Office of Clinical Pharmacology Review

NDA or BLA Number	BLA 761069 S-47; SDN 2189 BLA 761289 S-6; SDN 82
Type/Category	Labeling Supplement
Submission Date	BLA 761289/S-6: 1/26/2024 BLA 761069/S-47: 1/26/2024
Submission Type	Standard
Brand Name	IMFINZI® (durvalumab) IMJUNDO® (tremelimumab)
Generic Name	durvalumab & tremelimumab
Dosage Form and Strength	INFINZI: intravenous (IV) injection; 500 mg/10 mL solution IMJUDO: IV injection; 25 mg/1.25 mL solution
Route of Administration	IV infusion
Approved Indication	**IMJUDO®**: • in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). • in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. **IMFINZI®**: • for the treatment of adult patients with unresectable, NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. • in combination with tremelimumab and platinum-based chemotherapy, for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. • 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 combination with gemcitabine and cisplatin, as treatment of adult patients with locally

	advanced or metastatic biliary tract cancer (BTC). • in combination with tremelimumab, for the treatment of adult patients with uHCC.
Approved Dosing Regimen	Refer to section 2.2.1 below for details on approved dosing regimen
Applicant	BLA 761289: AstraZeneca AB BLA 761069: AstraZeneca UK Limited
OCP Divisions	Division of Cancer Pharmacology II (DCPII) and Division of Pharmacometrics (DPM)
OND Divisions	Division of Oncology 3 (DO3)
OCP Review Team	Hairat Sabit, Ph.D. and Abiy Eyakem, Ph.D.
OCP Team Leaders	Hong Zhao, Ph.D. and Youwei Bi, Ph.D.
OCP/DCPII Deputy Director	Stacy Shord, PharmD

Table of Contents

1. EXECUTIVE SUMMARY

AstraZeneca submitted two labeling supplements, one (BLA 761289/S-6) for IMJUDO (tremlimumab-actl) and one (BLA 761069/S-47) for IMFINZI (durvalumab) to update the labeling to include the results of 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*"; this study was conducted to fulfill a postmarketing requirement (PMR). FDA initially issued PMR #4333-1 in the approval letter for trememlimumab (BLA 761289) to conduct a pediatric study (D419EC00001). Due to recruitment challenges and a general lack of activity of trememlimumab in combination with durvalumab in pediatric patients p, the AstraZeneca, submitted a PMR Release and Replace Request to modify PMR #4333-1 to require 21 patients instead of 45 patients in the dose expansion portion of the study to reflect study modifications and outcomes. On September 5, 2023, FDA released PMR #4333-1 and replaced it with PMR #4333-6.

> PMR #4333-6: Conduct Study D419EC00001 (A Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of tremelimumab in combination with durvalumab in pediatric patients) to further characterize the safety, pharmacokinetics, and efficacy of tremelimumab in combination with durvalumab in patients from birth to <18 years of age with relapsed/refractory malignant solid tumors for whom no standard treatment is available. Include at least 12 patients in the dose escalation cohort and at least 21 patients in the dose expansion cohort.

No pediatric indication is being requested based on the results of this study due to limited efficacy. A description of the differences in the pharmacokinetics (PK) between pediatric pateitns and that observed in adults patients will be incorporated in **Section 8.4 Pediatric Use** of IMJUDO® and IMFINZI® labeling.

1.1 Recommendations:

The data from Study D419EC00001 do not support a pediatric indication; however, a description of the study will be incorporated in **Section 8.4 Pediatric Use** of IMJUDO and IMFINZI labeling consistent with the recommendations found in the Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019, which states "When it is determined that available evidence regarding safety or effectiveness does not support a pediatric indication, relevant pediatric information related to the unapproved use that is included in labeling generally should be placed only in the Pediatric Use subsection. Negative studies and inconclusive studies should be briefly summarized in this subsection... Furthermore, when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the Pediatric Use subsection." PMR #4333-6 is considered fulfilled.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Labeling Recommendations

IMJUDO

Patient Population	Applicant Proposed Updates	FDA Recommendation
Section 8.4 Pediatric Use	(b) (4)	The safety and effectiveness of IMFINZI have not been established in pediatric patients. Safety and efficacy were assessed but not established in a multi-center, open-label study (NCT03837899) in 45 pediatric patients aged 1 to <17 years with solid tumors who received IMFINZI in combination with tremelimumab followed by IMFINZI alone. No new safety signals were observed in pediatric patients in this study. Durvalumab systemic exposures in pediatric patients weighing ≥ 35 kg were within the range of values previously observed in adults given the same weight-based dosage, whereas the systemic exposures in pediatric patients weighing <35 kg were lower than those observed in adults.

	(b) (4)	

IMFINZI

Patient Population	Applicant Proposed Updates	FDA Recommendation
Section 8.4 Pediatric Use	(b) (4)	The safety and effectiveness of IMJUDO have not been established in pediatric patients. Safety and efficacy were assessed but not established in a multi-center, open-label study (NCT03837899) in which 42 pediatric patients aged 1 to < 17 years with advanced solid tumors received IMJUDO in combination with durvalumab. No new safety signals were observed in pediatric patients in this study. Tremelimumab-actl systemic exposures in pediatric patients ≥ 35 kg were within the range of the values previously observed in adults given the same weight-based dosage, whereas the systemic exposures in pediatric patients < 35 kg were lower than those of adults.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

No recommended dosage is proposed for pediatric patients given no efficacy was observed.

2.2.2 Therapeutic individualization

Refer to section 2.2.1 above for therapeutic individualization based on body weight.

2.3 Outstanding Issues

There are no outstanding issues in this submission.

3. Clinical Pharmacology Review

3.1 Review of Study D419EC00001

Study Title: Phase I/II, Open-Label 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

3.1.1 Study design

Study D419EC00001 had a dose-finding and a dose-expansion phase. Patients from 1 to < 18 years of age with relapsed or refractory malignant solid tumors (except primary central nervous system tumors) were eligible to participate in this study. A total of 50 pateints were enrolled in the study: 29 patients in the dose-finding phase and 21 patients in the dose-expansion phase. Patients were assigned to a treatment arm by body weight (BW, ≥ 35 kg and < 35 kg) and adminsitered one of two dosing regimens (durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W or durvalumab 30 mg/kg + tremelimumab 1 mg/kg Q4W) during the dose-finding phase.

1) Dose-finding phase

   The dose-finding phase of the study was conducted using a modified 3 + 3 design to determine whether durvalumab and tremelimumab could be administered safely in pediatric patients and if adult exposures could be achieved. Pediatric patients with relapsed or refractory malignant solid tumors including osteosarcoma and Ewing sarcoma (SARC-1 cohort), rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, and other sarcomas (SARC-2 cohort), neuroblastoma (NB cohort), and other solid tumors (STO) were enrolled in 2 arms:

   Arm A, with patients weighing ≥ 35 kg

   Arm B, with patients weighing < 35 kg

   Based on the available clinical and PK data and simulations, the administration of an adult weight-adjusted dose in pediatrics with a body weight of ≥ 35 kg was anticipated to result in PK and target engagement profiles similar to adults; however, patients with a body weight < 35 kg were hypothesized to have exposures lower than those in adults, and thus could require higher doses to achieve exposures similar to adults.

Three dose levels could be explored in each of the arms (**Figure 1**). Dose level 1 was 100% of the recommended adult dose of both durvalumab and tremelimumab administered as weight-adjusted doses.

i. Cycle 1 (durvalumab monotherapy): durvalumab 20 mg/kg

ii. Cycles 2 to 5 (durvalumab in combination with tremelimumab): durvalumab 20 mg/kg and tremelimumab 1 mg/kg (4 cycles administered every 28 days)

iii. From Cycle 6 onwards, treatment was to continue until a discontinuation criterion was met, with durvalumab monotherapy administered at 20 mg/kg every 28 days.

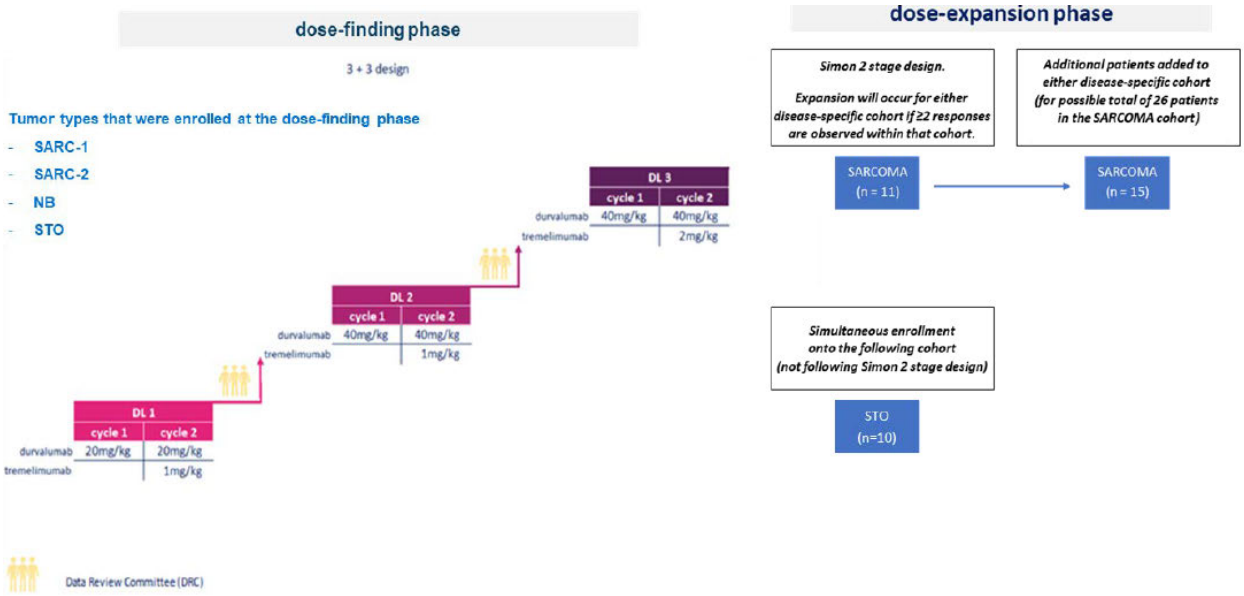
2) Dose-expansion phase

The dose-expansion phase was conducted using a Simon 2-stage optimal design with an additional provision to include one mixed disease cohort (other malignant solid tumors). Once the RP2D was established, patients were recruited to each of the following cohorts: SARCOMA (bone sarcomas: osteosarcoma, Ewing sarcoma; soft-tissue sarcomas [≥ 40% of enrollment]: rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, and other sarcomas); STO (other solid tumors).

For the SARCOMA cohort, the initial stage allowed 11 evaluable patients to be dosed. If 2 or more responses were observed in this cohort, additional patients were to be accrued, as part of the second stage, into the expansion cohort; 15 patients were to be accrued into the SARCOMA expansion cohort for a total of 26 evaluable patients. If there was ≤ 1 objective response in the SARCOMA cohort (11 patients) at the time that evaluable patients dosed in the initial stage had been followed/assessed for at least 3 cycles, the cohort was to be discontinued for lack of benefit.

For the STO cohort, 10 evaluable patients were enrolled into this mixed disease cohort; Simon rules were not applicable for this cohort.

Figure 1. D419EC00001 Study Design



(Data source: module 2.5 Clinical Overview, Figure 1; BLA761069; SDN 2189)

Study Objectives**:**

1) **Primary Objectives**

Dose-finding Phase

- Recommended Phase 2 dose (RP2D) of durvalumab in combination with tremelimumab followed by durvalumab monotherapy

Dose-expansion Phase

- Preliminary anti-tumor activity in pediatric solid tumors

2) **Key Secondary Objectives**

- PK of durvalumab and tremelimumab in pediatric patients
- Safety in pediatric patients

3.1.2 General pharmacology and pharmacokinetic characteristics

In the dose-finding phase, PK results were summarized by treatment and body weight:

Arm A: ≥ 35 kg

- Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg Q4W
- Durvalumab 30 mg/kg + Tremelimumab 1 mg/kg Q4W

Arm B: < 35 kg

- Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg Q4W
- Durvalumab 30 mg/kg + Tremelimumab 1 mg/kg Q4W

The PK of tremelimumab and durvalumab in tremelimumab + durvalimumab combination therapy were assessed in Study D419EC00001 and 7 supportive studies of patients with different types of solid tumor (HIMALAYA, ATLANTIC, Study 1108, PACIFIC, Japan Study 02, Study 06, and Study 10).

1) **Durvalumab**

Pharmacokinetics:

Geometric mean durvalumab $AUC_{0\text{-}28d}$ was approximately 25% lower for pediatric patients (aged 1 to <17 years) < 35 kg compared to pediatric patients with ≥ 35 kg at both dose levels of 20 mg/kg or 30 mg/kg (**Table 1**). Between the 20 mg/kg and 30 mg/kg, durvalumab exposure appeared to increase slightly more than proportionally, as $AUC_{0\text{-}28d}$ and C_{max} increased by 2- to 3-fold and C_{min} increased by 3- to 5-fold.

Table 1. 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.

(Source: section 2.7; Summary of Clinical Pharmacology; Table 2; BLA761069; SDN 2189)

Based on population PK analysis, durvalumab exposure was similar between adults receiving 20 mg/kg Q4W, pediatric patients with WT < 35 kg receiving 30 mg/kg Q4W and pediatric patients with WT ≥ 35 kg receiving 20 mg/kg Q4W.

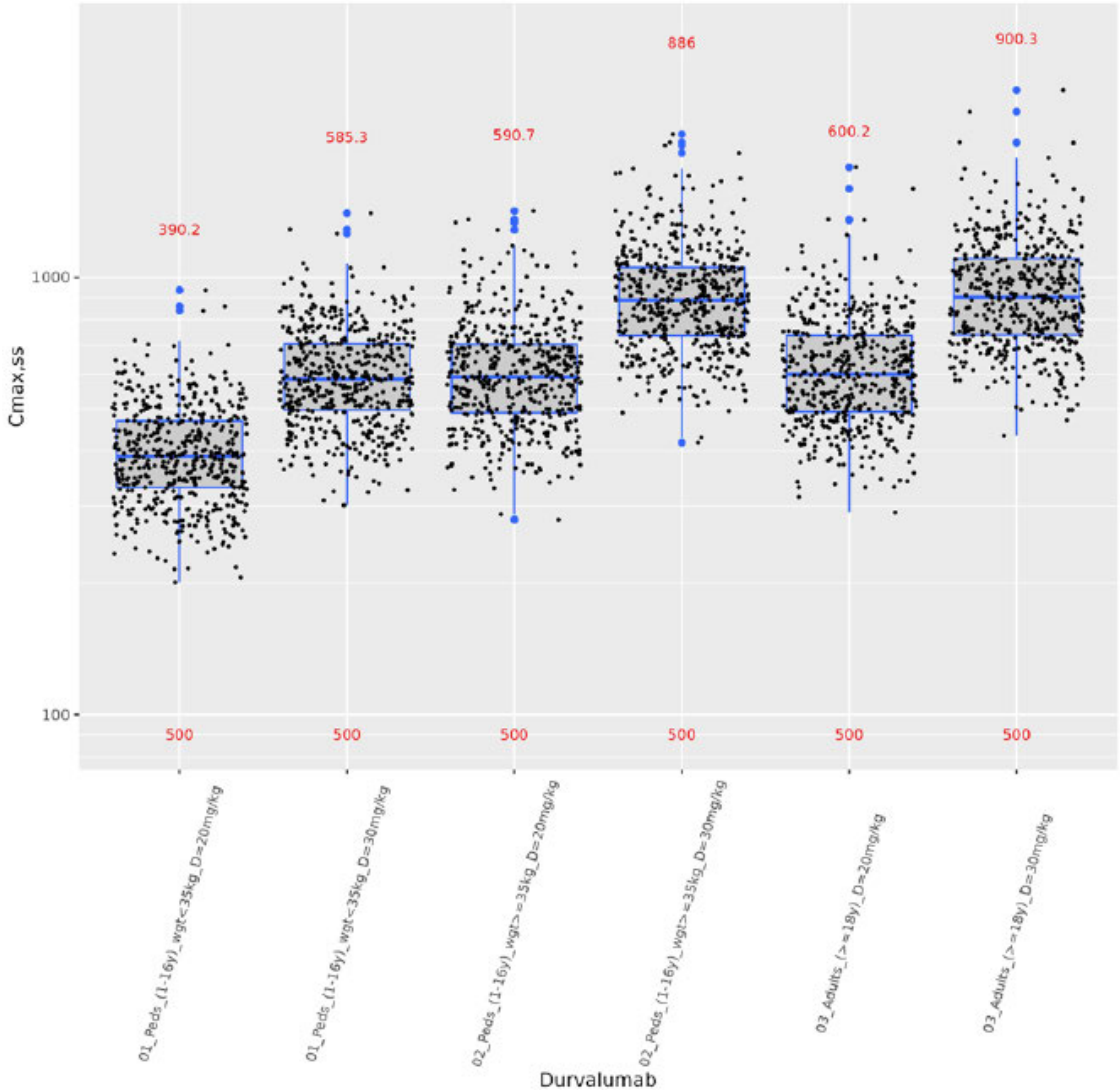
Reviewer's Comments:

*The Applicant's conclusion that durvalumab exposure in pediatric patients with body weight ≥35 kg or <35 kg is within range of that observed in adult patients is generally acceptable with some exception. Based on the population PK analysis, both steady state $C_{max,ss}$ (**Figure 2**) and AUC_{ss} (*

APPEARS THIS WAY ON ORIGINAL

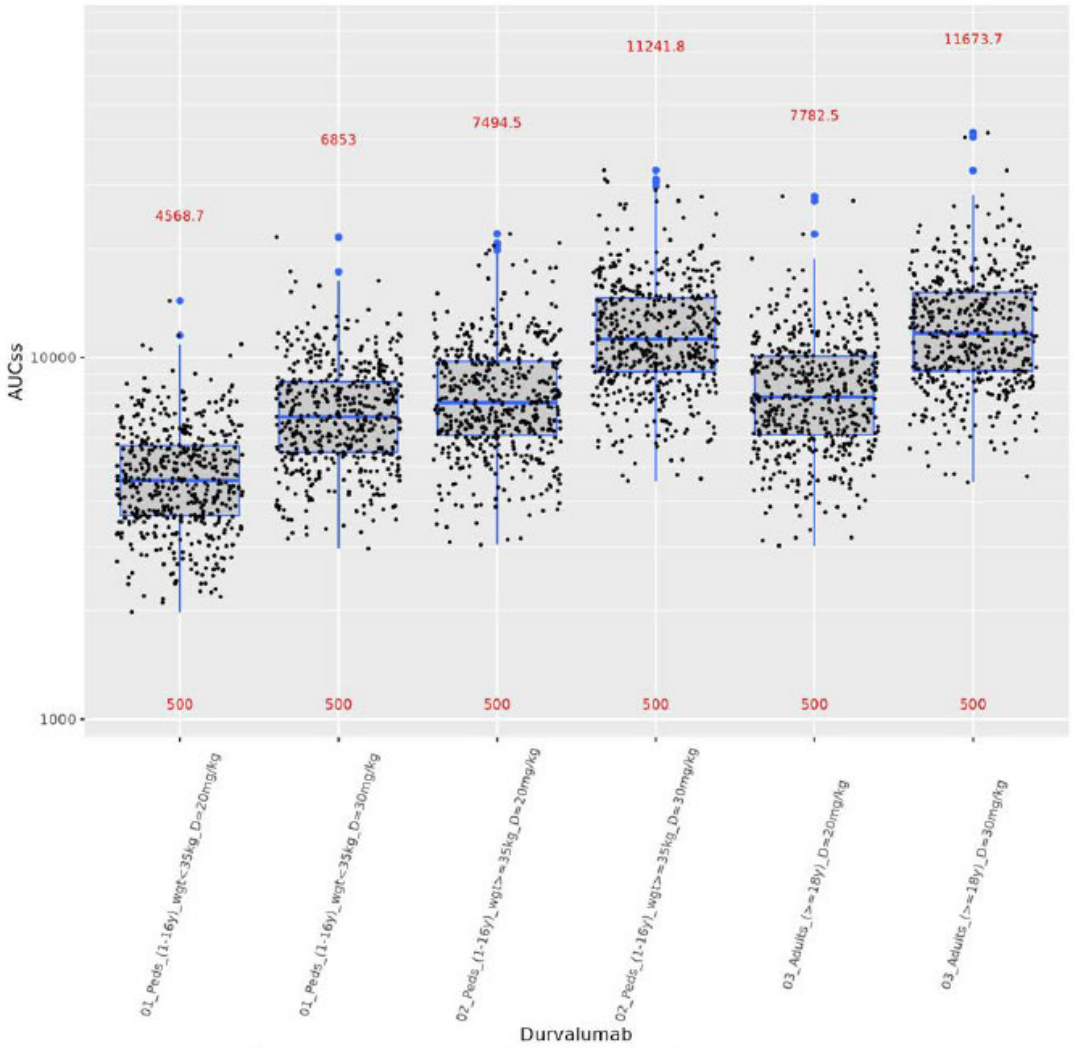
Figure* 3) in pediatric patients with either body weight ≥ 35 kg receiving durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W or body weight < 35 mg receiving durvalimumab 30 mg/kg + tremelimumab 1 mg/kg Q4W are comparable to that of adult patients receiving durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W. However, in the dosing-finding portion of the Study D419EC00001, durvalumab $AUC_{0\text{-}28d}$ in pediatric patients with body weight of ≥ 35 kg receiving durvalumab 20 mg/kg Q4W + tremelimumab 1 mg/kg Q4W is almost half the $AUC_{0\text{-}28d}$ for pediatric patients with body weight of < 35 kg receiving durvalumab 30 mg/kg + tremelimumab 1 mg/kg Q4W, which is different from population PK prediction results (**Error! Reference source not found.**). Caution should be taken when interpretation of the data given the small sample size in the study.*

Figure 2 Durvalumab Boxplot of Simulated Cmax,ss Factored by Population and Dose



(Source: section 5.3.3.5; D419EC00001-pop-pk-report; Figure 5; BLA761069; SDN 2317)

Figure 3 Durvalumab Boxplot of Simulated AUCss Factored by Population and Dose



(Source: section 5.3.3.5; D419EC00001-pop-pk-report; Figure 4; BLA761069; SDN 2317)

Anti-drug Antibodies (ADA):
Because none of the evaluated pediatric patients were found to have treatment-emergent ADA, the influence of ADA on pediatric durvalumab PK could not be evaluated.

2) Tremelimumab

Pharmacokientics:

Geometric mean tremelimumab $AUC_{0\text{-}28d}$ was lower for pediatric patients (aged 1 to <17 years) < 35 kg receiving tremelimumab 1mg/kg + durvalumab 30 mg/kg Q4W compared to pediatric patients with ≥ 35 kg receiving tremelimumab 1mg/kg + durvalumab 20 mg/kg Q4W (**Table 2**).

Table 2. 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
$t^{1}/_{2}\lambda z$ (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); $t^{1}/_{2}\lambda z$ = 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.

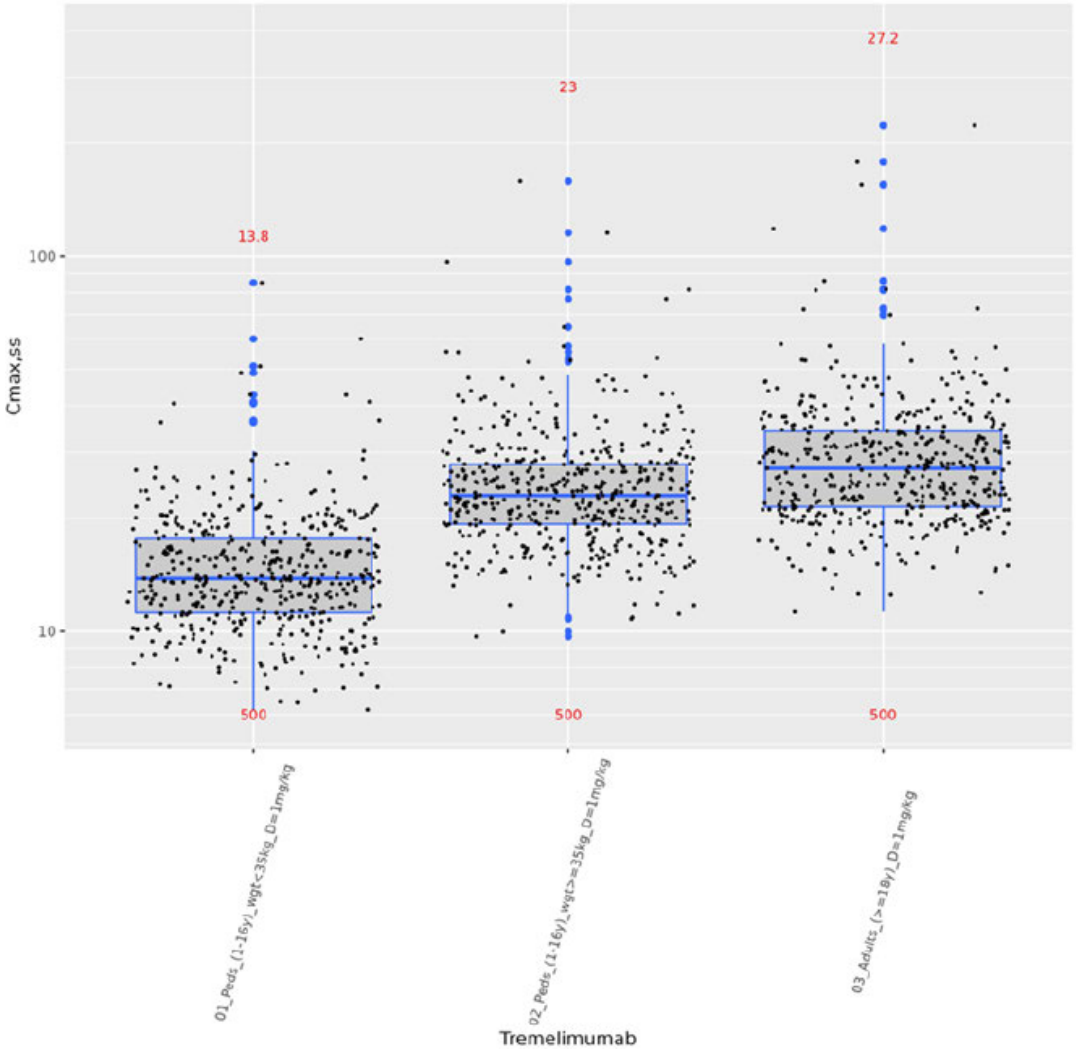
(Source: section 2.7; Summary of Clinical Pharmacology; Table 3; BLA761069; SDN 2189)

Based on population PK analysis, tremelimumab-actl systemic exposure in pediatric patients ≥ 35 kg receiving IMJUDO 1 mg/kg Q4W was similar to exposure in adults receiving 1 mg/kg Q4W, whereas in pediatric patients < 35kg, exposure was lower relative to adults.

Reviewer's Comments:

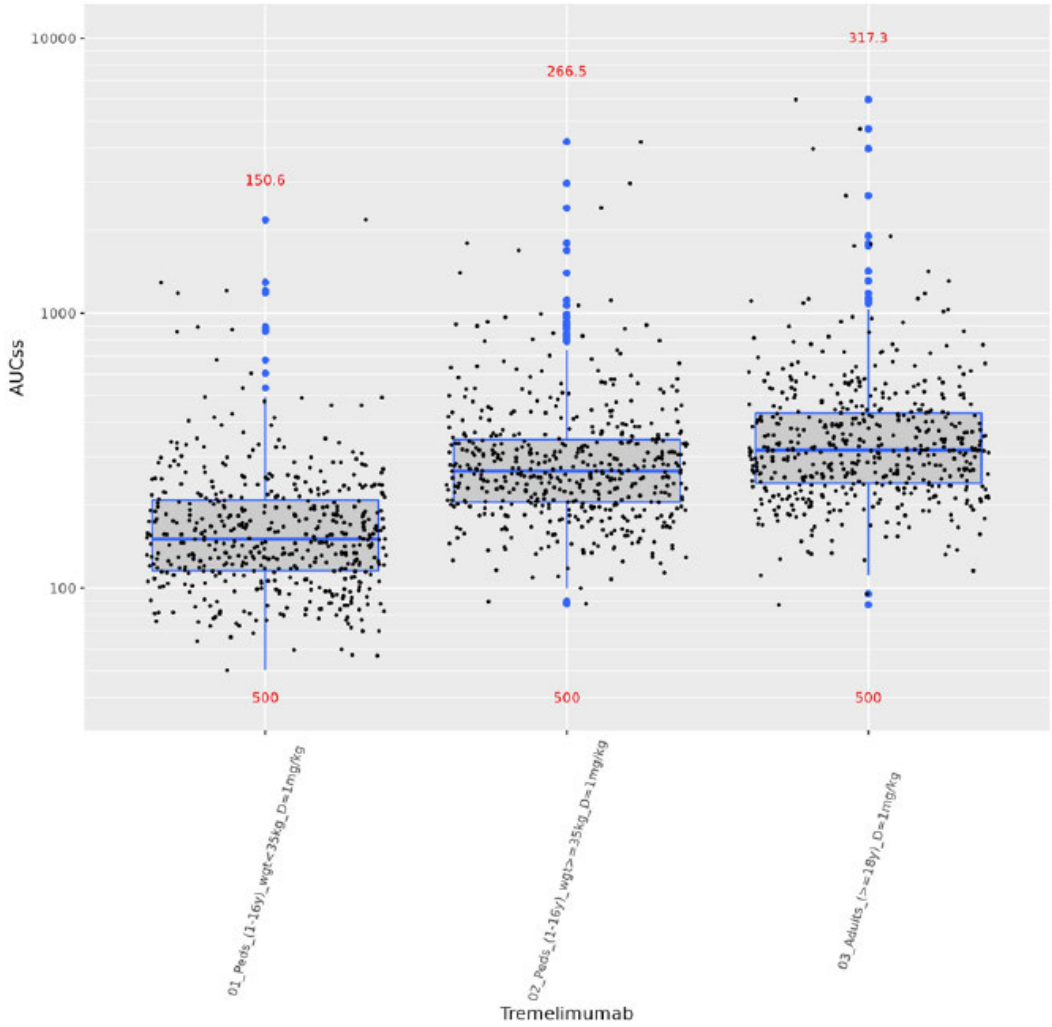
*The Applicant's conclusion regarding how tremelimumab exposure in pediatric patients with body weight ≥ 35 kg or < 35 kg compared to that observed in adult patients is acceptable. Based on the population PK analysis, both tremelimumab steady state $C_{max,ss}$ (**Figure 4**) and AUC_{ss} (**Figure 5**) of pediatric patients with body weight ≥ 35 kg receiving durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W are comparable to that of adult patients receiving same dosage, whereas the $C_{max,ss}$ and AUC_{ss} of pediatric patients with body weight < 35 kg receiving durvalumab 30 mg/kg + tremelimumab 1 mg/kg Q4W were less than those of adult patients receiving durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W combination therapy.*

Figure 4. Tremelimumab Boxplot of Simulated Cmax,ss Factored by Population



(Source: section 5.3.3.5; D419EC00001-pop-pk-report; Figure 8; BLA761069; SDN 2317)

Figure 5. Tremelimumab Boxplot of Simulated AUCss Factored by Population



(Source: section 5.3.3.5; D419EC00001-pop-pk-report; Figure 7; BLA761069; SDN 2317)

Anti-drug Antibodies (ADA):

No ADA evaluable patients were ADA positive to tremelimumab at any time during the study. Because none of the evaluable pediatric patients were found to have treatment-emergent ADA, the influence of ADA on pediatric tremelimumab PK could not be evaluated in pediatric population.

3.1.3 Dose-finding in pediatric patients

The Applicant selected the dosing regimen for durvalumab in combination with tremelimumab for the study, D419EC00001 with the goal of selecting dosing regimen that would yield similar systemic exposures in pediatric patients to that observed in adults, have an acceptable safety profile, and demonstrate promising efficacy. The Applicant provided the following information to support the dosing regimens evaluated in the dose-finding and expansion portions of the pediatric study.

PK data from the dose-finding cohort of durvalumab 20 mg/kg Q4W revealed that the geometric mean exposure, regardless of weight, failed to achieve the equivalent adult exposure for durvalumab. Based on modeling, a dosage of durvalumab 30 mg/kg Q4W was predicted to achieve the equivalent target exposure and was initiated for the second cohort as the dose-level 2. This dosing regimen was therefore declared as the RP2D to be evaluated in the dose-expansion phase. Population PK modeling and simulation of pediatric patients in both the dose-finding and dose-expansion cohorts showed that durvalumab exposure was similar in adults receiving a dosage of 20 mg/kg Q4W, pediatric patients ≥ 35 kg receiving a dosage of 20 mg/kg Q4W, and pediatric patients < 35 kg receiving a dosage of 30 mg/kg Q4W. Similar to what was seen in the dose-finding phase, population PK modeling also indicated that pediatric patients ≥ 35 kg have approximately 1.5-fold higher systemic exposure than adults when given a dosage of 30 mg/kg Q4W.

PK data from the dose-finding phase for tremelimumab at a dosage of 1 mg/kg Q4W revealed that tremelimumab exposure was similar to that of adults in both weight groups (<35 kg and ≥35 kg). Therefore, this dosing regimen was declared as the RP2D of tremelimumab to be evaluated in the dose-expansion phase. PopPK modeling and simulation of pediatric 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 pediatric patients ≥ 35 kg, but lower than adults for pediatric patients < 35 kg.

Overall, in the study D419EC00001, the durvalumab systemic exposures, in combination with tremelimumab in pediatric patients with body weight < 35 kg were lower than adult systemic exposures at a durvalumab dosage of 20 mg/kg Q4W but were generally similar to adult systemic exposures at a dosage of 30 mg/kg Q4W. However, PopPK modeling and simulation data showed that systemic exposures in pediatric patients with body weight ≥ 35 kg were generally similar to adult systemic exposures at a durvalumab dosage of 20 mg/kg Q4W, but higher compared to adults systemic exposures (approximately 1.5-fold) at a durvalumab dosage of 30 mg/kg Q4W. Tremelimumab systemic exposures, in combination with durvalumab, were generally comparable to adult systemic exposures at a tremelimumab dosage of 1 mg/kg Q4W in pediatric patients with body weight ≥ 35 kg but were lower relative to adult systemic exposures in pediatric patients with body weight < 35 kg.

Reviewer's Comments:

The Applicant's dosing rationale for the durvalumab + tremelimumab combination therapy in pediatric patients in Study D419EC00001 is acceptable.

3.1.4 Safety summary

The incidence of adverse events (AEs) was comparable between DL1 and DL2 dose groups (90% and 95%, respectively). The most commonly reported AEs (≥ 20%) in any dose group were vomiting, anemia, headache, nausea, and increased alanine aminotransferase. The majority of the AEs were of Grade 1 or Grade 2 with 40% patients in the DL1 and 32% patients in the DL2 dose group having AEs of ≥ Grade 3 during the dose-finding phase (**Table 3**).

The incidence of AEs during the dose-expansion phase was 91% in the SARCOMA cohort and 90% in the STO cohort (

Table 4). The most commonly reported AEs (≥ 20%) in the SARCOMA cohort were pyrexia (64%), anemia (36%) and abdominal pain (36%); and the most commonly reported AEs (≥ 20%) in the STO cohort were pyrexia (40%), anemia, decreased appetite, cough (30% each), headache, constipation, diarrhea, vomiting, rash, asthenia, fatigue, increased gamma glutamyl transferase (20% each).

Table 3. Adverse Events by Category – Dose-finding Phase (Safety Analysis Set)

	Number (%) of patients [a]	
Adverse event category	**Durva 20 mg/kg + Treme 1 mg/kg (N = 10)**	**Durva 30 mg/kg + Treme 1 mg/kg (N = 19)**
Any AE	9 (90.0)	18 (94.7)
Any AE possibly related to treatment [b]	5 (50.0)	12 (63.2)
Any AE of CTCAE Grade 3 or 4	4 (40.0)	6 (31.6)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [b]	0	3 (15.8)
Any AE with outcome = death	0	0
Any SAE (including events with outcome = death)	1 (10.0)	2 (10.5)
Any SAE (including events with outcome = death), possibly related to treatment [b]	0	2 (10.5)
Any AE leading to discontinuation of durvalumab	0	0
Any AE leading to discontinuation of tremelimumab	0	1 (5.3)
Any AESIs or AEPIs	4 (40.0)	11 (57.9)
Any AESIs or AEPIs possibly related to treatment [b]	1 (10.0)	6 (31.6)
Immune-mediated AEs	0	2 (10.5)
Infusion reaction AEs	0	2 (10.5)

(Source: section 2.7; Clinical Overview; Table 3; BLA761069; SDN 2189)

Table 4. Adverse Events in Any Category - Patient Level (Safety Analysis Set) – Dose-expansion Phase

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 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 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 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 AE leading to discontinuation of tremelimumab	0	1 (10.0)	1 (4.8)
Any AESIs or AEPIs	5 (45.5)	6 (60.0)	11 (52.4)
Any AESIs or AEPIs possibly related to treatment [b]	3 (27.3)	5 (50.0)	8 (38.1)
Immune-mediated AEs	2 (18.2)	2 (20.0)	4 (19.0)
Infusion reaction AEs	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.

AE = adverse event; AEPI = adverse event of possible interest; AESI = adverse event of special interest; 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.

Source: Study D419EC00001 report Table 14.3.2.1.B, Table 47.

(Source: section 2.7; Clinical Overview; Table 4; BLA761069; SDN 2189)

Reviewer's Comment:
There were no new safety signals of durvalumab in combination with tremelimumab observed in pediatric patients relative to the known safety profiles of this combination therapy in adults.

3.1.5 Efficacy summary

Three objective responses were reported (2 patients in the dose-finding phase and 1 patient in the dose-expansion phase) including a partial response (PR) in each of a patient with osteosarcoma, renal cell carcinoma, or chordoma.

No objective response was observed in the first 11 patients treated in the SARCOMA expansion cohort; thus, this cohort did not meet the protocol-specified criteria for continuing the second stage of the expansion cohort**.**

In the "solid tumor other" (STO; n=10) dose-expansion cohort, one clinical response was observed; however, due to small numbers of patients per tumor types and the overall heterogeneity of the STO cohort, an efficacy signal for the durvalumab and tremelimumab combination could not be established**.**

Reviewer's Comment:

The reviewer agrees with the Applicant that the sample size for the pediatric patients is too small to have a meaningful conclusion on efficacy of durvalumab and tremelimumab combination therapy in pediatric patients.

3.2 Population PK Analysis

3.2.1. Population PK for Durvalumab

Executive Summary

The FDA's Assessment:

The Applicant conducted a population pharmacokinetic (PopPK) modeling and simulation analysis of durvalumab. Previously, PopPK models of durvalumab was developed using pooled PK data from 7 clinical studies in adult patients. Durvalumab was characterized by a 2-compartment model with a time-dependent clearance. Significant covariates identified on clearance were albumin levels (ALB), creatinine CL, ECOG status, LDH, sex, body weight (WT), tumor types and combination therapy. WT and sex had also significant impact on central volume of distribution. However, none of these covariates were considered as clinically relevant since their impact on CL and V1 were less than or about 30%.

In the current submission, the Applicant seeks to update the approved labeling of IMFINZI (Durvalumab) based on the results of the study conducted on the pooled adult patients' data from the previous 7 studies with the addition of a new data in pediatric patients (D419EC00001). Initially, the previously established PopPK model of durvalumab with the same covariate model structures was adopted. And, due to the inclusion of pediatric data, age was additionally investigated as a covariate on selected parameters.

Using the updated final PopPK model, simulations were performed to compare the PK behavior of durvalumab between adult and pediatric patients. Based on the simulations, the Applicant concluded that durvalumab exposure was similar between adults at 20 mg/kg, pediatric patients with WT < 35 kg at 30 mg/kg and pediatric patients with WT ≥35 kg at 20 mg/kg. The current submission for updating the USPI were supported by these simulation results.

Overall, the review team generally agrees that the final PopPK model can adequately describe the observed data and the simulation results are reliable. Based on the simulation results, the exposures ($AUC_{0\text{-}28d}$ and C_{max}) in pediatric patients ≥ 35 kg receiving durvalumab 20 mg/kg every 4 weeks (Q4W) was comparable to exposures in adults receiving durvalumab 20 mg/kg Q4W. In pediatric patients (≥ 35 kg) receiving durvalumab 30 mg/kg Q4W, the exposure was

approximately 1.5-fold higher compared to exposure in adults receiving durvalumab 20 mg/kg Q4W. In pediatric patients < 35 kg receiving durvalumab 30 mg/kg Q4W, the exposure was similar to adults receiving durvalumab 20 mg/kg Q4W.

The review team has confirmed the statement related to exposure in pediatric patients in USPI section 8.4 and found them acceptable.

PPK Assessment Summary

General Information			
Objectives of PPK Analysis		To evaluate if the pharmacokinetic (PK) behavior of durvalumab is similar between adults and pediatric patients with advanced solid malignancies who have progressed or are refractory to standard therapies and for whom no standard of care treatments exists.	
Study Included		**Table 5**	
Dose(s) Included		**Table 5**	
Population Included		**Table 5**	
Population Characteristics	General	**Table 6 and Table 7**	
	Organ Impairment	**Table 7**	
	Pediatrics (if any)	**Table 6 and Table 7**	
No. of Patients, PK Samples, and BLQ		**Table 8**	
Sampling Schedule	Rich Sampling	**Table 5**	
	In ITT Population	**Table 5**	
Covariates Evaluated	Static	**Table 6 and Table 7**	
	Time-varying	**Table 6 and Table 7**	
Final Model		Summary • The selected final model: • Two-compartmental distribution model with time-dependent clearance. • Inter-subject variability (IIV) was characterized on clearance (CL), central volume (V1), peripheral volume (V2) and the	Acceptable. The review team generally agrees with the selected final model. Two-compartment distribution with time dependent clearance adequately described the data **(Figure 6)**. ETA terms were characterized on CL, V1, V2 and Tmax (maximum change for time-dependent clearance). The residual error model was characterized by a

	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, tumor type and age as statistically significant covariates on CL. • WT, sex and age had a statistically significant impact on V1 (Page 46).	combination of proportional and additive error model. The reviewer also agrees that while ALB, creatinine CL, ECOG status, LDH, sex, body weight, combination therapy, tumor type and age as statistically significant covariates on CL, body weight, sex and age had a statistically significant impact on V1.
Software and Version	The PopPK analysis was performed using NONMEM 7, Version 7.5 (ICON Development Solutions; Ellicott City, Maryland, USA) in Metworx as a computational environment, Perl Speaks NONMEM (PsN) Version 5.2 (Uppsala University, Sweden), and R (R Foundation for Statistical Computing, Vienna, Austria) (Page 35).	Acceptable.
Estimation Algorithm	First Order Conditional Estimation (FOCE)	Acceptable.
Model Structure	Durvalumab PK was characterized by a 2-compartmental distribution model with time-dependent clearance **(Figure 6)**.	Acceptable. The reviewer agrees that the utilized model structures employed for durvalumab adequately described the data **(Figure 6)**. The previous structural model was basically used with the identification age as a covariate on CL and V1

		due to the addition of new pediatric data.
Model Parameter Estimates	**Table 9**	Acceptable. The review team replicated the model and reproduced similar model parameter estimates as shown in **Table 10**.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All population parameters were well estimated, with the % RSE of fixed effects well below 20%. Moreover, the impacts of covariates on population parameter estimates were also reasonably estimated as %RSE were below 20% except ECOG, LDH, COMB, Tumortype on CL where the %RSE were above 20%. All the IIV and RV estimates were also below 20% RSE. Shrinkage values: CL = 15.8%, V1 = 29.8%; Tmax = 70%; V2 = 57.4% **(Table 9)**. Bootstrap values were comparable to the parameter estimates of the original dataset.	The review team agrees that uncertainty and variability measures of most estimated model parameters were within acceptable range (< 20%). The shrinkage values are also generally acceptable specially for critical model parameters (CL and V1) as they were < 30% suggesting that the parameter estimates are more reliable although parameters V2 and Tmax had greater shrinkage **(Table 9)**.
BLQ for Parameter Accuracy	Exclusion of BLQ is not expected to impact PopPK parameter estimates as only approximately 1.46% (221 of 15166) of total PK concentrations had BLQ **(Table 8)**.	The review team agrees that censoring of the BLQ (1.5%) was not expected to impact PopPK model parameter estimates given the size of the analyzed samples **(Table 8)**.
GOF, VPC	Initially, an external evaluation by means of pcVPC methodology was used to evaluate if the previous adult PopPK model was able to predict the new pediatric PK data. Due to most of the pediatric observations are within the prediction intervals of adult PopPK model, a similar PK	The review team generally agrees that the previously established adults' model was able to capture the pediatrics data. Also, the review team agrees that the GOFs and VPC plots indicated that the final model adequately described the observed data. The GOF plots lines of identify and

	behavior between adults and pediatrics was concluded **(Figure 7)**. Then, with the addition of pediatrics data, the model was rerun and the GOF and the pc-VPC plots were generated. The GOF plots **(Figure 8)** indicated an adequate description of the data by the model. Observations versus population and individual predictions were generally symmetrically distributed around the line of identity. In addition, the pc-VPC plots **(Figure 9)**, either for all durvalumab concentration data or stratified by studies or by age-groups, showed overall good coverage of simulated 95% prediction intervals to the observed 5th, 50th (median) and 95th percentiles of durvalumab concentrations (Page 82).	unity of the observed vs predicted concentrations generally align and divide the data nearly in equal parts **(Figure 8)**. The VPC plots show that the model and the model parameters produced simulated data that are similar to the observed data **(Figure 9)**.
Significant Covariates and Clinical Relevance	Using univariate approach, the only covariate that had an impact on CL and V1 was bodyweight (WT), with a maximum change of -46.9% [CL] and -56.9% [V1] for the 5th percentile of pediatric WT distribution **(Figure 11 and Figure 12)**. All other tested covariates changed CL and V1 by < 30%, therefore were not considered to be of clinical relevance in pediatrics. Based on this finding, only WT showed a significant impact on durvalumab CL and V1 in pediatric population, predicting a	The review team generally, agrees that while the impact of other covariates did not appear to be clinically significant, the impact of bodyweight on CL and V1 appears clinically significant in pediatric patients since the changes in CL and V1 were around 50% **(Figure 11 and Figure 12)**. This impact was predicted to cause an increase in exposure ($AUC_{,ss}$) by 89% **(Figure 13)**.

	significant increase of AUCss (+88.2%) in pediatric patients with lower WT **(Figure 13)**.	
Analysis Based on Simulation (optional)	Since pediatric population was administered by dose normalized by weight, simulation administering 20 and 30 mg/kg in three different populations were performed: pediatric patients with WT < 35kg, pediatric patients with WT ≥ 35kg, and adults. Results from the simulations showed that durvalumab drug exposure was similar between adults at 20 mg/kg, pediatric patients with WT < 35 kg at 30 mg/kg and pediatric patients with WT ≥35 kg at 20 mg/kg **(Figure 14 and Figure 15).**	The review team generally agrees that exposures were comparable between adult patients receiving 20 mg/kg and pediatric patients with the body weight < 35 kg receiving 30 mg/kg dose and pediatric patients with the body weight ≥ 35 kg receiving 20 mg/kg **(Figure 14 and Figure 15).**
Labeling Language	Description 8.4. Pediatric Use Based on population PK analysis, durvalumab systemic exposure in pediatric patients ≥ 35 kg receiving IMFINZI 20 mg/kg every 4 weeks was similar to exposure in adults receiving IMFINZI 20 mg/kg every 4 weeks, whereas in pediatric patients (≥ 35 kg) receiving IMFINZI 30mg/kg every 4 weeks, exposure was approximately 1.5-fold higher compared to exposure in adults receiving IMFINZI 20 mg/kg every 4 weeks. In pediatric patients < 35 kg receiving IMFINZI 30 mg/kg every 4 weeks, the systemic exposure was	Acceptable. Based on the simulation results, the review team generally agrees with the labeling descriptions included under section 8.4 Pediatric Use.

	similar to exposure in adults receiving IMFINZI 20 mg/kg every 4 weeks.	
12.3 PK	NA	NA

Table 5. Clinical Studies, Study Population, Dosing Regimen and PK Sampling included in the Analysis

Study Number Phase	Subject Population	Nr of Subj.	Durvalumab Dose and Regimen [a]	PK Sampling
CD-ON-MEDI4736-1108 "Study 1108" Phase 1/2	Advanced solid tumors	1012	Dose escalation phase: 0.1, 0.3, 1, 3, 10 mg/kg Q2W Dose exploration phase: 20 mg/kg Q4W Dose escalation cohort: 15 mg/kg Q3W	Q2W schedule: 1st dose: D1 (pre-dose and after end of infusion) [b], D3, D5, D10 2nd dose: D1 (pre-dose and after end of infusion) [b], D8 Then pre-dose and post-infusion for all even-numbered doses (4, 6, etc.) Q4W schedule: 1st dose: D1 (pre-dose and 3 h after end of infusion), D15 2nd dose: D1 (pre-dose and 3 h after end of infusion) All following doses: Pre-dose, after end of infusion [b], 2 h after end of infusion. Further samples taken at EOT, 30 days and 3 months after the last dose.
D4191C00003 "ATLANTIC" Phase 2	Locally advanced or metastatic NSCLC (Stage IIIB-IV)	443	10 mg/kg Q2W up to 12 months	Pre: W0, 4, 16, 28, 40, 52 Post: W0 Further samples taken 30 days and 3 months after the last dose.
D4191C00001 "PACIFIC" Phase 3	Locally advanced, unresectable NSCLC (Stage III)	473	10 mg/kg Q2W up to 12 months	Pre: W0, 4, and every 12 weeks thereafter (16, 28, etc.) Post: W0 An additional sample was taken 3 months after the last dose.
D419QC00001 "CASPIAN" Phase 3	Extensive stage SCLC	260	1500 mg Q3W	Pre: W0, 4, 16, 28, 40, 52 Post: W0
D419MC00004 (POSEIDON) Phase 3	Metastatic NSCLC	326	Durvalumab 1500 mg ± tremelimumab 75 mg IV Q3W concurrently with chemotherapy for 4 cycles. Durvalumab monotherapy was then continued Q4W. One further tremelimumab dose was administered in W16.	Durvalumab: Pre: D1, D22, W12 Post: D1
D4190C00022 (Study 22) Phase 1/2	Advanced Hepatocellular Carcinoma	~248	Durvalumab 20mg/kg or 1500 mg+ tremelimumab	Pre: W1D1, W13D1, W5D1 and W25D1. Post: W1D1, W13D1
D419CC00002 (HIMALAYA) Phase 3	First-line advanced Hepatocellular Carcinoma	~540	Durvalumab 1500 mg (Q4W) + tremelimumab 300mg x1 Or Durvalumab 1500 mg (Q4W) + tremelimumab 75mg x4	Durvalumab mono, Durvalumab and tremelimumab 75 mg×4, Durvalumab and tremelimumab 300 mg ×1 dose Pre: C1D1, C2D1, C4D1 Post: C4D1
D419EC00001 Phase 1/2	Pediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumors	~50 (29 dose finding + 21 dose expansion)	Durvalumab (20 or 30 mg/kg) in C1, followed by durvalumab (20 or 30 mg/kg) + tremelimumab (1 mg/kg) for 4 cycles.	Durvalumab: 4 PK samples (pre-dose and end-of -infusion on Day 1 and on Day 8 and Day 15 in C1) + 2 PK samples (Pre- and post-infusion) in C4, C6, C8, C10, and C12. Tremelimumab: 4 PK samples (pre-dose and end-of -infusion on Day 1 and on Day 8 and Day 15 in C2) + 2 PK samples (Pre- and post-infusion) in C3, C4, and C5 + random sample in C8.

[a] Doses < 3 mg/kg were excluded from population PK modeling (no dose-proportionality in low doses)
[b] For Cohort 1 subjects only, an additional sample was taken 2 hours after start of infusion
D = day; EOT = end of treatment; h = hour; NSCLC = non-small cell lung cancer; Post = post-dose sample collected within 5-10 min after end of infusion; Pre = Pre-dose sample, collected up to 60 min pre-dose; Q = every; SCLC = small cell lung cancer; W = week

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 17-9)

Table 6. Summary of Continuous Covariates Evaluated (baseline characteristics and laboratory values)

	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%)

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 37-8)

Table 7. Summary of Categorical Covariates Evaluated (baseline characteristics and laboratory values)

Individuals			
N	4100	4050	50
Sex			
Region of enrollment			
South America	76 (1.85%)	76 (1.88%)	--
Africa	25 (0.610%)	25 (0.617%)	--
Asia	1199 (29.2%)	1199 (29.6%)	--
Europe	1556 (38.0%)	1520 (37.5%)	36 (72.0%)
North America	1212 (29.6%)	1198 (29.6%)	14 (28.0%)
Other	32 (0.780%)	32 (0.790%)	--
Tumor Type			
Lung	2165 (52.8%)	2165 (53.5%)	--
Bladder	191 (4.66%)	191 (4.72%)	--
Liver	1263 (30.8%)	1263 (31.2%)	--
Solid	481 (11.7%)	431 (10.6%)	50 (100%)
Age Group			
<18	50 (1.22%)	--	50 (100%)
18-64	2220 (54.1%)	2220 (54.8%)	--
65-75	1379 (33.6%)	1379 (34.0%)	--
>=75	451 (11.0%)	451 (11.1%)	--
Renal Status			
Anti-drug antibody status post-baseline			
Negative	3225 (78.7%)	3207 (79.2%)	18 (36.0%)
Positive	135 (3.29%)	135 (3.33%)	--
Missing	740 (18.0%)	708 (17.5%)	32 (64.0%)
Primary indication			
NSCLC	1884 (46.0%)	1884 (46.5%)	--
Advanced solid tumor	712 (17.4%)	662 (16.3%)	50 (100%)
ES-SCLC	281 (6.85%)	281 (6.94%)	--
HCC	1223 (29.8%)	1223 (30.2%)	--
NCI scale - hepatic function			
Normal	2913 (71.0%)	2876 (71.0%)	37 (74.0%)
Mild	1088 (26.5%)	1078 (26.6%)	10 (20.0%)
Moderate	51 (1.24%)	51 (1.26%)	--
Severe	1 (0.0244%)	1 (0.0247%)	--
Missing	47 (1.15%)	44 (1.09%)	3 (6.00%)
Combination therapy			
Durvalumab	2407 (58.7%)	2407 (59.4%)	--
Durvalumab + Chemo [a]	1316 (32.1%)	1316 (32.5%)	--
Treme + Durva + Chemo	377 (9.20%)	327 (8.07%)	50 (100%)
Individuals by study			
Previous Studies	4050 (98.8%)	--	--
Pediatrics	50 (1.22%)	--	--

[a] durvalumab + tremelimumab for Study 22 and HIMALAYA and durvalumab + chemotherapy for study CASPIAN and POSEIDON

Chemo = chemotherapy; Durva = durvalumab; ES-SCLC = extensive stage small cell lung cancer; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; Treme = tremelimumab; -- = not applicable

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 38-40)

Table 8. Summary of the Population PK Analysis 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)

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 36)

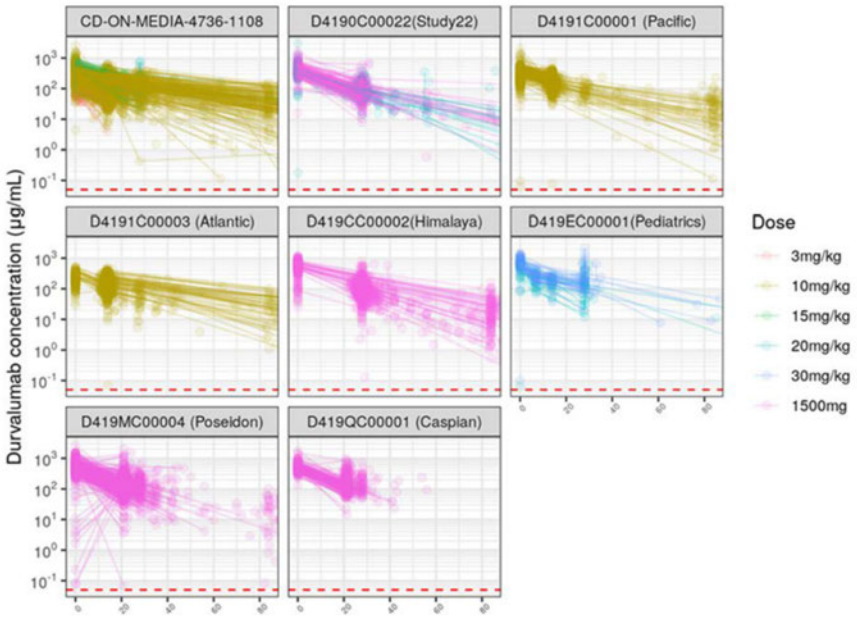
Table 9. Parameter Estimates and %RSE from Final Population PK Model

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	--	--	--	--
Parameter	**Estimate**	**RSE (%)**	**95% CI**	**Shrinkage (%)**	**Unit**
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]	--	--
COMB 2 on CL	-0.0358	50.6	[-0.0712 ; -0.000333]	--	--
Bodyweight on CL	0.395	7.82	[0.335 ; 0.456]	--	--
Tumortype 1 on CL	-0.0381	47.7	[-0.0737 ; -0.00251]	--	--
Tumortype 2 on CL	0.0724	49.4	[0.00223 ; 0.143]	--	--
Tumortype 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					
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

CI = confidence interval; CL = clearance; COMB1 = durvalumab+SOC or treme, 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; SOC = standard of care; TC50 = time to 50% change of CL over time; Tmax = maximum 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; -- = not applicable

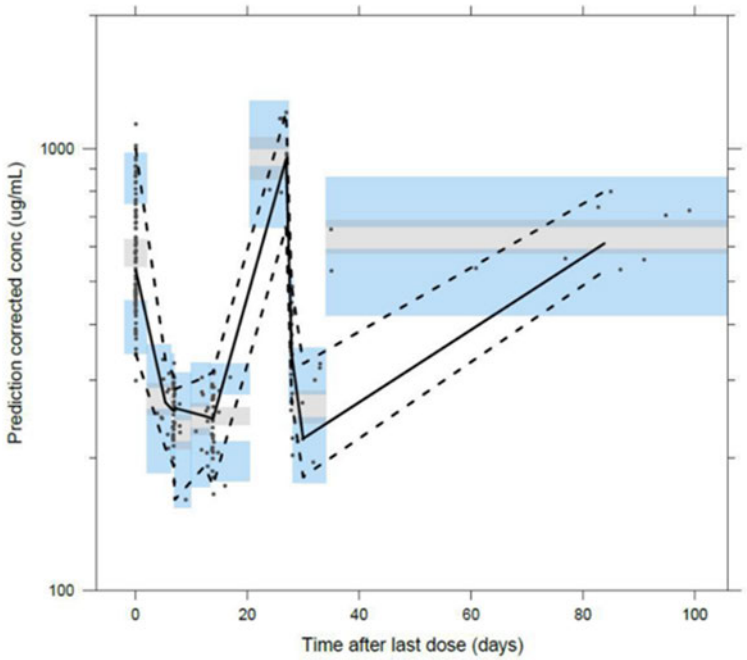
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 47-48)

Figure 6. Concentration vs Time Since Last Dose of Durvalumab by Study



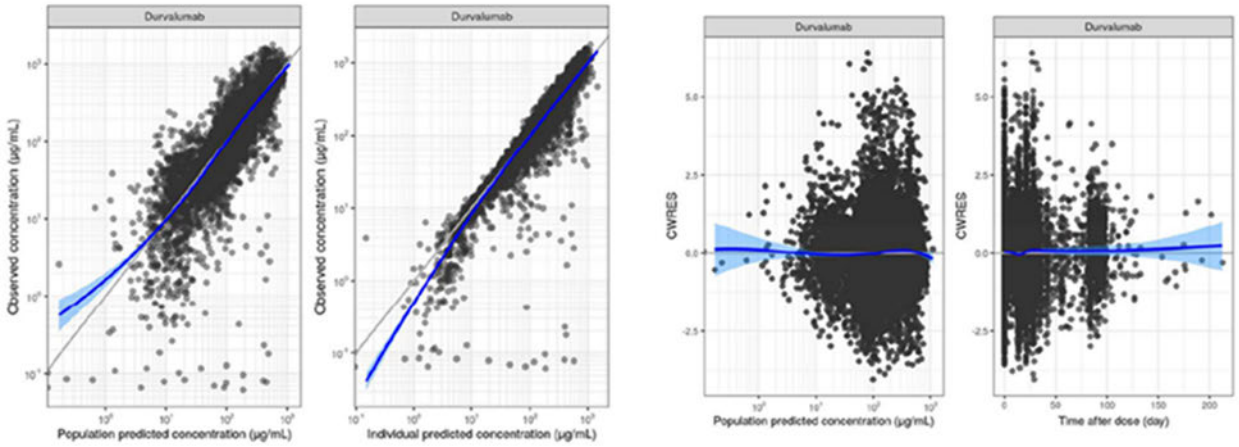
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 41)

Figure 7. Prediction-Corrected Visual Predictive Check Plot of the External Dataset (pediatric PK data) for the Previously Established Adult PopPK Model



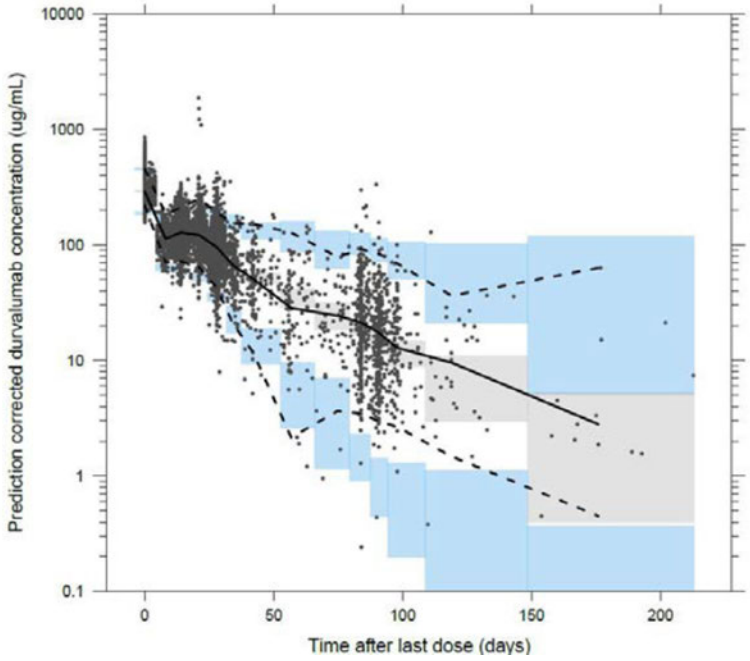
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 42)

Figure 8. Goodness-of-fit Plots for the Final Population PK Model



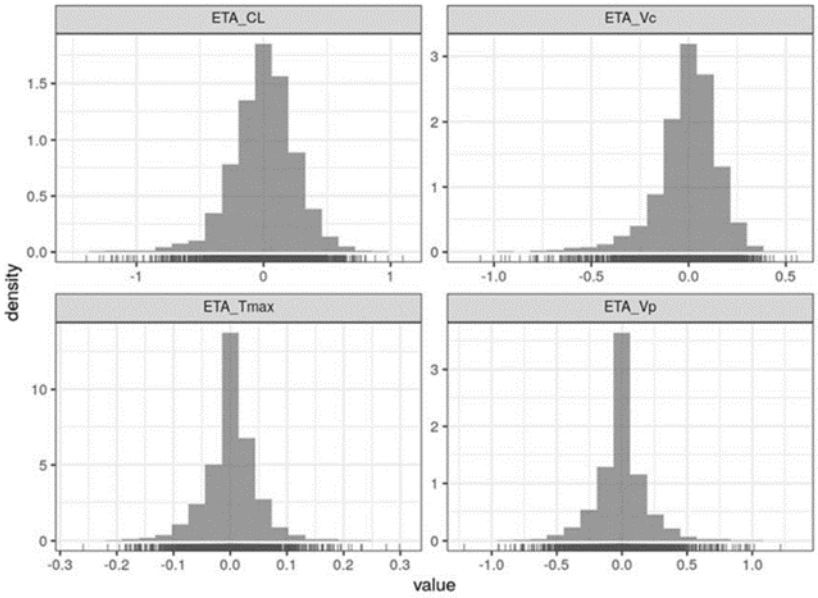
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 49-50)

Figure 9. Prediction-corrected Visual Predictive Check of Durvalumab Concentrations vs Time After Last Dose of the Final Model



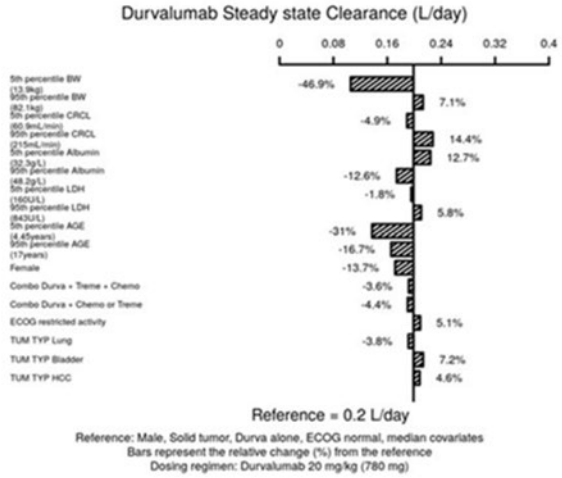
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 51)

Figure 10. Interindividual Random Effect Histograms for the Durvalumab Final Population PK Model



(Source: The Applicant's Pharmacometrics Report; D419EC00001; [Appendix C, Additional Tables and Figures); Page 13]

Figure 11. Impact of Pediatric Covariates on Clearance at Steady State -Tornado Plot

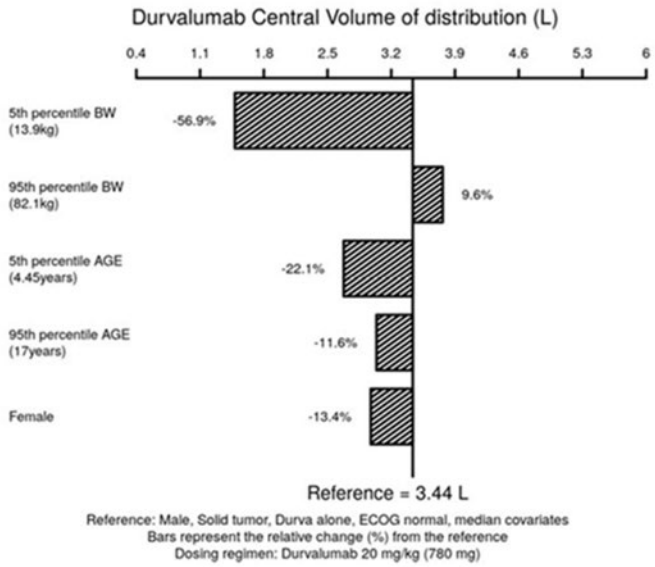


Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates)

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

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 52)

Figure 12. Impact of Pediatric Covariates on Durvalumab Central Volume - Tornado Plot

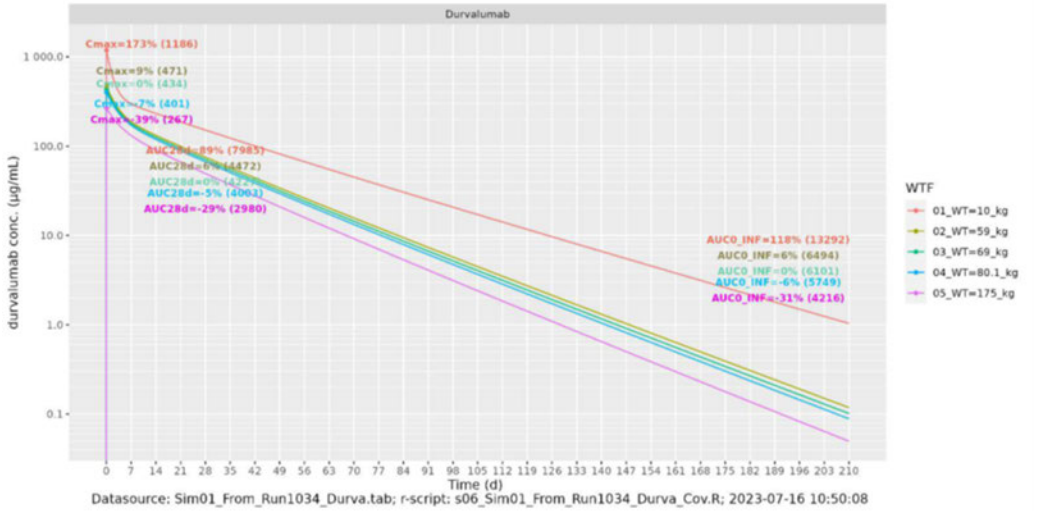


Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates)

Durva = durvalumab; ECOG = Eastern Cooperative Oncology Group

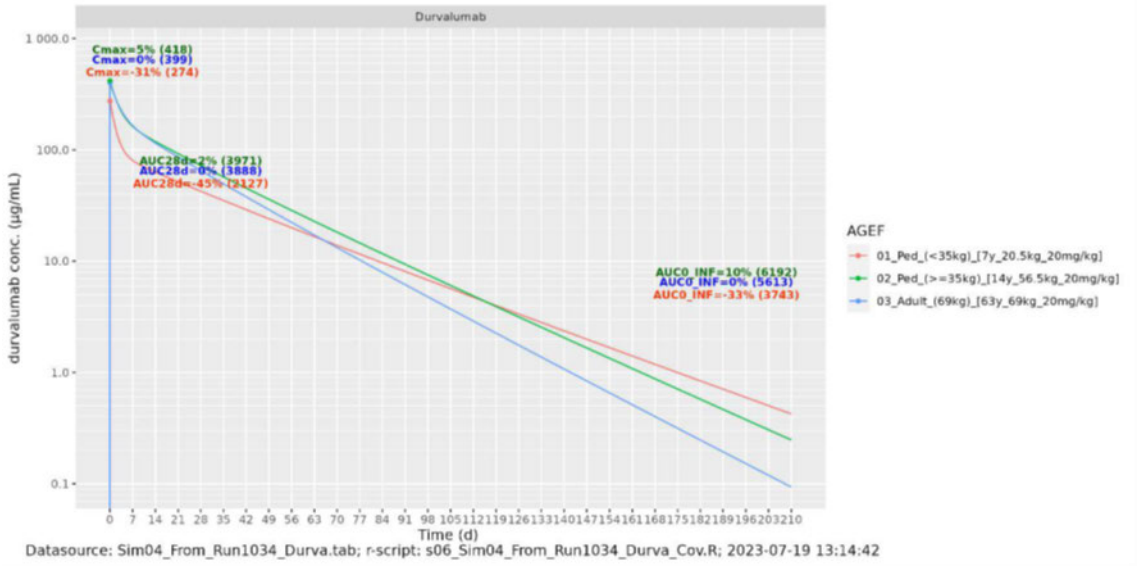
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 53)

Figure 13. Influence of Total Body Weight (WT) on Durvalumab PK Behavior at a Flat Dose of 1500 mg



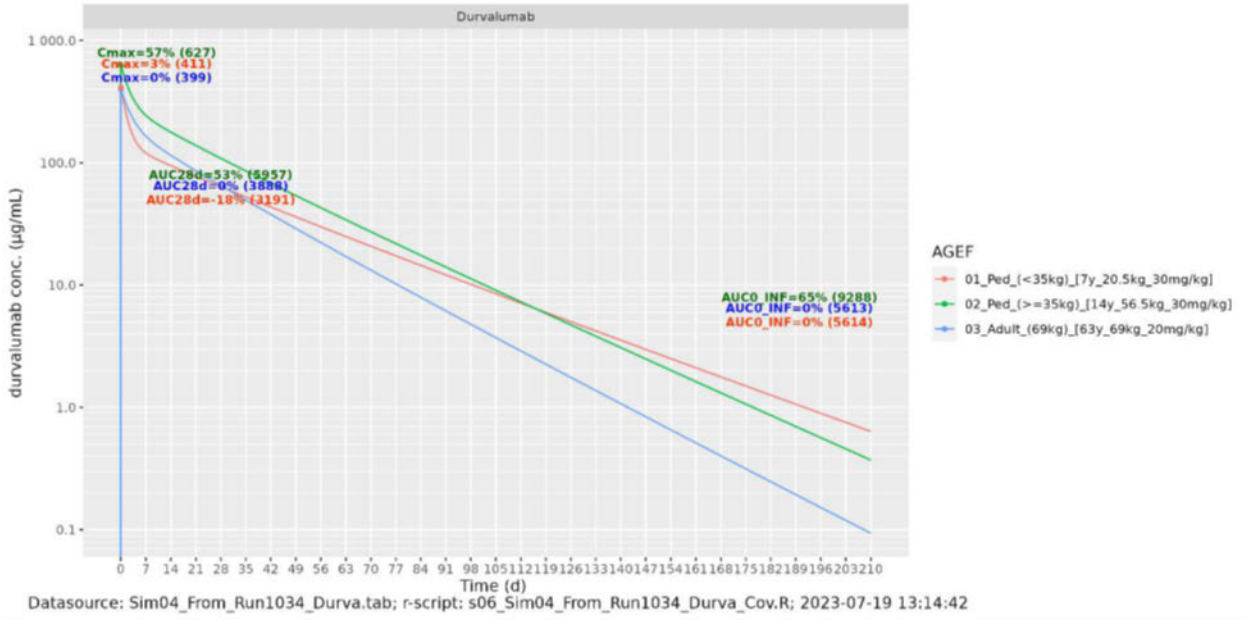
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 54)

Figure 14. Influence of Age and Body Weight on Durvalumab PK Behavior in Pediatric Population at a Dose of 20 mg/kg Compared with Adult Exposure at 20 mg/kg Dose



(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 59)

Figure 15. Influence of Age and Body Weight on Durvalumab PK Behavior in Pediatric Population at a Dose of 30 mg/kg Compared with Adult Exposure at 20 mg/kg Dose



(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 59)

PPK Review Issues

Upon the review, the following key PPK review issue was identified:

The Applicant had conducted body weight-based simulations using the adult and pediatric patient population to update the final model. To support the application of the model to external patient population and avoid any possible bias raising from data interpolation, stochastic simulations using virtual patient population from reliable database such as NHANES database were suggested by the review team and information request (IR) was issued to the Applicant.

In the IR, the Applicant was requested to conduct simulation comparing exposures between pediatric patients with body weight < 35 kg and pediatric patients with body weight ≥ 35kg receiving the dosage of 20 mg/kg Q4W or 30 mg/kg Q4W to adult patients receiving the dose 20 mg/kg Q4W using virtual patient population from reliable database such as NHANES.

Reviewer's Independent Analysis

Initially, the review team reran the Applicant's NONMEM based PopPK model on the pooled PK data obtained from the previous studies that involved adult patients in addition to the new data from pediatric patients. The model parameter estimates of the Applicant and the review team are in an agreement **(Table 10**). The standard goodness-of-fit diagnostic plots obtained from the reviewer's analysis are shown in (**Figure 16)**.

Based on the recommendation, using the model parameter estimates, the Applicant performed simulations exploring the influence of age and bodyweight exert on variability of the exposure parameters (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) of durvalumab (D=20 and 30 mg/kg) after 12 administrations Q4W in 500 virtual pediatric and adult populations where the demographic (age and weight) information were obtained from the NHANES database.

Briefly, 3 virtual populations of 500 subjects were created for simulations: pediatric patients with bodyweight < 35 kg, pediatric patients with bodyweight ≥ 35 kg and adult patients. **Table 11** summarizes the demographic data that were obtained after random selection for each subpopulation group, and then, these demographic data was used to construct the virtual datasets. The individual PK profile for each virtual subject included in the different dosing schedule groups were simulated and exposure parameters at steady state (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) were calculated for each patient using non-compartmental approach. Based on the simulations, the Applicant concluded comparable predicted exposure ($AUC_{,ss}$) between adults at 20 mg/kg, pediatric patients with WT < 35 kg at 30 mg/kg and pediatric patients with WT ≥35 kg at 20 mg/kg (7782, 6853 and 7494 (μg/mL)·d, respectively) **(Table 12)**.

The review team assessed the results and reproduced the stochastic simulations using the program codes and simulation datasets supplied by the Applicant. The simulation results were similar with the findings of the Applicant **(Figure 17)**.

Table 10. Comparison of Population PK Parameter Estimates between Reviewer's and Applicant's Analysis

Parameter [RSE%]	Reviewer's Analysis	Applicant's Analysis
CL (L/day)	0.286 [2%]	0.286 [2.16%]
V_1 (L)	3.45 [1%]	3.45[0.802%]
Q (L/day)	0.474 [6]	0.474 [5.78]
V_2 (L)	2.08 [3%]	2.08 [2.74%]
Tmax change CL	-0.346 [5]	-0.346 [4.52]
TC50 change CL	42.9 [13]	42.9 [13]
LAM change CL	1.00	1.00
Albumin on CL	-0.635[3]	-0.635[2.99]
Creatinine clearance on CL	0.147[15]	0.147[14.9]
ECOG status on CL	-0.0484 [22]	-0.0484 [21.8]
LDH on CL	0.0447 [23.0]	0.0447 [23.0]
Sex on CL	-0.137 [8]	-0.137 [8.46]
COMB1 on CL	-0.0438 [28]	-0.0438 [28.2]
COMB2 on CL	-0.0358 [51]	-0.0358 [50.6]
Bodyweight on CL	0.395 [8]	0.395 [7.82]
Tumortype 1 on CL	-0.0381 [48]	-0.0381 [47.7]
Tumortype 2 on CL	0.0724 [49]	0.0724 [49.4]
Tumortype 3 on CL	0.0465 [47]	0.0465 [46.6]
Age on CL	0.140 [19]	0.140 [19.2]
Sex on V_1	-0.134 [8]	-0.134 [7.75]
Bodyweight on V_1	0.525 [4]	0.525 [4.42]
Age on V_1	0.0941 [19]	0.0942 [19.2]

IIV for CL	0.0880 [3]	0.0880 [2.92]
IIV for V_1	0.0517 [3]	0.0517 [3.26]
IIV for V_2	0.209 [9]	0.209 [9.06]
IIV for T_{max}	0.0226 [19]	0.0226 [18.8]
Correlation V_1~CL	0.0366 [5]	0.0366 [5.61]
Proportional residual error (%)	0.246 [0.511]	0.246 [0.511]
Additive residual error (μg/mL)	3.22 [8.79]	3.22 [8.79]

(Source: Reviewer's Analysis based on dataset "d1_durva_d01_data_02_derived-nonmem_durvaadultped.csv")

Table 11. Summary of Age and Body Weight Selected for Each Virtual Population

Parameter	Population	Median	Min	Max	Mean	SD	Gmean	n
AGE	01_Peds_(1-16y)_wgt<35kg	5.0	1.0	13.0	4.8	2.9	3.7	500
AGE	02_Peds_(1-16y)_wgt>=35kg	13.0	4.0	16.0	12.4	2.5	12.1	500
AGE	03_Adults_(>=18y)	52.0	18.0	80.0	50.6	18.1	46.9	500
WT	01_Peds_(1-16y)_wgt<35kg	18.4	8.2	34.7	19.9	7.1	18.7	500
WT	02_Peds_(1-16y)_wgt>=35kg	54.5	35.1	138.7	58.9	19.0	56.4	500
WT	03_Adults_(>=18y)	79.8	32.6	254.3	84.0	24.7	80.8	500

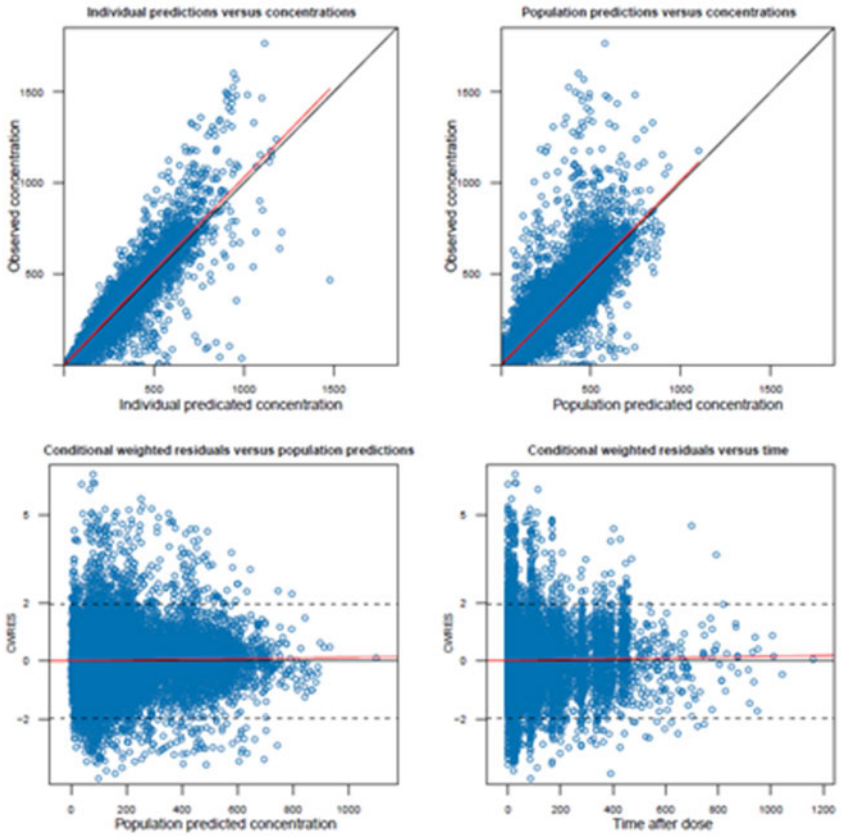
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Additional Simulation PK Report; Page 11)

Table 12. Simulated Exposure Parameters for Each Population after 20 or 30 mg/kg dose Q4W

Dose (mg/kg)	PK Param	Population	Median	Min	Max	Mean	SD	Geom mean	n
20	AUCss	01_Peds_(1-16y)_wgt<35kg	4,568.7	1,978.8	14,342.1	4,831.2	1,639.2	4,578.0	500
20	AUCss	02_Peds_(1-16y)_wgt>=35kg	7,494.5	3,037.6	21,961.8	8,100.6	3,019.8	7,606.5	500
20	AUCss	03_Adults_(>=18y)	7,782.5	3,015.8	27,880.4	8,349.8	3,142.7	7,834.0	500
20	Cmaxss	01_Peds_(1-16y)_wgt<35kg	390.2	200.8	934.3	403.6	106.6	390.5	500
20	Cmaxss	02_Peds_(1-16y)_wgt>=35kg	590.7	279.1	1,416.3	615.5	178.1	592.3	500
20	Cmaxss	03_Adults_(>=18y)	600.2	289.9	1,784.5	630.6	188.3	605.7	500
20	Cminss	01_Peds_(1-16y)_wgt<35kg	109.4	17.3	418.4	117.9	50.2	107.8	500
20	Cminss	02_Peds_(1-16y)_wgt>=35kg	164.6	21.6	604.1	180.0	86.2	161.0	500
20	Cminss	03_Adults_(>=18y)	160.5	17.5	719.1	173.6	87.0	153.9	500
30	AUCss	01_Peds_(1-16y)_wgt<35kg	6,853.0	2,968.2	21,513.1	7,246.7	2,458.7	6,866.9	500
30	AUCss	02_Peds_(1-16y)_wgt>=35kg	11,241.8	4,556.4	32,942.6	12,150.9	4,529.7	11,409.8	500
30	AUCss	03_Adults_(>=18y)	11,673.7	4,523.6	41,820.8	12,524.7	4,714.0	11,751.0	500
30	Cmaxss	01_Peds_(1-16y)_wgt<35kg	585.3	301.2	1,401.4	605.5	159.8	585.7	500
30	Cmaxss	02_Peds_(1-16y)_wgt>=35kg	886.0	418.6	2,124.4	923.2	267.2	888.5	500
30	Cmaxss	03_Adults_(>=18y)	900.3	434.8	2,676.8	945.9	282.5	908.6	500
30	Cminss	01_Peds_(1-16y)_wgt<35kg	164.0	26.0	627.5	176.9	75.3	161.8	500
30	Cminss	02_Peds_(1-16y)_wgt>=35kg	246.9	32.4	906.1	270.0	129.4	241.5	500
30	Cminss	03_Adults_(>=18y)	240.8	26.3	1,078.6	260.4	130.4	230.9	500

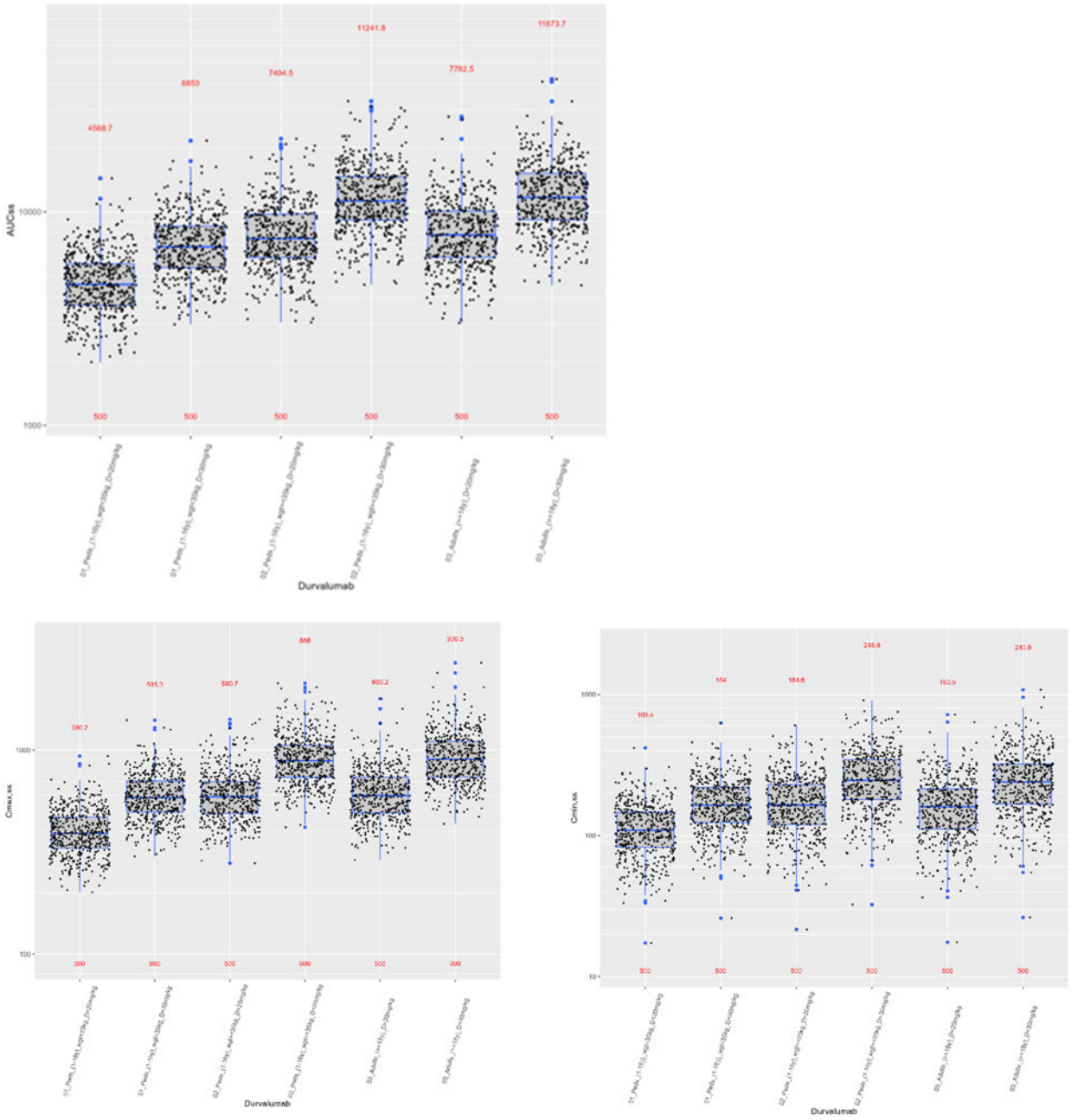
(Source: Reproduced by the Reviewer's Analysis from the Applicant's supplied program code)

Figure 16. Goodness-of-fit Plots in the Reviewer's Population PK Analysis



(Source: The Reviewer's Analysis)

Figure 17. Comparisons of Simulated Steady-State Exposure Parameters (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) after 20 or 30 mg/kg between Different Pediatric Weight-groups and Adult



(Source: Reproduced by the Reviewer's Analysis from the Applicant's supplied program code)

The FDA's Assessment:

The review team assessed and replicated the Applicant's PopPK analysis during this review based on several standard criteria including visual inspection of diagnostic plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time, pc-VPC plot and histograms of individual random effects, successful convergence of the minimization routine, plausibility of parameter estimates, and precision of parameter estimates. The reviewer also assessed the simulation performed based on the model.

The GOF plots indicated an adequate description of the data by the model suggesting that the model was able to predict the observed data since the observed versus population and individual predictions were generally symmetrically distributed around the line of identity **(Figure 8)**. In addition, the pc-VPC plots showed a reasonable coverage of simulated 95% prediction intervals to the observed 5th, 50th (median) and 95th percentiles of durvalumab concentrations **(Figure 9)**. The histograms of individual random effects were generally centered around zero suggesting the ETAs were drawn reasonably from a normal distribution **(Figure 10)**. The model rerun by the review team led to a successful convergence of the minimization routine indicating the stability of the model in estimating the model parameters. The estimated model parameters were assessed to be plausible. The precisions of most of the estimated parameters, including the critical parameters (CL and V1), were < 20% suggesting that the model parameter estimates were reliable **(Table 9)**.

The review team generally agrees with the Applicant's statement that simulated exposure was similar between adults at 20 mg/kg, pediatric patients with WT < 35 kg at 30 mg/kg and pediatric patients with WT ≥ 35 kg at 20 mg/kg **(Figure 14 and Figure 15)**.

In overall, the review team generally agrees with the following descriptions. Based on the simulation results, the exposures ($AUC_{0\text{-}28d}$ and C_{max}) in pediatric patients ≥ 35 kg receiving of durvalumab 20 mg/kg Q4W was similar to exposures in adults receiving durvalumab 20 mg/kg Q4W. In pediatric patients (≥ 35 kg) receiving durvalumab 30 mg/kg Q4W, exposure was approximately 1.5-fold higher compared to exposure in adults receiving durvalumab 20 mg/kg Q4W. In pediatric patients < 35 kg receiving durvalumab 30 mg/kg Q4W, the exposure was similar to adults receiving durvalumab 20 mg/kg Q4W.

3.2.2. Population PK for Tremelimumab

Executive Summary

The FDA's Assessment:

The Applicant conducted a population pharmacokinetic (PopPK) modeling and simulation analysis of tremelimumab. Previously, PopPK models of tremelimumab was developed using pooled PK data from 8 clinical studies in adult patients. Tremelimumab was characterized by a 2-compartmental distribution model with linear elimination (as a monotherapy) and with time-dependent elimination in combination therapy. 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%).

In the current submission, the Applicant seeks to update the labeling for IMJUDO (Tremelimumab-actl) based on the results of the study conducted on the pooled adult patients' data from the previous 8 studies with the addition of a new data from pediatric patients (D419EC00001). Initially, the previously established PopPK model of tremelimumab with the same covariate model structures was adopted. And, due to the inclusion of pediatric data, age was additionally investigated as a covariate on selected parameters.

Using the updated final PopPK model, simulations were performed to compare the PK behavior of tremelimumab between adult and pediatric patients. Based on the simulations, the Applicant concluded that predicted tremelimumab exposure at 1 mg/kg was similar between pediatric patients with WT ≥ 35 kg and adults and predicted drug exposure was lower than adults for pediatric patients with WT < 35kg. The current submission for updating the labeling were supported by these simulation results.

In overall, the review team generally agrees that the final PopPK model can adequately describe the observed data and the simulation results are reliable. Based on the simulation results, exposures ($AUC_{0\text{-}28d}$ and C_{max}) in pediatric patients ≥ 35 kg were within the range of the values previously observed in adults given the same weight-based dose, whereas the systemic exposure in pediatric patients < 35 kg was lower than that of adults. The review team has confirmed the statement related to exposure in pediatric patients in USPI section 8.4 and found them acceptable.

PPK Assessment Summary

General Information		
Objectives of PPK Analysis		To evaluate if the pharmacokinetic behavior of tremelimumab is similar between adults and pediatric patients with advanced solid malignancies who have progressed or are refractory to standard therapies and for whom no standard of care treatments exists.
Study Included		**Table 13**
Dose(s) Included		**Table 13**
Population Included		**Table 13**
Population Characteristics	General	**Table 14 and Table 15**
	Organ Impairment	**Table 3**
	Pediatrics (if any)	**Table 14 and Table 15**
No. of Patients, PK Samples, and BLQ		**Table 16**
Sampling Schedule	Rich Sampling	**Table 13**
	In ITT Population	**Table 13**
Covariates	Static	**Table 14 and Table 15**

Evaluated	Time-varying	**Table 14 and Table 15**	
Final Model		Summary The selected 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 (Page 71).	Acceptability The reviewer generally agrees with the selected final model. Two-compartment distribution with linear and time dependent elimination adequately described the data **(Figure 18)**. ETA terms were characterized on CL, V1, V2 and Tmax (maximum change for time-dependent clearance). The residual error model was characterized by a combination of proportional and additive error model. The reviewer also agrees that while body weight, albumin level, sex, combination therapy, and primary indication were identified to significantly impact CL, body weight and sex showed statistically significant impact on V1.
Software and Version		The PopPK analysis was performed using NONMEM 7, Version 7.5 (ICON Development Solutions; Ellicott City, Maryland, USA) in Metworx as a computational environment,	Acceptable

	Perl Speaks NONMEM (PsN) Version 5.2 (Uppsala University, Sweden), and R (R Foundation for Statistical Computing, Vienna, Austria) (Page 35).	
Estimation Algorithm	First Order Conditional Estimation (FOCE)	Acceptable
Model Structure	Tremelimumab PK was characterized by 2-compartmental distribution model with both linear and time-dependent elimination (for monotherapy, elimination was linear only) **(Figure 18)**.	Acceptable. The reviewer agrees that the utilized model structure employed for tremelimumab adequately described the data **(Figure 18)**. The previous structural model was basically used with the addition of new pediatric data.
Model Parameter Estimates	**Table 17**	Acceptable. The reviewer replicated the model and reproduced similar model parameter estimates as shown in the **Table 18**.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	**Table 17**	The reviewer agrees that uncertainty and variability measures of all estimated model parameters were within acceptable range (< 20%). The ETA shrinkage values are also generally acceptable (< 30%) suggesting that the parameter estimates are more reliable although shrinkage of ETA on Tmax was 65% **(Table 17)**.
BLQ for Parameter Accuracy	From a total of 7611 serum PK samples, 286(3.76%) below the lower limit of quantification (LLOQ) samples were excluded from current analysis **(Table 16)**.	The reviewer agrees that censoring of the BLQ (3.76%) was not expected to impact PopPK model parameter estimates given the size of the analyzed samples **(Table 16)**.
GOF, VPC	Initially, an external evaluation by means of	The reviewer generally agrees that the previously

	pcVPC methodology was used to evaluate if the previous adult PopPK model was able to predict the new pediatric PK data. Due to most of the pediatric observations are within the prediction intervals of adult PopPK model, a similar PK behavior between adults and pediatrics was concluded **(Figure 19)**. Then, with the addition of pediatrics data, the model was rerun and the GOF and the VPC plots were generated. The GOF plots **(Figure 20)** indicated an adequate description of the data by the model. Observations versus population and individual predictions were generally symmetrically distributed around the line of identity. In addition, the pc-VPC plots **(Figure 21)**, either for all tremelimumab concentration data, showed overall good coverage of simulated 95% prediction intervals to the observed 5th, 50th (median) and 95th percentiles of tremelimumab concentrations (Page 84).	established adults' model was able to capture the pediatrics data. Also, the reviewer agrees that the GOFs and pc-VPC plots indicated that the final model adequately described the observed data. The GOF plots lines of identify and unity of the observed vs predicted concentrations generally align and divide the data nearly in equal parts **(Figure 20)**. The pc-VPC plots shows that generally the model and the model parameters produced simulated data that are similar to the observed data **(Figure 21)**.
Significant Covariates and Clinical Relevance	Using univariate approach, only bodyweight had an impact on CL and V1 with a maximum change of -51% [CL] and -54.1% [V1] at the 5% of bodyweight (WT) percentile. With the exception of low WT, all other tested covariates are considered to have a minimal impact (< 30%) on	The reviewer generally agrees that while the impact of other covariates did not appear to be clinically significant, the impact of body weight on CL and V1 appear clinically significant since the changes in CL and V1 of pediatric patients with lower bodyweight percentiles were above 50%

	model parameters CL and V1 in pediatrics **(Figure 23 and Figure 24)**. Based on this finding, only WT showed a significant impact on tremelimumab CL and V1 in pediatric population, predicting a significant increase of AUC_{0-28d} (+100.6%) in pediatric patients with lower WT (Page 83) **(Figure 25)**.	**(Figure 23 and Figure 24)**. This impact was predicted to cause an increase in exposure (AUC_{0-28d}) by 100.6% **(Figure 25)**.
Analysis Based on Simulation	Model simulations showed that tremelimumab exposure at 1 mg/kg was similar between pediatric patients with WT ≥ 35 kg and adults and drug exposure was lower than adults for pediatric patients with WT< 35kg **(Figure 26)**.	The reviewer generally agrees that with the 1 mg/kg dose, the simulated exposures (AUC_{0-28d} and C_{max}) were similar between adult patients and pediatric patients with the body weight ≥ 35, but these exposures were predicted to be lower than adults in pediatric patients with the body weight < 35 kg **(Figure 26)**.
Labeling Language	Description 8.4. Pediatric Use Tremelimumab-actl systemic exposure in pediatric patients ≥ 35 kg was within the range of the values previously observed in adults given the same weight-based dose, whereas the systemic exposure in pediatric patients < 35 kg was lower than that of adults.	Acceptable. The reviewer generally agrees with the description that based on the simulation results, exposures (AUC_{0-28d} and C_{max}) in pediatric patients ≥ 35 kg was within the range of the values previously observed in adults given the same weight-based dose, whereas the systemic exposure in pediatric patients < 35 kg was lower than that of adults.
12.3 PK	NA	NA

Table 13.Clinical studies, study population, dosing regimen and PK sampling included in the analysis

Study Number Phase	Subject Population	Nr of Subj.	Tremelimumab Dose and Regimen [a]	PK Sampling
D4190C00010 "Study 10" Phase 1	UBC and other solid tumors	372	1 mg/kg or 3mg/kg IV Q4W×4 or ×7, then Q12W (Combination with durvalumab)	Pre: W 0, 1, 2, 4, 8, 12, 24, 36 and 48 Post: W 0, 2, 12, 24, EOT, EOT+90
D4880C00003 "DETERMINE"Phase 2b	PMM	374	10 mg/kg Q4W×7, then Q12W (Monotherapy)	Pre: W 0, 4, 12, 24, and 48 Post: W 0, 12, EOT, EOT+90
D4884C00001 "BASKET" Phase 2	UBC, TNBC, and PDAC	61	750 mg IV Q4W×7, then Q12W×2 75 mg IV Q4W×4 w/durvalumab (Monotherapy; if PD, switch to durvalumab or combination with durvalumab)	Pre: W 0, 4, 12, and 24 Post: W 0, 12, and 24
D419MC00004 (POSEIDON) Phase 3	Metastatic NSCLC	326	Durvalumab 1500 mg ± tremelimumab 75 mg IV Q3W concurrently with chemotherapy for 4 cycles. Durvalumab monotherapy was then continued Q4W. One further tremelimumab dose was administered in W16.	Pre: D1, D22, W12 Post: D1 One additional tremelimumab sample 3 months after tremelimumab discontinuation
D4190C00022 (Study 22) Phase 1/2	Advanced HepatocellularCarcinoma	~216	Durvalumab 20mg/kg or 1500 mg+ tremelimumab (1mg/kg, 10mg/kg, 75, 300 & 750 mg)	Pre: W1D1, W13D1, W5D1 and W25D1. Post: W1D1, W13D1 Arm D of Part 2B and Arm D of Part 3 Pre: W1D1, Post: W1D1 Anytime: W5D1,
Study Number Phase	**Subject Population**	**Nr of Subj.**	**Tremelimumab Dose and Regimen [a]**	**PK Sampling**
D419CC00002 (HIMALAYA) Phase 3	First-line advanced Hepatocellular Carcinoma	~540	Durvalumab 1500 mg (Q4W) + tremelimumab 300mg x1 Or Durvalumab 1500 mg (Q4W) + tremelimumab 75mg x4	Durvalumab and tremelimumab 75 mg×4 Pre: C1D1, C2D1, C4D1 Post: C4D1 Durvalumab and tremelimumab 300 mg×1 dose Pre: C1D1, C2D1 Post: C1D1
D419EC00001 Phase 1/2	Pediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumors	~50 (29 dose finding + 21 dose expansion)	Durvalumab (20 or 30 mg/kg) in C1, followed by durvalumab (20 or 30 mg/kg) + tremelimumab (1 mg/kg) for 4 cycles.	Durvalumab: 4 PK samples (pre-dose and end-of -infusion on Day 1 and on Day 8 and Day 15 in C1) + 2 PK samples (Pre- and post-infusion) in C4, C6, C8, C10, and C12. Tremelimumab: 4 PK samples (pre-dose and end-of -infusion on Day 1 and on Day 8 and Day 15 in C2) + 2 PK samples (Pre- and post-infusion) in C3, C4, and C5 + random sample in C8.

[a] Doses < 3 mg/kg were excluded from population PK modeling (no dose-proportionality in low doses)
BTC = biliary tract cancer; EC = esophageal cancer; EOT = end of treatment; EOT+(X) = (X) days after end of treatment; IV = intravenous; NSCLC = non-small cell lung cancer; PD = progression of disease; PDAC = pancreatic ductal adenocarcinoma; PMM = pleural or peritoneal malignant mesothelioma; Pre = Pre-dose sample, to be collected up to 60 min pre-dose; Post = post-dose sample, to be collected within 5-10 minutes after end of infusion; Q = every; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple-negative breast cancer; UBC = urothelial bladder cancer; W = week

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 19-21)

Table 14. Summary of Continuous Covariates Evaluated (baseline characteristics and laboratory values)

	Total	Previous Studies	Pediatrics
Individuals			
N	2448	2406	42
Body weight (kg)			
Mean (SD)	71.3 (17.1)	71.8 (16.6)	44.3 (21.1)
Median (IQR)	69.8 (59.5-81.3)	70.0 (60.0-81.5)	39.5 (28.3-59.0)
Min-max	10.0-149	34.0-149	10.0-99.0
Missing	6 (0.245%)	6 (0.249%)	0 (0%)
Age (years)			
Mean (SD)	61.8 (12.6)	62.7 (10.8)	12.0 (4.05)
Median (IQR)	64.0 (56.0-70.0)	64.0 (57.0-70.0)	12.5 (9.50-15.8)
Min-max	1.00-87.0	18.0-87.0	1.00-17.0
Missing	0 (0%)	0 (0%)	0 (0%)
Albumin (g/L)			
Mean (SD)	38.5 (9.08)	38.5 (9.13)	41.8 (4.67)
Median (IQR)	39.0 (35.0-42.0)	39.0 (35.0-42.0)	42.0 (39.0-45.0)
Min-max	0.300-396	0.300-396	31.9-52.0
Missing	39 (1.59%)	33 (1.37%)	6 (14.3%)
Lactate Dehydrogenase (IU/L)			
Mean (SD)	300 (274)	300 (271)	337 (418)
Median (IQR)	229 (180-338)	228 (180-340)	236 (205-299)
Min-max	12.0-5570	12.0-5570	130-2650
Missing	63 (2.57%)	58 (2.41%)	5 (11.9%)
Creatinine clearance (mL/min)			
Mean (SD)	97.8 (325)	88.0 (32.0)	677 (2480)
Median (IQR)	83.1 (64.9-106)	82.6 (64.8-105)	129 (91.8-172)
Min-max	22.5-13500	22.5-299	58.4-13500
Missing	34 (1.39%)	32 (1.33%)	2 (4.76%)
s-PDL1 (pg/mL)			
Mean (SD)	136 (51.8)	136 (51.8)	NA (NA)
Median (IQR)	128 (98.7-168)	128 (98.7-168)	NA (NA-NA)
Min-max	67.1-349	67.1-349	--
Missing	2021 (82.6%)	1979 (82.3%)	42 (100%)
Neutrophil-to-Lymphocyte Ratio			
Mean (SD)	4.80 (6.64)	4.81 (6.68)	3.71 (3.54)
Median (IQR)	3.51 (2.40-5.55)	3.53 (2.41-5.56)	2.61 (1.55-3.92)
Min-max	0-253	0-253	0.452-18.0
Missing	125 (5.11%)	123 (5.11%)	2 (4.76%)

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

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 62-3)

Table 15. Summary of Categorical Covariates Evaluated (baseline characteristics and laboratory values)

	Total	Previous Studies	Pediatrics
Individuals			
N	2448	2406	42
Sex			
Male	1742 (71.2%)	1722 (71.6%)	20 (47.6%)
Female	706 (28.8%)	684 (28.4%)	22 (52.4%)
Race			
White	1512 (61.8%)	1485 (61.7%)	27 (64.3%)
Black	56 (2.29%)	54 (2.24%)	2 (4.76%)
Asian	776 (31.7%)	773 (32.1%)	3 (7.14%)
Native Hawaiian or Other Pacific Islander	8 (0.327%)	8 (0.333%)	--
American Indian/Alaskan Native	16 (0.654%)	15 (0.623%)	1 (2.38%)
Other	78 (3.19%)	69 (2.87%)	9 (21.4%)
Multiple	1 (0.0408%)	1 (0.0416%)	--
Missing	1 (0.0408%)	1 (0.0416%)	--
Region of enrollment			
Europe	834 (34.1%)	804 (33.4%)	30 (71.4%)
Asia	732 (29.9%)	732 (30.4%)	--
North America	800 (32.7%)	788 (32.8%)	12 (28.6%)
South America	33 (1.35%)	33 (1.37%)	--
Africa	15 (0.613%)	15 (0.623%)	--
Other	34 (1.39%)	34 (1.41%)	--
Primary indication			
Advanced Non-small Cell Lung Cancer	749 (30.6%)	707 (29.4%)	42 (100%)
Bladder Cancer	213 (8.70%)	213 (8.85%)	--
Triple-negative breast-cancer	43 (1.76%)	43 (1.79%)	--
Pleural	358 (14.6%)	358 (14.9%)	--
BTC	64 (2.61%)	64 (2.66%)	--
EC	58 (2.37%)	58 (2.41%)	--
HPV positive anogenital cancer, MSI-H CRC, Ovarian, STS	146 (5.96%)	146 (6.07%)	--
Peritoneal	16 (0.654%)	16 (0.665%)	--
HCC	801 (32.7%)	801 (33.3%)	--
Tumor type			
Lung	676 (27.6%)	676 (28.1%)	--
Bladder	213 (8.70%)	213 (8.85%)	--
Missing	12 (0.490%)	12 (0.499%)	--
Liver	801 (32.7%)	801 (33.3%)	--
Solid	372 (15.2%)	330 (13.7%)	42 (100%)
Malignant mesothalioma	374 (15.3%)	374 (15.5%)	--
Eastern Cooperative Oncology Group performance status			
Normal activity	1052 (43.0%)	1052 (43.7%)	--
Restricted activity	1350 (55.1%)	1350 (56.1%)	--
In bed less than or equal to 50% of the time	2 (0.0817%)	2 (0.0831%)	--
Missing	44 (1.80%)	2 (0.0831%)	42 (100%)
Smoking status			
Current	149 (6.09%)	147 (6.11%)	2 (4.76%)
Former	647 (26.4%)	647 (26.9%)	--
Never	253 (10.3%)	213 (8.85%)	40 (95.2%)
Missing	1399 (57.1%)	1399 (58.1%)	--
Age Group			
<18	42 (1.72%)	--	42 (100%)
18-64	1246 (50.9%)	1246 (51.8%)	--
>=65	1160 (47.4%)	1160 (48.2%)	--
Renal Status			
Normal	997 (40.7%)	966 (40.1%)	31 (73.8%)
Mild	977 (39.9%)	970 (40.3%)	7 (16.7%)
Moderate	436 (17.8%)	434 (18.0%)	2 (4.76%)
Severe	38 (1.55%)	36 (1.50%)	2 (4.76%)
Anti-drug antibody status post-baseline			
Negative	1505 (61.5%)	1476 (61.3%)	29 (69.0%)
Positive	165 (6.74%)	165 (6.86%)	--
Missing	778 (31.8%)	765 (31.8%)	13 (31.0%)

(Source: The Applicant's Pharmacometrics Report; D419EC0000; Page 64-6)

Table 16. Summary of the Population PK Analysis 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)

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 62)

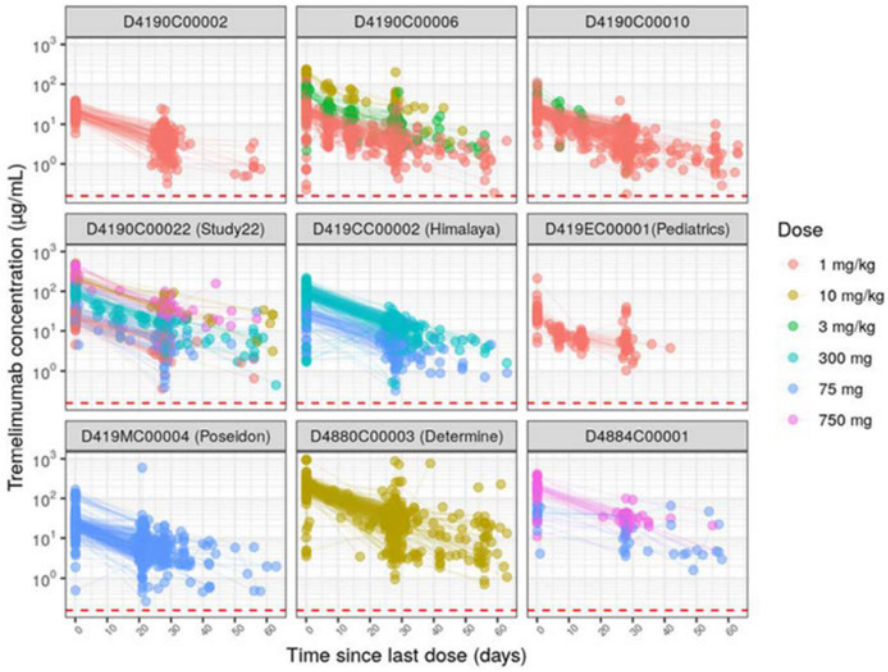
Table 17. Parameter Estimates and %RSE from Final Population PK Model

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	--
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

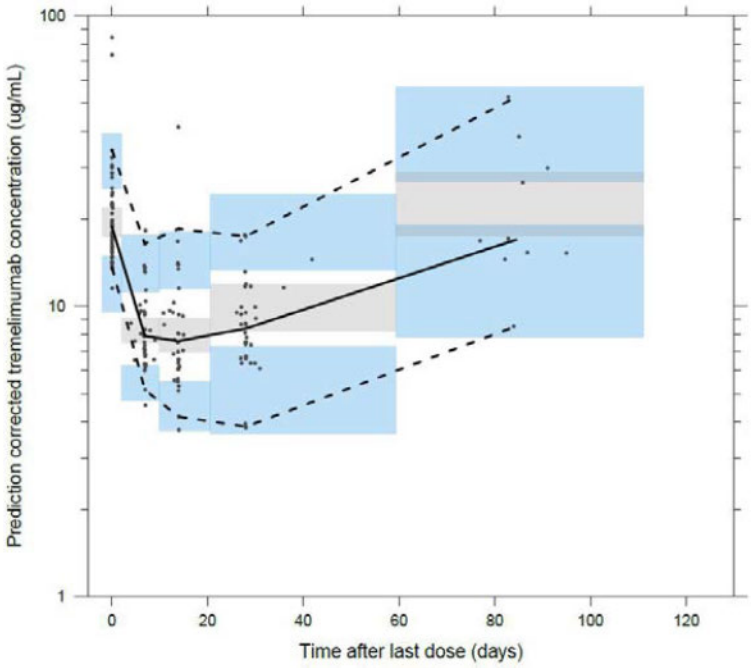
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 72-3)

Figure 18. Concentration vs Time Since Last Dose of Tremelimumab by Study



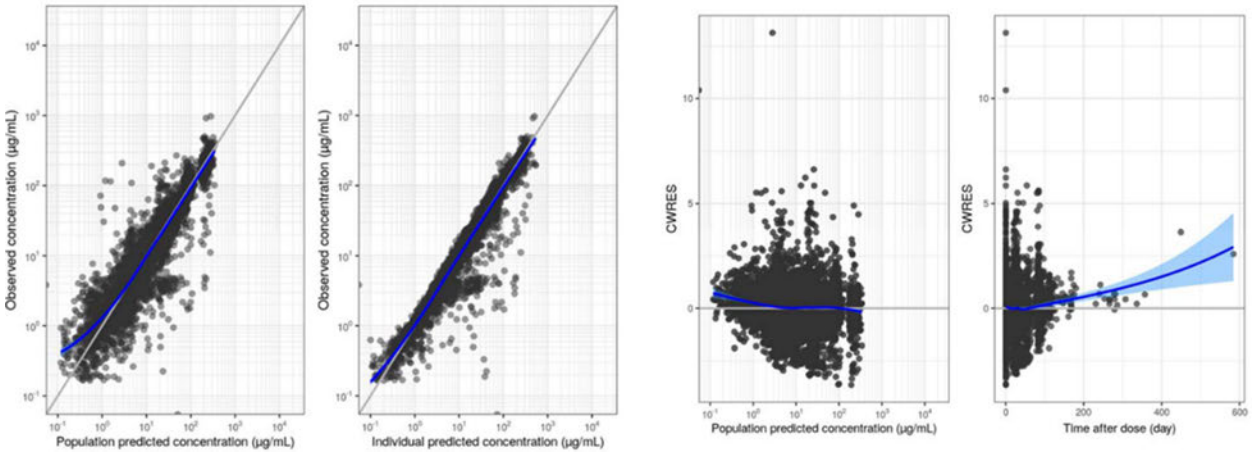
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 67)

Figure 19. Prediction-Corrected Visual Predictive Check Plot of the External Dataset (pediatric PK data) for the Previously Established Adult PopPK Model



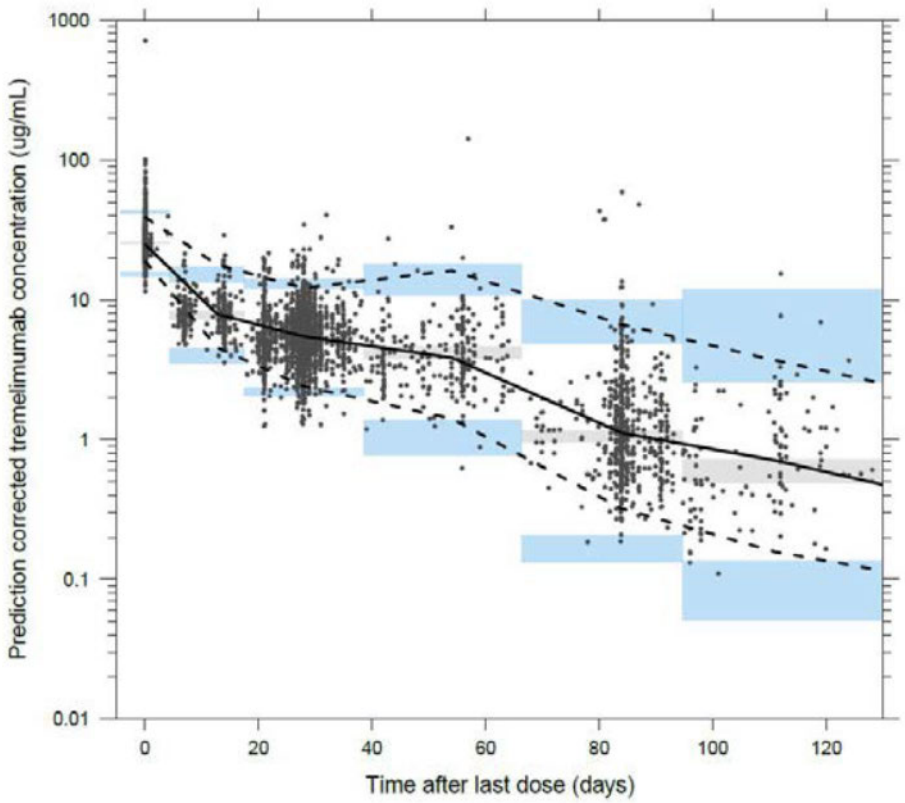
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 68)

Figure 20. Goodness-of-fit Plots for the Final Population PK Model



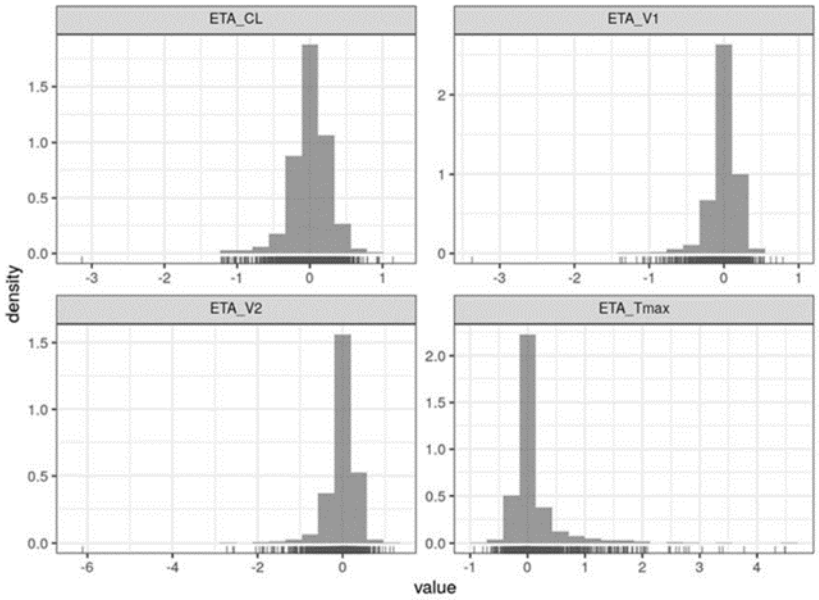
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 73-4)

Figure 21. Prediction-corrected Visual Predictive Check of Tremelimumab concentrations vs time after last dose of the final model



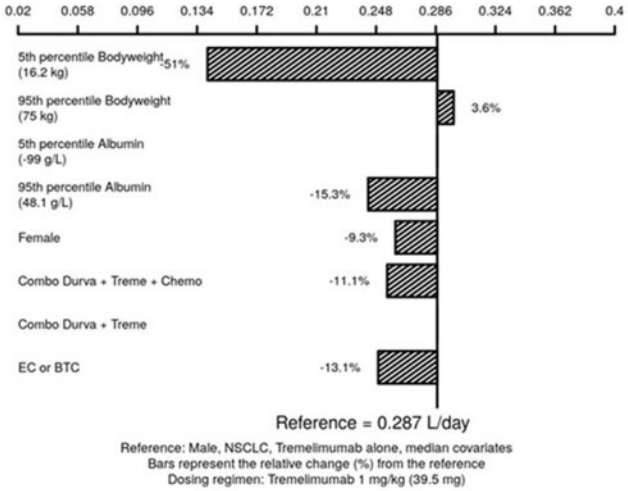
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 75)

Figure 22. Interindividual Random Effect Histograms for the Durvalumab Final Population PK Model



(Source: The Applicant's Pharmacometrics Report; D419EC00001; Appendix F, Additional Tables and Figures; Page 13)

Figure 23. Impact of Pediatric Covariates on Tremelimumab Clearance at Cycle 1 - Tornado Plot



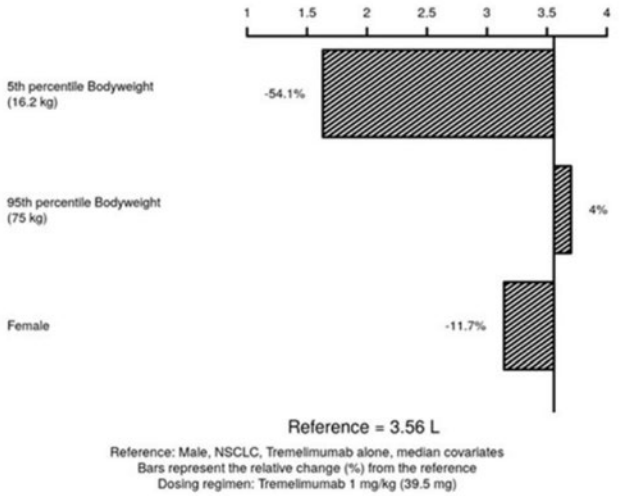
Covariate effects were expressed as a percentage change from the typical value of the reference patient

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

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 76)

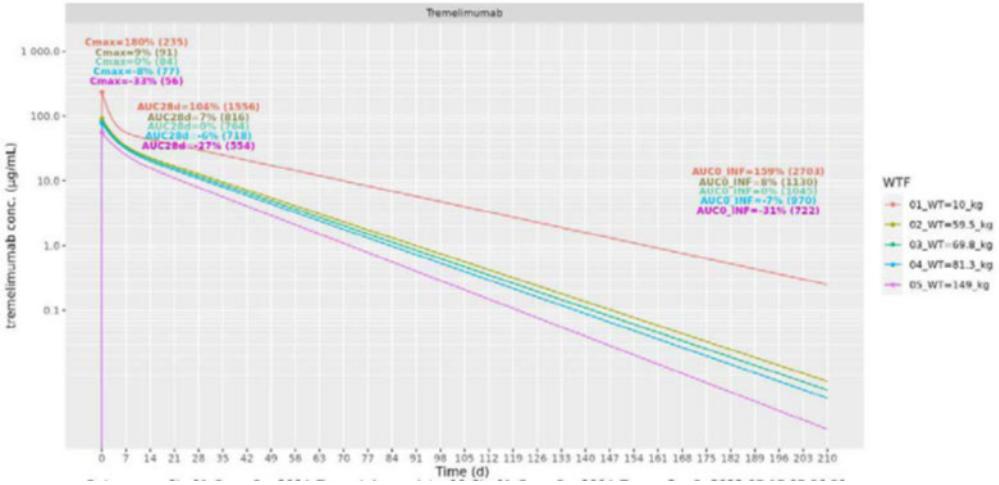
Figure 24. Impact of Pediatric Covariates on Tremelimumab Central Volume –Tornado Plot



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

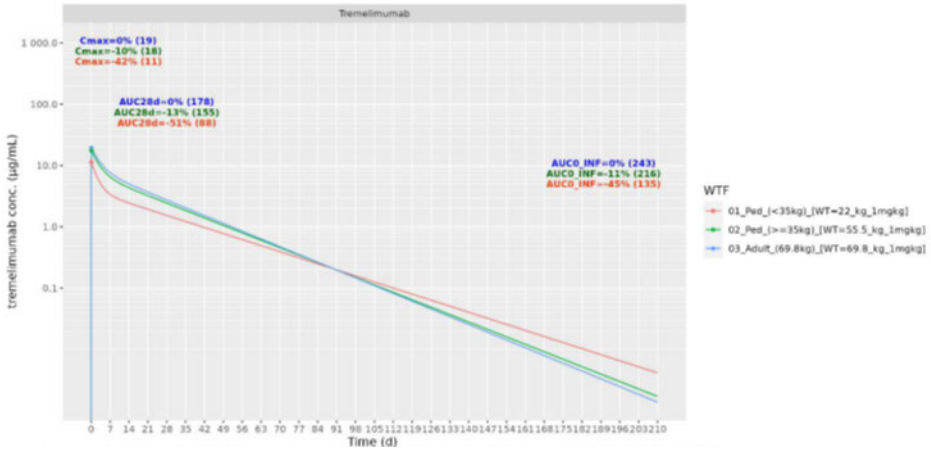
(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 77)

Figure 25. Influence of Total Body Weight (WT) on Tremelimumab PK Behavior at a Flat Dose of 300 mg



(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 78)

Figure 26. Influence of Bodyweight (WT) on Tremelimumab PK Behavior in Pediatric Population at Dose of 1 mg/kg



(Source: The Applicant's Pharmacometrics Report; D419EC00001; Page 80)

PPK Review Issues

Upon the review, the following key PPK review issue was identified:

> The Applicant had conducted body weight-based simulations using the adult and pediatric patient population used to update the final model. To support the application of the model to external patient population and avoid any possible bias raising from data interpolation, stochastic simulations using virtual patient population from reliable database such as NHANES database were suggested by the reviewers and information request (IR) was issued to the Applicant.
>
> In the IR, the Applicant was requested to conduct simulation comparing tremelimumab exposure between pediatric patients with body weight < 35kg, pediatric patients with body weight ≥ 35kg and adult patients receiving the dose 1 mg/kg every 4 weeks using virtual patient population from reliable database such as NHANES.

Reviewer's Independent Analysis

Initially, the reviewer replicated the Applicant's NONMEM based PopPK model on the pooled PK data obtained from the previous studies that involved adult patients in addition to the new data from pediatric patients. The model parameter estimates of the Applicant and the reviewer were compared and they were found to be similar **(Table 18)**. The standard goodness-of-fit diagnostic plots obtained from the reviewer's analysis were found to be generally acceptable **(Figure 27)**.

Based on the recommendation, using the model parameter estimates, the Applicant performed simulations exploring the influence of age and weight exert on variability of the exposure parameters (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) of tremelimumab (D=1 mg/kg) after 12 administrations every four weeks (Q4W) in 500 virtual pediatric and adult population where the demographic (age and bodyweight) information were obtained from the NHANES database **(Table 19)**.

Briefly, 3 virtual populations of 500 subjects were created for simulations: pediatric patients with bodyweight < 35kg, pediatric patients with bodyweight ≥ 35kg and adult patients. **Table 19** summarizes the demographic data that were obtained after random selection for each subpopulation group, and then, these demographic data was used to construct the virtual datasets. The individual PK profile for each virtual subject included in the different dosing schedule groups were simulated and exposure parameters at steady state (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) were calculated for each patient using non-compartmental approach. Based on the simulations, the Applicant concluded comparable predicted exposures (AUC_{ss} was 266 and 317 (µg/mL)*d, respectively) between pediatric patients with WT ≥ 35 kg and adults at 1 mg/kg while for pediatric patients with WT < 35kg, exposure (AUC_{ss} was 151 (µg/mL)*d) was lower than adults **(Table 20)**.

The reviewers assessed the results and reproduced the stochastic simulations using the program codes and simulation datasets supplied by the Applicant. The simulation results were similar with the findings of the Applicant **(Figure 28)**.

Table 18. Comparison of population PK Parameter Estimates between the Reviewer's and the Applicant's Analysis.

Parameter [RSE%]	The Reviewer's Analysis	The Applicant's Analysis
CL (L/day)	0.288 [1]	0.288[1.23]
V_1 (L)	3.57[1]	3.57[1.06]
Q (L/day)	0.423 [9]	0.425 [1.03]
V_2 (L)	2.5 [4]	2.51 [2.59%]
Tmax change CL	-0.145 [15]	-0.145 [14.7]
TC50 change CL	65.6 [11]	68.0 [9.16]
Albumin on CL	-0.791[6]	-0.793[5.61]
Sex on CL	-0.0927 [19]	-0.0927 [19.4]
COMB0 on CL	0	0
COMB2 on CL	-0.111 [3]	-0.111 [16.7]
Bodyweight on CL	0.488 [7]	0.489 [7.09]
Primary Tumor 6-7 on CL	-0.131 [19]	-0.131 [19.4]
Sex on V_1	-0.117[14]	-0.117[14]
Bodyweight on V_1	0.534 [5]	0.534 [5.41]
IIV for CL	0.11 [4]	0.110 [3.6]
IIV for V_1	0.066 [2]	0.066 [1.68]

IIV for V_2	0.224 [12]	0.224 [11.4]
IIV for Tmax	1.34 [11]	1.35 [10.5]
Covariance V_1~ V_2	0.117[7.1]	0.117[7.1]
Covariance V_2~CL	0.0905[9.35]	0.0905[9.35]
Covariance V_1~CL	0.0654 [3.65]	0.0654 [3.65]
Proportional residual error (%)	0.283 [1]	0.283 [0.788]
Additive residual error (μg/mL)	0.37 [1]	0.370 [0.923]

(Source: Reviewer's Analysis based on dataset "d2_treme_d01_data_02_derived-nonmem_tremeadultped.csv")

Table 19. Summary of Age and Body Weight Selected for Each Virtual Population.

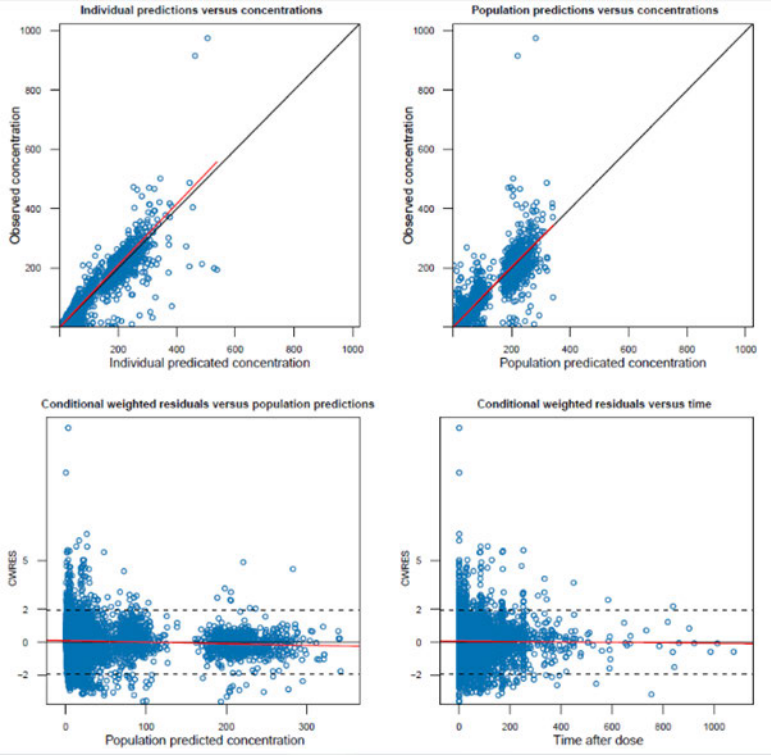
Parameter	Population	Median	Min	Max	Mean	SD	Gmean	n
AGE	01_Peds_(1-16y)_wgt<35kg	5.0	1.0	13.0	4.8	2.9	3.7	500
AGE	02_Peds_(1-16y)_wgt>=35kg	13.0	4.0	16.0	12.4	2.5	12.1	500
AGE	03_Adults_(>=18y)	52.0	18.0	80.0	50.6	18.1	46.9	500
WT	01_Peds_(1-16y)_wgt<35kg	18.4	8.2	34.7	19.9	7.1	18.7	500
WT	02_Peds_(1-16y)_wgt>=35kg	54.5	35.1	138.7	58.9	19.0	56.4	500
WT	03_Adults_(>=18y)	79.8	32.6	254.3	84.0	24.7	80.8	500

(Source: The Applicant's Pharmacometrics Report; D419EC00001; Additional Simulation PK Report; Page 11)

Dose (mg/kg)	PK Param	Population	Median	Min	Max	Mean	SD	Geom mean	n
1	AUCss	01_Peds_(1-16y)_wgt<35kg	150.61	50.30	2,184.80	185.01	157.25	158.45	500
1	AUCss	02_Peds_(1-16y)_wgt>=35kg	266.46	87.64	4,201.39	327.95	296.47	280.09	500
1	AUCss	03_Adults_(>=18y)	317.31	86.95	5,988.20	404.22	428.54	337.22	500
1	Cmaxss	01_Peds_(1-16y)_wgt<35kg	13.82	6.19	85.06	15.25	6.87	14.23	500
1	Cmaxss	02_Peds_(1-16y)_wgt>=35kg	23.04	9.70	158.44	25.23	11.86	23.58	500
1	Cmaxss	03_Adults_(>=18y)	27.20	11.27	222.98	30.13	16.60	27.83	500
1	Cminss	01_Peds_(1-16y)_wgt<35kg	3.19	0.71	77.53	4.38	5.38	3.41	500
1	Cminss	02_Peds_(1-16y)_wgt>=35kg	5.04	0.92	149.29	7.15	10.27	5.32	500
1	Cminss	03_Adults_(>=18y)	5.74	0.95	212.94	8.72	14.91	6.18	500

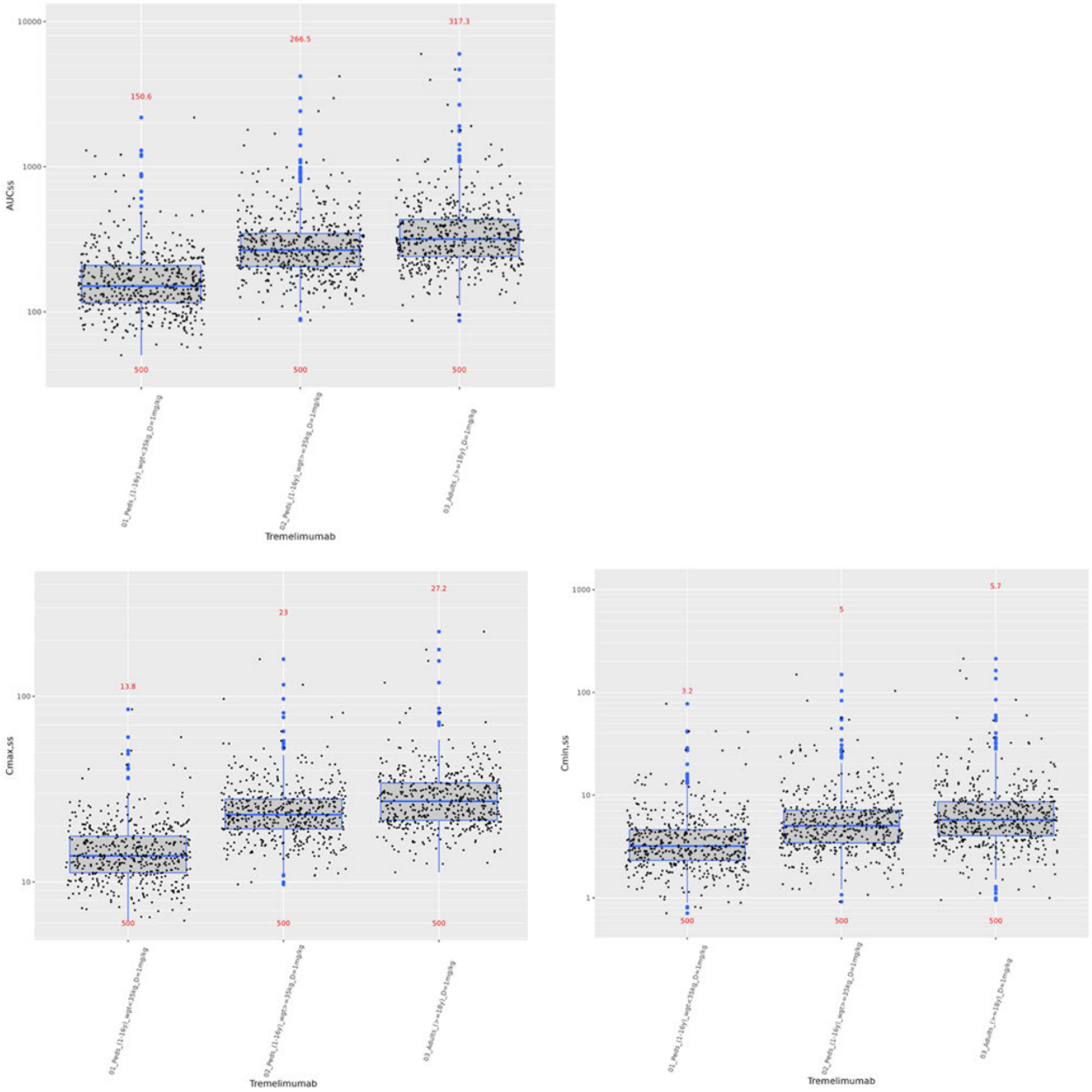
Table 20. Simulated Exposure Parameters for Each Population after 1 mg/kg dose Q4W
(Source: Reproduced by the Reviewer's Analysis from the Applicant's supplied program code)

Figure 27. Goodness-of-fit Plots in Reviewer's Population PK Analysis.



(Source: The Reviewer's Analysis)

Figure 28. Comparisons of Simulated Steady-State Exposure Parameters (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) after 1 mg/kg between Different Pediatric Weight-groups and Adult.



(Source: Reproduced by the Reviewer's Analysis from the Applicant's supplied program code)

The FDA's Assessment:

The reviewer assessed the Applicant's PopPK analysis during this review based on several standard criteria including visual inspection of diagnostic plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time, pc-VPC plot and histograms of individual random effects, successful convergence of the minimization routine, plausibility of parameter estimates, and precision of parameter estimates. The reviewer also assessed the simulation performed based on the model.

The GOF plots indicated an adequate description of the data by the model suggesting that the model was able to predict the observed data since the observed versus population and individual predictions were generally symmetrically distributed around the line of identity **(Figure 20)**. In addition, the pc-VPC plots showed a reasonable coverage of simulated 95% prediction intervals to the observed 5th, 50th (median) and 95th percentiles of tremelimumab concentrations **(Figure 21)**. The histograms of individual random effects were generally centered around zero suggesting the ETAs were drawn reasonably from a normal distribution **(Figure 22)**. The model replicated by the reviewer led to a successful convergence of the minimization routine indicating the stability of the model in estimating the model parameters. The estimated model parameters were assessed to be plausible. The precisions of most of the estimated parameters, including the critical parameters (CL and V1), were < 20% suggesting that the model parameter estimates were reliable **(Table 17)**.

The reviewer generally agrees with the Applicant's statement that with the 1 mg/kg dose, the simulated exposures ($AUC_{0\text{-}28d}$ and C_{max}) were generally similar between adult patients and pediatric patients with the body weight ≥ 35, but these exposures were predicted to be lower than adults in pediatric patients with the body weight < 35 kg **(Figure 28)**.

In overall, the reviewer generally agrees with the description that based on the simulation results, exposures ($AUC_{0\text{-}28d}$ and C_{max}) in pediatric patients ≥ 35 kg were within the range of the values previously observed in adults given the same weight-based dose, whereas the systemic exposure in pediatric patients < 35 kg was lower than that of adults.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAIRAT SABIT
06/13/2024 03:01:41 PM

HONG ZHAO
06/13/2024 03:12:22 PM

STACY S SHORD
06/13/2024 03:37:17 PM