) months and actual treatment duration was 1.84 (0.9 to 3.6) months. One patient received durvalumab as monotherapy for a total duration of 15.7 months, and an actual duration of 14.7 months. In the STO cohort, the median (range) durvalumab + tremelimumab total treatment duration was 1.72 (0.9 to 3.7) months and actual treatment duration was 1.72 (0.9 to 3.7) months. One patient received durvalumab as monotherapy for a total duration of 8.3 months, and an actual duration of 8.2 months.

Adverse events

Dose-finding phase

In the D20+T1 group, 9/10 (90.0%) patients experienced a total of 60 AEs (Table 33), including AEs considered possibly related to study treatment by the Investigator in 5/10 (50.0%) patients, Grade 3 or Grade 4 AEs in 4/10 (40.0%) patients, an SAE in 1/10 (10.0%) patient, and an AESI/AEPI considered possibly related to durvalumab by the Investigator in 1/10 (10.0%) patient.

In the D30+T1 group, 18/19 (94.7%) patients experienced a total of 198 AEs (Table 33), including AEs considered possibly related to study treatment by the Investigator in 12/19 (63.2%) patients, Grade 3 or Grade 4 AEs in 6/19 (31.6%) patients, SAEs in 2/19 (10.5%) patients, an AE leading to the discontinuation of tremelimumab in 1/19 (5.3%) patient, AEs leading to dose interruption in 2/19 (10.5%) patients, AESIs/AEPIs considered possibly related to durvalumab and tremelimumab by the Investigator in 6/19 (31.6%) patients and 3/19 (15.8%) patients, respectively, and imAEs as assessed by the Investigator and infusion reaction AEs in 2/19 (10.5%) patients each. No patient had an AE with the outcome of death.

Table 33 Adverse events in any category - patient level (safety analysis set) - dose finding

Adverse event category	Number (%) of patients [a]					
	Arm A: ≥ 35 kg		Arm B: < 35 kg		Total	
	Durva 20 mg/kg + Treme 1 mg/kg (N = 7)	Durva 30 mg/kg + Treme 1 mg/kg (N = 11)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)	Durva 20 mg/kg + Treme 1 mg/kg (N = 10)	Durva 30 mg/kg + Treme 1 mg/kg (N = 19)
Any AE	6 (85.7)	11 (100.0)	3 (100.0)	7 (87.5)	9 (90.0)	18 (94.7)
Any AE possibly related to treatment [b]	5 (71.4)	7 (63.6)	0	5 (62.5)	5 (50.0)	12 (63.2)
Any AE possibly related to durvalumab only [b]	4 (57.1)	6 (54.5)	0	4 (50.0)	4 (40.0)	10 (52.6)
Any AE possibly related to tremelimumab only [b]	0	0	0	0	0	0
Any AE possibly related to durvalumab and tremelimumab [b]	3 (42.9)	4 (36.4)	0	4 (50.0)	3 (30.0)	8 (42.1)
Any AE of CTCAE Grade 3 or 4	2 (28.6)	4 (36.4)	2 (66.7)	2 (25.0)	4 (40.0)	6 (31.6)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [b]	0	2 (18.2)	0	1 (12.5)	0	3 (15.8)
Any AE of CTCAE Grade 3 or 4, possibly related to durvalumab only [b]	0	0	0	0	0	0
Any AE of CTCAE Grade 3 or 4, possibly related to tremelimumab only [b]	0	0	0	0	0	0
Any AE of CTCAE Grade 3 or 4, possibly related to durvalumab and tremelimumab [b]	0	2 (18.2)	0	1 (12.5)	0	3 (15.8)
Any AE with outcome = death	0	0	0	0	0	0
Any SAE (including events with outcome = death)	1 (14.3)	1 (9.1)	0	1 (12.5)	1 (10.0)	2 (10.5)
Any SAE (including events with outcome = death), possibly related to treatment [b]	0	1 (9.1)	0	1 (12.5)	0	2 (10.5)
Any SAE (including events with outcome = death), possibly related to durvalumab only [b]	0	0	0	0	0	0
Any SAE (including events with outcome = death), possibly related to tremelimumab only [b]	0	0	0	0	0	0
Any SAE (including events with outcome = death), possibly related to durvalumab and tremelimumab [b]	0	1 (9.1)	0	1 (12.5)	0	2 (10.5)
Any AE leading to discontinuation of durvalumab	0	0	0	0	0	0
Any AE leading to discontinuation of tremelimumab	0	1 (9.1)	0	0	0	1 (5.3)
Any SAE leading to discontinuation of tremelimumab	0	0	0	0	0	0
Any AE leading to dose interruption [c]	0	2 (18.2)	0	0	0	2 (10.5)
Any AESIs or AEPIs related to durvalumab	1 (14.3)	4 (36.4)	0	2 (25.0)	1 (10.0)	6 (31.6)
Any AESIs or AEPIs related to tremelimumab	0	2 (18.2)	0	1 (12.5)	0	3 (15.8)
Immune-mediated AEs [b]	0	2 (18.2)	0	0	0	2 (10.5)
Infusion reaction AEs [b]	0	1 (9.1)	0	1 (12.5)	0	2 (10.5)

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

[b] As assessed by the Investigator.

[c] Adverse events on the AE CRF form with Action taken = Drug interrupted.

Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).

Percentages were calculated from number of patients in the safety analysis set in each dose level/cohort.

AESI/AEPI version 17.1.

CTCAE version 5.0.

AE = adverse event; AEPI = adverse event of possible interest; AESI = adverse event of special interest; CRF = Case Report Form; CTCAE = Common Terminology Criteria for Adverse Events; Durva = durvalumab; N = number of patients in safety analysis set within each dose level/cohort; SAE = serious adverse event; Treme = tremelimumab.

Dose-expansion-phase

In the SARCOMA cohort, 10/11 (90.9%) patients experienced a total of 91 AEs (Table 34), including AEs considered possibly related to study treatment by the Investigator in 7/11 (63.6%) patients, Grade 3 or Grade 4 AEs in 5/11 (45.5%) patients, SAEs in 6/11 (54.5%) patients, AESIs/AEPIs

considered possibly related to durvalumab and tremelimumab by the Investigator in 3/11 (27.3%) patients each, imAEs as assessed by the Investigator in 2/11 (18.2%) patients, and infusion reaction AEs in 1/11 (9.1%) patient.

In the STO cohort, 9/10 (90.0%) patients experienced a total of 87 AEs (Table 34), including AEs considered possibly related to study treatment by the Investigator in 9/10 (90.0%) patients, Grade 3 or Grade 4 AEs in 5/10 (50.0%) patients, SAEs in 3/10 (30.0%) patients, AEs leading to the discontinuation of durvalumab in 2/10 (20.0%) patients, an AE leading to the discontinuation of tremelimumab in 1/10 (10.0%) patient, an AE leading to dose interruption in 1/10 (10.0%) patient, AESIs/AEPIs considered possibly related to durvalumab and tremelimumab by the Investigator in 5/10 (50.0%) patients and 3/10 (30.0%) patients, respectively, and imAEs as assessed by the Investigator in 2/10 (20.0%) patients. No patient had an AE with the outcome of death.

Table 34 Adverse events in any category - patient level (safety analysis set) - dose expansion

Adverse event category	Number (%) of patients [a]		
	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Any AE	10 (90.9)	9 (90.0)	19 (90.5)
Any AE possibly related to treatment [b]	7 (63.6)	9 (90.0)	16 (76.2)
Any AE possibly related to durvalumab only [b]	3 (27.3)	2 (20.0)	5 (23.8)
Any AE possibly related to tremelimumab only [b]	0	0	0
Any AE possibly related to durvalumab and tremelimumab [b]	6 (54.5)	8 (80.0)	14 (66.7)
Any AE of CTCAE Grade 3 or 4	5 (45.5)	5 (50.0)	10 (47.6)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [b]	2 (18.2)	2 (20.0)	4 (19.0)
Any AE of CTCAE Grade 3 or 4, possibly related to durvalumab only [b]	0	1 (10.0)	1 (4.8)
Any AE of CTCAE Grade 3 or 4, possibly related to tremelimumab only [b]	0	0	0
Any AE of CTCAE Grade 3 or 4, possibly related to durvalumab and tremelimumab [b]	2 (18.2)	1 (10.0)	3 (14.3)
Any AE with outcome = death	0	0	0
Any SAE (including events with outcome = death)	6 (54.5)	3 (30.0)	9 (42.9)
Any SAE (including events with outcome = death), possibly related to treatment [b]	3 (27.3)	1 (10.0)	4 (19.0)
Any SAE (including events with outcome = death), possibly related to durvalumab only [b]	1 (9.1)	1 (10.0)	2 (9.5)
Any SAE (including events with outcome = death), possibly related to tremelimumab only [b]	0	0	0
Any SAE (including events with outcome = death), possibly related to durvalumab and tremelimumab [b]	2 (18.2)	0	2 (9.5)
Any AE leading to discontinuation of durvalumab	0	2 (20.0)	2 (9.5)
Any SAE leading to discontinuation of durvalumab	0	2 (20.0)	2 (9.5)
Any SAE leading to discontinuation of durvalumab, possibly related to treatment [b]	0	1 (10.0)	1 (4.8)
Any AE leading to discontinuation of tremelimumab	0	1 (10.0)	1 (4.8)
Any SAE leading to discontinuation of tremelimumab	0	1 (10.0)	1 (4.8)
Any AE leading to dose interruption [c]	0	1 (10.0)	1 (4.8)
Any AESIs or AEPIs related to durvalumab	3 (27.3)	5 (50.0)	8 (38.1)
Any AESIs or AEPIs related to tremelimumab	3 (27.3)	3 (30.0)	6 (28.6)
Immune-mediated AEs [b]	2 (18.2)	2 (20.0)	4 (19.0)
Infusion reaction AEs [b]	1 (9.1)	0	1 (4.8)

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

[b] As assessed by the Investigator.

[c] Adverse events on the AE CRF form with Action taken = Drug interrupted.

Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).

Percentages were calculated from number of patients in the safety analysis set in each cohort.

AESI/AEPI version 17.1.

CTCAE version 5.0.

AE = adverse event; AEPI = adverse event of possible interest; AESI = adverse event of special interest; CRF = Case Report Form; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in safety analysis set within each cohort; SAE = serious adverse event; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

No treatment-emergent ADA was observed against durvalumab or tremelimumab.

Dose-finding phase

In the D20+T1 group:

• Patients most commonly experienced AEs in the SOCs of blood and lymphatic system disorders, investigations (5/10 [50.0%] patients each), metabolism and nutrition disorders, gastrointestinal disorders, and musculoskeletal and connective tissue disorders (4/10 [40.0%] patients each);

• The most common AE PTs reported were anaemia (4/10 [40.0%] patients), vomiting (3/10 [30.0%] patients), upper respiratory tract infection, leukopenia, neutropenia, thrombocytopenia, hyperglycaemia, pyrexia, and GGT increased (2/10 [20.0%] patients each).

In the D30+T1 group:

• Patients most commonly experienced AEs in the SOCs of gastrointestinal disorders (13/19 [68.4%] patients), nervous system disorders (10/19 [52.6%] patients), and investigations (9/19 [47.4%] patients);

• The most common AE PTs reported were nausea (7/19 [36.8%] patients), headache (6/19 [31.6%] patients), vomiting, and ALT increased (5/19 [26.3%] each).

The most common AE PTs, with a frequency of ≥ 20% overall for patients in the dose-finding phase, are summarized in Table 35.

Table 35 Adverse events; most common (frequency of ≥ 20%) (safety analysis set) - dose finding

	Number (%) of patients [a]					
	Arm A: ≥ 35 kg		Arm B: < 35 kg		Total	
MedDRA Preferred Term	Durva 20 mg/kg + Treme 1 mg/kg (N = 7)	Durva 30 mg/kg + Treme 1 mg/kg (N = 11)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)	Durva 20 mg/kg + Treme 1 mg/kg (N = 10)	Durva 30 mg/kg + Treme 1 mg/kg (N = 19)
Patients with any AE	6 (85.7)	11 (100.0)	3 (100.0)	7 (87.5)	9 (90.0)	18 (94.7)
Vomiting	3 (42.9)	2 (18.2)	0	3 (37.5)	3 (30.0)	5 (26.3)
Anaemia	3 (42.9)	2 (18.2)	1 (33.3)	1 (12.5)	4 (40.0)	3 (15.8)
Headache	1 (14.3)	4 (36.4)	0	2 (25.0)	1 (10.0)	6 (31.6)
Nausea	0	7 (63.6)	0	0	0	7 (36.8)
Alanine aminotransferase increased	0	4 (36.4)	1 (33.3)	1 (12.5)	1 (10.0)	5 (26.3)

[a] Number (%) of patients with AEs, sorted in decreasing frequency for PT (total).

Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than one PT were counted once in each of those PTs.

Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).

Percentages were calculated from number of patients in the safety analysis set in each dose level/cohort.

MedDRA version 25.1.

AE = adverse event; Durva = durvalumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in safety analysis set within each dose level/cohort; PT = Preferred Term; Treme = tremelimumab.

Dose-expansion phase

In the SARCOMA cohort:

• Patients most commonly experienced AEs in the SOCs of general disorders and administration site conditions (8/11 [72.7%] patients), gastrointestinal disorders (5/11 [45.5%] patients), and blood and lymphatic system disorders (4/11 [36.4%] patients);

• The most common AE PTs reported were pyrexia (7/11 [63.6%] patients), anaemia, abdominal pain (4/11 [36.4%] patients each), thrombocytopenia, somnolence, ascites, diarrhoea, vomiting, back pain, asthenia, and ALT increased (2/11 [18.2%] patients each).

In the STO cohort:

• Patients most commonly experienced AEs in the SOCs of general disorders and administration site conditions (7/10 [70.0%] patients), investigations (5/10 [50.0%] patients), gastrointestinal disorders, infections and infestations, metabolism and nutrition disorders, and respiratory, thoracic, and mediastinal disorders (4/10 [40.0%] patients each);

• The most common AE PTs reported were pyrexia (4/10 [40.0%] patients), anaemia, decreased appetite, cough (3/10 [30.0%] patients each), headache, constipation, diarrhoea, vomiting, rash, asthenia, fatigue, and GGT increased (2/10 [20.0%] patients each).

The most common AE PTs, with a frequency of ≥ 20% overall for patients in the dose-expansion phase, are summarized in Table 36.

Table 36 Adverse events; most common (frequency of≥ 20%) (safety analysis set) - dose expansion

MedDRA Preferred Term	Number (%) of patients [a]		
	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Patients with any AE	10 (90.9)	9 (90.0)	19 (90.5)
Pyrexia	7 (63.6)	4 (40.0)	11 (52.4)
Anaemia	4 (36.4)	3 (30.0)	7 (33.3)
Abdominal pain	4 (36.4)	1 (10.0)	5 (23.8)

[a] Number (%) of patients with AEs, sorted in decreasing frequency for PT (total).

Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than one PT were counted once in each of those PTs.

Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).

Percentages were calculated from number of patients in the safety analysis set in each cohort.

MedDRA version 25.1.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in safety analysis set within each cohort; PT = Preferred Term; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; STO = other solid tumors.

Dose-finding phase

Adverse events of Grade 3 or Grade 4 were reported in the minority of patients in any dose-level group (Table 37).

In the D20+T1 group, 4/10 (40.0%) patients experienced Grade 3 or Grade 4 AEs, with AEs in the SOCs of blood and lymphatic system disorders and investigations reported in 2/10 (20.0%) patients each. All Grade 3 or Grade 4 AE PTs were reported in a maximum of 1/10 (10.0%) patient each.

In the D30+T1 group, 6/19 (31.6%) patients experienced Grade 3 or Grade 4 AEs, with AEs in the SOCs of investigations (3/19 [15.8%] patients) and nervous system disorders (2/19 [10.5%] patients) reported in ≥ 2 patients each. With the exception of neutrophil count decreased, reported in 2/19

(10.5%) patients, all other Grade 3 or Grade 4 AE PTs were reported in a maximum of 1/19 (5.3%) patient each.

Grade 3 or Grade 4 AEs of dehydration, transverse sinus thrombosis, nausea, amylase increased, lipase increased, and neutrophil count decreased were considered possibly related to durvalumab and tremelimumab by the Investigator and were all reported in 1/19 (5.3%) patient each in the D30+T1 group. No Grade 3 or Grade 4AE in the dose-finding phase was considered possibly related to durvalumab only or tremelimumab only by the Investigator.

Table 37 Adverse events of CTCAE Grade 3 or 4 by System Organ Class and Preferred Term (safety analysis set) - dose finding

System Organ Class/ MedDRA Preferred Term	Number (%) of patients [a]					
	Arm A: ≥ 35 kg		Arm B: < 35 kg		Total	
	Durva 20 mg/kg + Treme 1 mg/kg (N = 7)	Durva 30 mg/kg + Treme 1 mg/kg (N = 11)	Durva 20 mg/kg + Treme 1 mg/kg (N = 3)	Durva 30 mg/kg + Treme 1 mg/kg (N = 8)	Durva 20 mg/kg + Treme 1 mg/kg (N = 10)	Durva 30 mg/kg + Treme 1 mg/kg (N = 19)
Patients with AE of CTCAE Grade 3 or 4	2 (28.6)	4 (36.4)	2 (66.7)	2 (25.0)	4 (40.0)	6 (31.6)
Blood and lymphatic system disorders	1 (14.3)	1 (9.1)	1 (33.3)	0	2 (20.0)	1 (5.3)
Anaemia	1 (14.3)	0	0	0	1 (10.0)	0
Leukopenia	0	0	1 (33.3)	0	1 (10.0)	0
Lymphopenia	0	1 (9.1)	0	0	0	1 (5.3)
Neutropenia	0	0	1 (33.3)	0	1 (10.0)	0
Thrombocytopenia	0	0	1 (33.3)	0	1 (10.0)	0
Metabolism and nutrition disorders	0	1 (9.1)	0	0	0	1 (5.3)
Dehydration	0	1 (9.1)	0	0	0	1 (5.3)
Hypokalaemia	0	1 (9.1)	0	0	0	1 (5.3)
Nervous system disorders	0	0	0	2 (25.0)	0	2 (10.5)
Dysaesthesia	0	0	0	1 (12.5)	0	1 (5.3)
Transverse sinus thrombosis	0	0	0	1 (12.5)	0	1 (5.3)
Respiratory, thoracic, and mediastinal disorders	0	1 (9.1)	0	0	0	1 (5.3)
Dyspnoea	0	1 (9.1)	0	0	0	1 (5.3)
Gastrointestinal disorders	0	1 (9.1)	0	0	0	1 (5.3)
Nausea	0	1 (9.1)	0	0	0	1 (5.3)
Musculoskeletal and connective tissue disorders	1 (14.3)	0	0	0	1 (10.0)	0
Bone pain	1 (14.3)	0	0	0	1 (10.0)	0
Investigations	1 (14.3)	3 (27.3)	1 (33.3)	0	2 (20.0)	3 (15.8)
Amylase increased	0	1 (9.1)	0	0	0	1 (5.3)
Blood alkaline phosphatase increased	0	1 (9.1)	0	0	0	1 (5.3)
Gamma-glutamyltransferase increased	1 (14.3)	0	0	0	1 (10.0)	0
Lipase increased	0	1 (9.1)	0	0	0	1 (5.3)
Neutrophil count decreased	0	2 (18.2)	0	0	0	2 (10.5)
Platelet count decreased	0	0	1 (33.3)	0	1 (10.0)	0
White blood cell count decreased	0	1 (9.1)	0	0	0	1 (5.3)

[a] Number (%) of patients with AEs of CTCAE Grade 3 or 4, sorted by international SOC order and alphabetical PT. Patients with multiple AEs of CTCAE Grade 3 or 4 were counted once for each PT. Patients with events in more than one PT were counted once in each of those PTs.
Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).
Percentages were calculated from number of patients in the safety analysis set in each dose level/cohort.
CTCAE version 5.0.
MedDRA version 25.1.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; Durva = durvalumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in safety analysis set within each dose level/cohort; PT = Preferred Term; SOC = System Organ Class; Treme = tremelimumab.

Dose-expansion phase

Adverse events of Grade 3 or Grade 4 were reported in 45.5% to 50.0% of patients in any cohort (Table 38).

In the SARCOMA cohort, 5/11 (45.5%) patients experienced Grade 3 or Grade 4 AEs, with AEs in the SOC of blood and lymphatic system disorders reported in 2/11 (18.2%) patients. With the exception of anaemia, reported in 2/11 (18.2%) patients, all other Grade 3 or Grade 4 AE PTs were reported in a maximum of 1/11 (9.1%) patient each.

In the STO cohort, 5/10 (50.0%) patients experienced Grade 3 or Grade 4 AEs. All Grade 3 or Grade 4 AEs by SOC and PT were reported in a maximum of 1/10 (10.0%) patient each. Grade 3 or Grade 4 AEs of anaemia and ascites in the SARCOMA cohort (1/11 [9.1%] patient each) and decreased appetite in the STO cohort (1/10 [10.0%] patient) were considered possibly related to durvalumab and tremelimumab by the Investigator. The Grade 3 AE of platelet count decreased was considered possibly related to durvalumab only by the Investigator and was reported in 1/10 (10.0%) patient in the STO cohort. No Grade 3 or Grade 4 AE in the dose-expansion phase was considered possibly related to tremelimumab only by the Investigator.

Table 38 Adverse events of CTCAE Grade 3 or 4 by System Organ Class and Preferred Term (safety analysis set) - dose expansion

System Organ Class/ MedDRA Preferred Term	Number (%) of patients [a]		
	SARCOMA (N = 11)	STO (N = 10)	Total (N = 21)
Patients with AE of CTCAE Grade 3 or 4	5 (45.5)	5 (50.0)	10 (47.6)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (10.0)	1 (4.8)
Pericardial effusion malignant	0	1 (10.0)	1 (4.8)
Blood and lymphatic system disorders	2 (18.2)	0	2 (9.5)
Anaemia	2 (18.2)	0	2 (9.5)
Thrombocytopenia	1 (9.1)	0	1 (4.8)
Metabolism and nutrition disorders	0	1 (10.0)	1 (4.8)
Decreased appetite	0	1 (10.0)	1 (4.8)
Vascular disorders	0	1 (10.0)	1 (4.8)
Hypertension	0	1 (10.0)	1 (4.8)
Respiratory, thoracic, and mediastinal disorders	1 (9.1)	1 (10.0)	2 (9.5)
Dyspnoea	0	1 (10.0)	1 (4.8)
Laryngospasm	1 (9.1)	0	1 (4.8)
Pleural effusion	0	1 (10.0)	1 (4.8)
Pneumonitis	0	1 (10.0)	1 (4.8)
Pulmonary thrombosis	0	1 (10.0)	1 (4.8)
Gastrointestinal disorders	1 (9.1)	1 (10.0)	2 (9.5)
Ascites	1 (9.1)	0	1 (4.8)
Constipation	0	1 (10.0)	1 (4.8)
General disorders and administration site conditions	1 (9.1)	1 (10.0)	2 (9.5)
Asthenia	1 (9.1)	0	1 (4.8)
Non-cardiac chest pain	0	1 (10.0)	1 (4.8)
Investigations	0	1 (10.0)	1 (4.8)
Platelet count decreased	0	1 (10.0)	1 (4.8)
Injury, poisoning and procedural complications	1 (9.1)	0	1 (4.8)
Fall	1 (9.1)	0	1 (4.8)
Femur fracture	1 (9.1)	0	1 (4.8)

[a] Number (%) of patients with AEs of CTCAE Grade 3 or 4, sorted by international SOC order and alphabetical PT. Patients with multiple AEs of CTCAE Grade 3 or 4 were counted once for each PT. Patients with events in more than one PT were counted once in each of those PTs.

Includes AEs with an onset date on or after the date of first dose of durvalumab or tremelimumab (or date before first treatment, but worsening following first dose), up to and including 90 days following the last dose of durvalumab or tremelimumab, or initiation of first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurred first).

Percentages were calculated from number of patients in the safety analysis set in each cohort.

CTCAE version 5.0.

MedDRA version 25.1.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in safety analysis set within each cohort; PT = Preferred Term; SARCOMA = osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, or other sarcomas; SOC = System Organ Class; STO = other solid tumors.

Adverse events leading to dose modifications and Dose-limiting toxicity events

Dose-finding phase

In the D20+T1 group, no patient had AEs leading to dose modifications.

In the D30+T1 group, AEs that led to dose modification were reported in 2/19 (10.5%) patients: 2/19 (10.5%) patients had COVID-19 that led to dose interruption and 1/19 (5.3%) patient had colitis that led to the permanent discontinuation of study treatment.

Dose-expansion phase

In the SARCOMA cohort, no patient had AEs leading to dose modifications.

In the STO cohort, AEs that led to dose modification were reported in 3/10 (30.0%) patients: 1/10 (10.0%) patient each had pneumonia that led to dose interruption, and pulmonary thrombosis and platelet count decreased that led to the permanent discontinuation of study treatment.

In the dose-finding phase, 8 DLT-evaluable patients received DL 1 and 12 DLT-evaluable patients received DL 2. No DLTs were reported in any DLT-evaluable patient.

8.3. Discussion

Assessment of safety was a primary objective for the dose-finding phase of this study. The safety profile was as expected for this patient population and consistent with the known safety profile of durvalumab administered as monotherapy or in combination with tremelimumab in adults.

No new safety concerns were identified.

No treatment-emergent ADA against durvalumab or tremelimumab were detected, thus no assessment of the potential impact of ADA on safety could be made.

Regarding the proposed amendment to section 4.8, due to the fact that safety data collected in Study D419EC00001 belongs to a paediatric development for an indication neither approved in children nor in adults, it is considered more appropriate to present the safety data together with the results of the paediatric clinical study in section 5.1 instead of section 4.8, in order to include both efficacy and safety data in one place and avoid confusions or off-label use in the paediatric population.

9. PRAC advice

None

10. Changes to the Product Information

As a result of this variation the SmPC's for Imfinzi and Imjudo are being updated.

Please refer to Attachment 1 which includes all proposed changes to the Product Information. Please note a comment to section 5.1.

11. Request for supplementary information

11.1. Major objections

None

11.2. Other concerns

Clinical aspects

1. The Applicant is asked to justify the lack of Nab testing after confirmation of ADA-positives according to Clinical Summary of Pharmacology.
2. The proposed updates in sections 4.2, 4.8 and 5.1 are not entirely supported. Please refer to the SmPC file for specific guidance.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

None

12.2. Other concerns

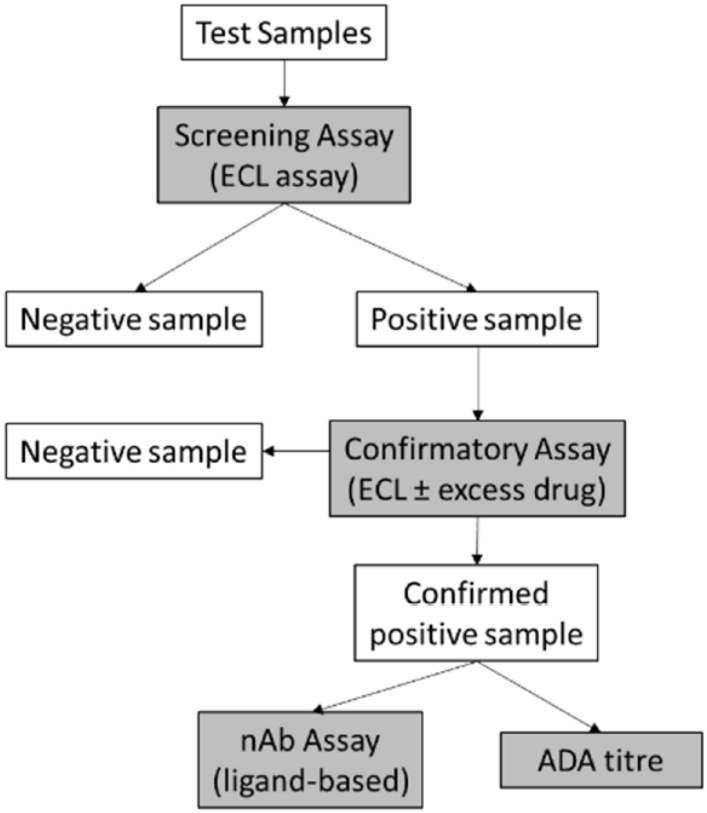
Clinical aspects

Question 1

The Applicant is asked to justify the lack of Nab testing after confirmation of ADA-positives according to Clinical Summary of Pharmacology.

Summary of the WSA's response

In the D419EC00001 study, a 3-tiered testing approach, which consisted of validated assays for detection (screening assay), specificity (confirmation assay) and characterization (titre assay), was used for the assessment of ADA responses to durvalumab and tremelimumab in clinical studies. Confirmed ADA-positive samples were subsequently tested for in vitro neutralizing activity as assessed by nAb assays (This approach is described in 2.7.2 HIMALAYA which is referenced in the submission).



Per the 3-tier testing and reporting strategy, ADA positive samples were indeed tested for neutralizing activity in study D419EC00001.

For durvalumab ADA evaluable patients, 2 patients each had 1 sample with confirmed ADA positive results. These two positive samples were further tested with nAb assay (Validation Report RJRG2, Method Number ICDIM 324, included in Module 5.3.1.4) and the nAb results were negative for both samples, these results were included in the summary tables of ADA responses to durvalumab in the CSR. The detailed nAb sample results are described in the D419EC00001 nAb Sample Analysis Report for durvalumab included in Module 5.3.1.4. It is of note that the two ADA-positive subjects were ADA-positive at baseline only, therefore, the ADA were characterized as non-treatment emergent (addressing reviewer comment at Assessment Report Page 64).

For tremelimumab ADA evaluable patients, the 3-tier testing and reporting strategy described above was followed. There was no ADA-positive subject, either at baseline or post-baseline, thus no nAb results were reported for tremelimumab (See Summary tables of tremelimumab ADA responses to tremelimumab in the CSR/CSR erratum.

*Please note the D419EC0001 clinical study report (CSR) provided in the submission included the statement that there were no tremelimumab ADA-evaluable patients in the dose finding phase of the study. With this submission, a CSR erratum is provided correcting this data point to 6 tremelimumab ADA evaluable patients, none of whom were ADA-positive. Updated tremelimumab immunogenicity summary tables for the dose finding phase of the study are provided with the enclosed CSR errata.

Assessment of the WSA's response

The Applicant was asked to justify the lack of Nab testing after confirmation of ADA-positive samples in study D419EC00001.

The Applicant clarified, that for durvalumab ADA evaluable patients, 2 patients each had 1 sample with confirmed ADA positive results, and that these two positive samples were further tested with nAb

assay – both with negative outcome. The detailed nAb sample results were described in the D419EC00001 nAb Sample Analysis Report for durvalumab included in Module 5.3.1.4.

For tremelimumab ADA evaluable patients, the Applicant referred to a CSR Erratum provided with the response and further clarified, that there was no ADA-positive subject, either at baseline or post-baseline, thus no nAb results were reported for tremelimumab.

Conclusion:

Issue considered resolved.

Question 2

The proposed updates in sections 4.2, 4.8 and 5.1 are not entirely supported. Please refer to the SmPC file for specific guidance.

Summary of the WSA's response

Please refer to the annotated Summary of Product Characteristics provided with this response document.

Assessment of the WSA's response

The applicant has satisfactorily addressed the concerns. Please refer to the attached SmPC' es.

☒Overall conclusion and impact on benefit-risk balance have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

13. Attachments

1. Product Information (changes highlighted) of Imfinzi and Imjudo as adopted by CHMP.