CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761069Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	761069
Link to EDR	\\CDSESUB1\evsprod\BLA761069\
Submission Date	10/13/2016
Submission Type	Priority review
Brand Name	IMFINZI
Generic Name	Durvalumab
Dosage Form and Strength	500 mg/10mL or 120 mg/2.4mL solution in single-dose vial
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)
Applicant	AstraZeneca
Associated INDs	IND 112249 IND (b) (4)
OCP Review Team	Yuhong Chen, MD & Ph.D., Stacy Shord, Pharm.D. Xiaofeng Wang, Ph.D., Jingyu Yu, Ph.D. Sarah Dorff, Ph.D., Rosane Charlab Orbach, Ph.D.
OCP Final Signatory	Atiqur Rahman, Ph.D. Director, Division of Clinical Pharmacology V

Table of Contents

1. EXECUTIVE SUMMARY 3
   1.1 Recommendations 3
   1.2 Post-Marketing Requirements and Commitments 4
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT 4
   2.1 Pharmacology and Clinical Pharmacokinetics 4
   2.2 Dosing and Therapeutic Individualization 6
      2.2.1 General dosing 6
      2.2.2 Therapeutic individualization 6
   2.3 Outstanding Issues 6
   2.4 Summary of Labeling Recommendations 6
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW 6
   3.1 Overview of the Product and Regulatory Background 6
   3.2 General Pharmacology and Pharmacokinetic Characteristics 7
   3.3 Clinical Pharmacology Review Questions 9

Reference ID: 4065384

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? 12
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors? 12
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy? 13
4. APPENDICES 13
4.1 Summary of Bioanalytical Method Validation and Performance 13
4.2 Clinical PK and PD Assessments 14
4.3 Population PK Analyses 18
4.3.1 Results of Applicant's Population PK Analysis 18
4.3.2 Reviewer's Analysis 29
4.4 Exposure-Response Analyses 31
4.4.1 Applicant's Exposure-Efficacy Analyses 31
4.4.2 Applicant's Exposure-Safety Analyses 36

Reference ID: 4065384

1. EXECUTIVE SUMMARY

The applicant seeks approval of durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) [redacted] (b) (4) Durvalumab is a humanized, immunoglobulin G1 monoclonal antibody targeting the programmed death-ligand 1 (PD-L1). The proposed dose is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks (Q2W). The efficacy and safety of durvalumab in this population was supported by an expansion cohort included in the first-in-human trial Study 1108 with additional safety data provided from Study ATLANTIC, which evaluated the efficacy and safety of durvalumab in non-small cell lung cancer.

No dedicated clinical pharmacology studies were conducted. The applicant submitted reports describing the population pharmacokinetic (PK) and exposure-response (ER) analyses, immunogenicity evaluation and the effect of durvalumab on the QT/QTc interval. The population PK analyses showed a number of factors have no clinically important effect on the PK parameters of durvalumab administrated at the proposed dose of 10 mg/kg including body weight, soluble PD-L1 (sPD-L1), creatinine clearance (CLcr), and renal or hepatic impairment. No ER relationship is evident for safety and the ER relationship for efficacy is inconclusive, because the expansion cohort included only one dose level without a comparator.

About 3.3 percent of patients (37 of 1124) tested positive for post-baseline anti-drug antibodies (ADA) in Study 1108; however, the assay is not reliable and the assessment is questionable at this time.

The proposed dose of 10 mg/kg Q2W is approvable from clinical pharmacology perspective. The review focuses on the clinical pharmacology aspects mentioned above.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of the BLA 761069 from a clinical pharmacology perspective, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The results of Study 1108, a single-arm, open-label, multicenter trial that included an expansion cohort to assess the safety of durvalumab in patients with locally advanced or metastatic urothelial carcinoma (N = 182), demonstrated a confirmed objective response rate (ORR) of 17.0% (95% CI: 11.9%, 23.3%). The patient subgroup classified as PD-L1 high (if immune cells (IC) involve >1% of the tumor area, tumor cells (TC) ≥25% or IC ≥25%; if IC involve <1% of the tumor area, TC >25% or IC 100%) based on the finalized VENTANA PD-L1 (SP263) immunohistochemistry (IHC) assay (N = 128) had an ORR of 19.0% compared to 3.6% for the patient subgroup classified as PD-L1 low or negative (did not meet criterion for

	PD-L1 high). Treatment differences, if clinically relevant, support a complementary diagnostic and labeling related to PD-L1 subgroup findings.
General dosing instructions	The proposed dose is 10 mg/kg as an intravenous infusion over 60 minutes administered Q2W. The applicant states that the dose selection was based on the following factors: manageable safety profile, clinically meaningful efficacy in the proposed patient population, and achievement of desired target trough concentration of 50 µg/mL in > 95% patients based on non-clinical and clinical data.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended for intrinsic factors, including renal and hepatic impairment.
Immunogenicity	The applicant reports 3.3 percent of patients (37 of 1124) tested positive for anti-drug antibodies (ADA); however, the immunogenicity assay may not be reliable. Several post marketing commitments+- will be issued to further validate the assay.
Labeling	Generally acceptable. A statement describing time-varying PK of durvalumab was added to section 12.3. The review team made recommendations for specific content and formatting changes.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was administered in the two trials that provided data to demonstrate the activity of durvalumab in the proposed population and the safety of durvalumab in patients with cancer.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Durvalumab is a monoclonal antibody (mAb) that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity.

Pharmacokinetics: Durvalumab demonstrated linear PK at dose greater than or equal to 3 mg/kg. Based on data from 1418 patients who received doses of 0.1 mg/kg to 10 mg/kg of durvalumab Q2W, 15 mg/kg of durvalumab for every 3 weeks or 20 mg/kg of durvalumab for

every 4 weeks, the population PK analyses show that durvalumab clearance (CL) decreases over time, with a mean maximal reduction (coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%). The following are the geometric mean (CV%) steady-state PK parameter estimates to be included in the labeling.

- Clearance of 8.2 mL/h (37.3%).
- Volume of distribution at steady-state (Vss) of 5.6 L (17.1%).
- Half-life of 17 days (23.2%).
- Time to reach steady-state concentrations was 16 weeks after a dose of 10 mg/kg Q2W and the systemic accumulation based on area under the curve (AUC), was approximately 4.3-fold.

Population Pharmacokinetic Analysis: Population PK analyses showed that the following factors have no clinically significant effects on the PK parameters of durvalumab administrated at the proposed dose: body weight, serum albumin, sex, post-baseline antidrug antibody (ADA), performance status, sPD-L1 level at baseline, creatinine clearance (CLcr), lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, tumor type, age, race, mild and moderate renal impairment (defined as CLcr 30 mL/min to 89 mL/min), and mild hepatic impairment (defined as total bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN) and aspartate transaminase $\leq 2.5 \times$ ULN). No dose individualization is recommended for these covariates.

Exposure or Dose-Response Relationship for Efficacy and Safety at 10 mg/kg Q2W: There appears to be no evident E-R relationships identified for safety (such as Grade 3 or greater adverse events (AEs), adverse events of special interest, and AEs leading to discontinuation); however, the event rate for safety was relatively low. The ER analysis is not conclusive for efficacy (i.e., ORR), because the expansion cohort included only one dose level without a comparator.

Immunogenicity: The percentages of evaluable patients who tested positive for ADA were 3.3% (37 of 1124) in Study 1108, and 4.3% (16 of 373) in Study ATLANTIC. The presence of ADAs did not have a clinically significant impact on PK based on population PK analysis, but their impact on safety or efficacy was not evaluable due to the small number of patient samples testing positive for treatment-emergent ADA and relatively low ORR.

Drug interaction potential*:* No drug interaction studies were conducted. No cytochrome P450 based drug interactions are anticipated as durvalumab is a mAb.

QT prolongation: There is no evidence from nonclinical or clinical data to suggest that durvalumab has the potential to delay ventricular repolarization.

PD-L1 status: PD-L1 expression was classified as high (45.3%), low (43.8%), or unknown (10.9%) in tumor tissue from patients enrolled in Study 1108 using the finalized assay (N = 128). Although clinical activity was observed across PD-L1 expression subgroups, a higher ORR was observed in the subgroup of patients with high PD-L1 expression (19.0% vs. 3.6% in the low subgroup).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 10 mg/kg Q2W as an intravenous infusion over 60 min. The dose selection was based on the following factors: manageable safety profile, clinically meaningful efficacy in the proposed patient population, and achievement of desired target trough concentration of 50 μg/mL in > 95% patients based on non-clinical and clinical data that suggests > 99% target saturation is expected with this concentration. Exposure-efficacy relationship for the primary endpoint (ORR) couldn't be adequately characterized with the limitation that only one dose was administered to the patients with UC and no comparator was included in the expansion cohort.

2.2.2 Therapeutic individualization

No dose individualization is recommended for the following intrinsic factors based on population PK analysis: body weight, serum albumin, sex, post-baseline ADA, performance status, sPD-L1 in serum, CLcr, LDH level, and tumor type, age, race, renal function (mild to moderate), and hepatic function (mild).

No drug interactions are anticipated with durvalumab, as it is a mAb.

2.3 Outstanding Issues

No outstanding issues from Clinical Pharmacology's perspective.

2.4 Summary of Labeling Recommendations

In general, the applicant has provided adequate clinical pharmacology information to support the product labeling. We recommend the following labeling concepts to be included in the final package insert:

- Durvalumab demonstrated linear PK at doses greater than or equal to 3 mg/kg.
- Durvalumab demonstrated time-dependent clearance.
- No intrinsic or extrinsic factors (e.g., renal or hepatic function, body weight, concomitant medications) appear to have a clinically important effect on durvalumab exposure.
- The exposure-response relationships could not be adequately evaluated.
- Durvalumab does not prolong the QT/QTc interval.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Durvalumab is a human IgG1κ mAb that binds PD-L1 and inhibits its binding to PD-1 and B.7.1 receptors. It has an approximate molecular weight of 149 kDa. Durvalumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. Durvalumab will be available as 500 mg/10 mL solution and 120 mg/2.4 mL solution in single-dose vial.

On 02/16/2016, FDA granted durvalumab the Breakthrough Therapy designation for monotherapy in second-line or later for patients with locally advanced or metastatic UC. On 05/18/2016, TECENTRIQ (ay67tezolizumab), a mAb that binds PD-L1, was approved for the same indication.

The to-be-marketed formulation was administered in Study 1108 and the supportive trial ATLANTIC. A premarket approval (PMA) application was submitted to Center for Devices and Radiological Health (CDRH) for the VENTANA PD-L1 (SP263) assay, which is being reviewed as a complementary diagnostic at this time.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Durvalumab is a mAb that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity.
Pharmacodynamics	Dose-dependent suppression in free serum sPD-L1 was observed following intravenous administration of durvalumab in all patients. sPD-L1 levels were below the study patient-based limit of detection (< 67.1 pg/mL) in most patients at all time points following the administration of durvalumab at doses greater than 0.3 mg/kg Q2W. Following a dose of 10 mg/kg Q2W, approximately 93.3% (781/837) of patients in Study 1108 demonstrated complete sPD-L1 suppression throughout the dosing interval. Increases in average proliferating CD8+ T-cell quantities on Day 10 (mean ± standard error of the mean [SEM]: 110% ± 27%) and 15 (mean ± SEM: 67% ± 15%) were observed in patients with UC (N=59) following administration of a dose of 10 mg/kg. These increases were elevated above the mean of the range of variability (RV) for the proliferating T-cell assay (Day 10: p = 0.003; Day 15: p = 0.01). Similar trends were observed for proliferating CD4+ T cells on Day 10 (mean ± SEM: 64% ± 18%); although, the magnitude of the increase was not significantly elevated above the RV (p = 0.053).
General Information	
Bioanalysis	The bioanalytical report and individual run data were submitted for Study 1108. Durvalumab concentrations in human serum were quantified by a validated enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) was 50 ng/mL with the minimum required dilution (MRD) at 1:20. The assay has 10-point standard curve consisting of 9 standards ranging from 1.25 ng/mL to 320 ng/mL prepared in human serum and 3 validation QCs (Low: 5 ng/mL; 20 ng/mL and 100 ng/mL). Long term storage stability at the appropriate storage conditions was demonstrated. Incurred sample reanalysis (ISR) for the quantitative determination of durvalumab in human serum appears acceptable. The assay appears acceptable to measure durvalumab plasma concentrations in Study 1108; refer to section 4.1 for detail data.

	Only the method validation reports were submitted for the immunogenicity assays and the PD endpoint assay. The immunogenicity confirmatory and neutralizing assays were inadequately developed and two PMCs will be issued by the OBP to address the assay issues.
PK Model	A two-compartment population PK model with both linear and nonlinear clearance components in parallel adequately described durvalumab PK profiles. This model is considered acceptable based on model evaluation criteria including goodness of fit, visual predictive check (VPC), plausibility of model parameters, etc.
Drug Exposure at Steady State	Based on the population PK analysis, steady state was achieved around Week 16 following a dose of 10 mg/kg Q2W for a typical patient. The median (CV%) minimal concentrations (C_{min}) at steady state was 182 ug/mL (57.3%).
Dose Linearity	Durvalumab exhibits nonlinear pharmacokinetics at doses less than 3 mg/kg and linear pharmacokinetics at doses greater than or equal to 3 mg/kg.
Body Weight	Body weight had no clinically significant effect on the exposure of durvalumab based on the population PK analysis. The confirmatory trial incorporates durvalumab at a dose of 1500 mg every 4 weeks (Q4W).
Renal or Hepatic Impairment	No formal trials were conducted to evaluate the effect of hepatic or renal impairment on the PK of durvalumab. The population PK analysis showed that renal impairment (defined as CLcr 30 mL/min to 89 mL/min) and hepatic impairment (defined as total bilirubin $\leq 1.5 \times$ ULN and AST $\leq 2.5 \times$ ULN) had no clinically important effects on durvalumab clearance or volume of distribution. The point estimate of CLcr covariate effect on CL is 0.00147; during model development, neither AST nor bilirubin levels were identified as significant covariate on clearance or volume of distribution and CLcr was not identified as significant covariate on volume of distribution.
ADME	
Absorption	Durvalumab was administered as an IV infusion. No studies were performed with other routes of administration.
Distribution	Based on population PK analysis, the estimated geometric mean (CV%) steady state volume of distribution was 5.6 L (17%).
Elimination	The geometric mean systemic clearance (CV%) at steady state was 8.2 mL/h (37.3%). As durvalumab is a mAb, it is expected to be metabolized into peptides and amino acids via catabolic pathway. The geometric mean (CV%) elimination half-life is 17 days (23.2%).
Immunogenicity	
Incidence	In Study 1108, approximately 3.3 percent of patients (37 of 1124) tested positive for ADA. In Study ATLANTIC, 4.3 percent of patients (16 of 373) tested positive for ADA; however, the assays were not appropriately validated.

Impact on PK	The development of ADA does not have clinically significant effects on durvalumab PK.
Impact on Efficacy and Safety	The effects of these antibodies on the safety and efficacy of durvalumab are not evaluable, because of the small number of patient samples testing positive for treatment-emergent ADA and the relatively low ORR.
QT	
Impact of durvalumab exposure on QT interval	In QTc substudy included in Study ATLANTIC, no relationship was identified between durvalumab serum concentration and ΔQTcF based on the concentration-ΔQTcF analysis. Linear mixed-effects modeling of QTcF as a function of durvalumab concentrations estimated a non-significant relationship between durvalumab concentration and change in QTcF. The slope for the relationship of the change in QTcF to durvalumab concentration was -0.00114 msec per µg/mL, with a p-value of 0.902, indicating that the slope is not significantly different from 0 or no effect, and the mean intercept was 2.16 msec (p-value: 0.253; 90% CI -0.956, 5.28 ms). The predicted mean change in QTcF and upper 90% CI at each of the post-therapy visits are below the threshold of clinical concern.
Biomarker	
In Vitro Diagnostic (IVD) Testing	In Study 1108, PD-L1 expression was prospectively assessed in TCs and tumor-infiltrating ICs in archival or fresh tumor tissue. According to the final PD-L1 assay (N = 128), patients were classified as having high (45.3%), low (43.8%), or unknown (10.9%) PD-L1 expression.

3.3 Clinical Pharmacology Review Questions

3.3.1 How does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The available clinical pharmacology information suggests that the proposed dose of 10 mg/kg Q2W is reasonably safe. Only the proposed dosing regimen was administered to patients with UC in the expansion cohort in Study 1108. The exposure-efficacy relationships couldn't be adequately characterized as only one dose was evaluated and no comparator was included in the expansion cohort. The applicant stated the dose selection was based on the following factors: manageable safety profile, clinically meaningful activity, and achieved desired target trough concentration based on clinical and non-clinical data.

Primary efficacy in the expansion cohort of Study 1108

An expansion cohort in Study 1108 provided the primary evidence for the effectiveness of durvalumab in patients with advanced or metastatic UC administered a dose of 10 mg/kg Q2W. Out of the 182 patients with UC whose disease had progressed during or after one standard platinum-based regimen, the overall response rate (ORR) was 17.0% after 13 weeks of follow-up as compared to the historical ORR of 10%. Furthermore, five patients achieved a complete response (CR).

Efficacy results were also assessed in PD-L1 expression subgroups. PD-L1 expression was prospectively assessed in TCs and ICs in archival or fresh tumor tissue using the VENTANA PD-L1 (SP263) IHC assay. Enrollment into Study 1108 was initially irrespective of PD-L1 expression (N = 20), was then limited to patients with TC expression ≥ 5% (N = 34), and was finally relaxed to no longer require a minimum TC expression (N = 128) through different amendments to the protocol. The PD-L1 expression cutoff (high vs. low) was determined using the first 20 patients with a minimum of 12 weeks of follow-up as an attempt to discriminate between responders and non-responders. The cutoff was further modified during the study for instances when the tumor area contained ≤1% ICs (final assay). The distribution of UC patients from Study 1108 by PD-L1 expression status is listed in **Table 1**. Fourteen patients were categorized as having unknown PD-L1 expression due to insufficient tumor sample (N = 13) or to the sample not being tested prior to the data cutoff (N = 1).

Table 1. PD-L1 Status in UC Patients with Disease Progression during or after One Standard Platinum-Based Regimen

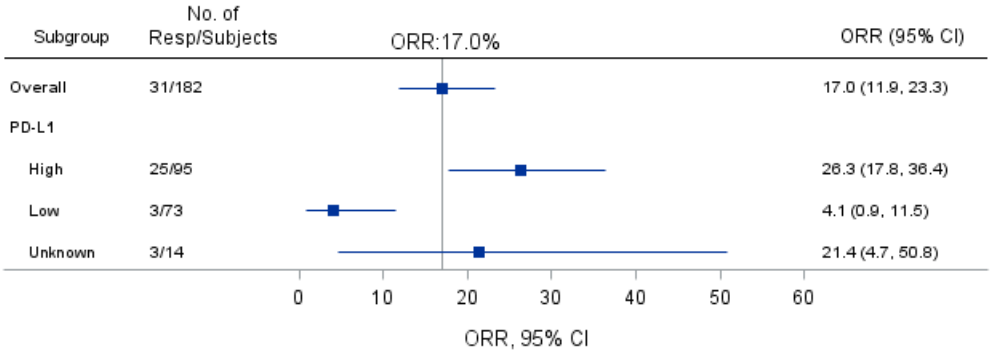
PD-L1 Expression*	All Patients (Total = 182) N (%)	Final PD-L1 Assay (Total = 128) N (%)
High (TC ≥ 25% or IC ≥ 25%)	95 (52.2)	58 (45.3)
Low (TC < 25% and IC < 25%)	73 (40.1)	56 (43.8)
Unknown	14 (7.7)	14 (10.9)

*When IC ≤ 1% of the total tumor area, PD-L1 High: TC ≥ 25% or IC = 100%, PD-L1 Low: TC < 25% and IC < 100%. UC: urothelial carcinoma.

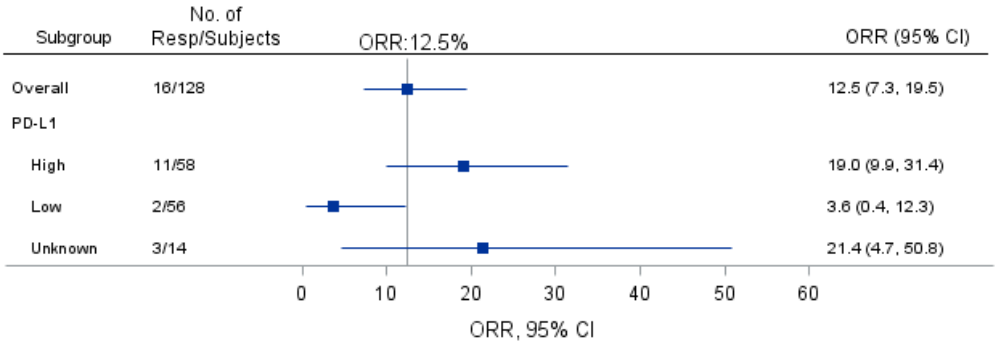
Source: Study CD-ON-MEDI4736-1108 updated efficacy report (data cutoff 24 October 2016), Table 14.1_1.1.5.

Evaluation of efficacy outcomes based on PD-L1 expression showed clinical activity across the PD-L1 high and PD-L1 low subgroups, however, a higher ORR was observed in the subgroup of patients with high PD-L1 expression (26.3% vs. 4.1% in the low subgroup, N = 182, **Figure 1A**). CRs were observed across subgroups (N = 182), with 3 (3.2%) CRs in the PD-L1 high subgroup, 1 (1.4%) CR in the PD-L1 low subgroup, and 1 (7.1%) CR in the PD-L1 unknown subgroup. Similar trends in ORR were observed in the subset of patients with prospectively assessed PD-L1 status using the final assay, and CRs were observed in the PD-L1 high (N = 2, 3.4%) and unknown (N = 1, 7.1%) subgroups (N = 128, **Figure 1B**). These results suggest that a complementary diagnostic based on PD-L1 expression may be appropriate. For details regarding the PMA, refer to the CDRH review by Dr. Aaron Schetter.

Figure 1. Forest Plot of ORR per BICR according to RECIST v1.1 by PD-L1 Subgroup



(A)



(B)

(A) ORR in all UC patients whose disease had progressed during or after one standard platinum-based regimen (N = 182). (B) ORR in patients with prospectively assessed PD-L1 status using the final complementary diagnostic assay (N = 128). ORR: Objective Response Rate, BICR: Blinded Independent Central Review, Resp: Number of patients with response (CR or PR).

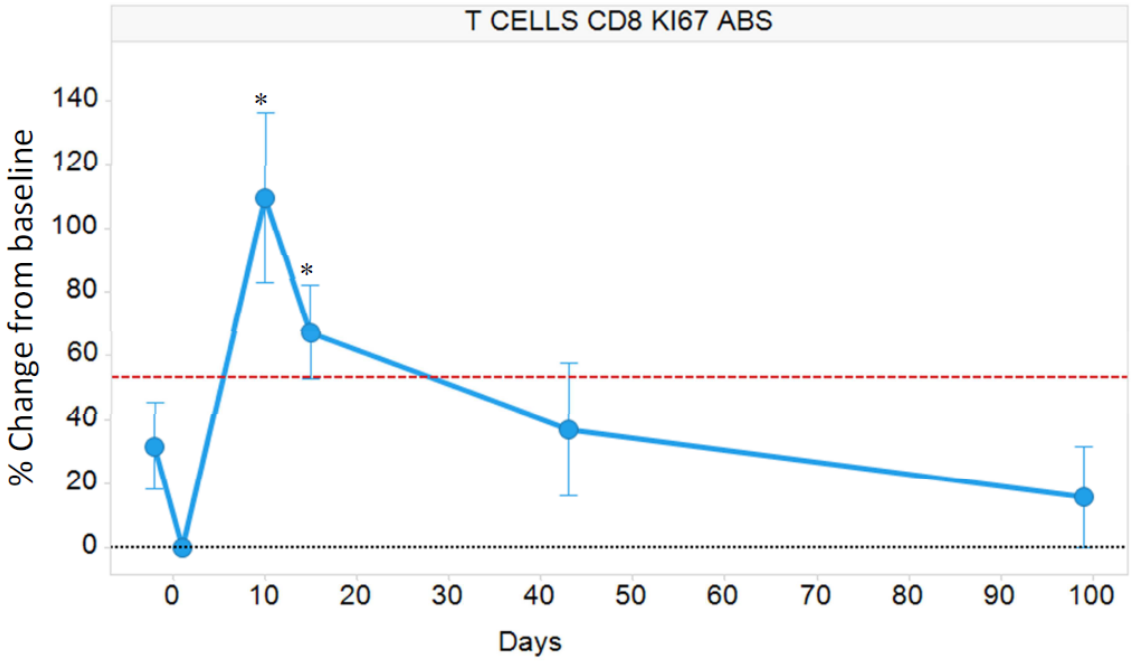
Source: Reviewer generated plots based on Study CD-ON-MEDI4736-1108 updated efficacy report (data cutoff 24 October 2016) with modification of response for 1 patient to "not evaluable" due to lack of measurable disease at baseline (see Clinical review by Dr. Daniel Suzman).

Pharmacodynamics

Target engagement was assessed by measuring sPD-L1 in serum. Following a dose of 10 mg/kg Q2W, approximately 93.3% patients demonstrated complete sPD-L1 suppression throughout the dosing interval. The target engagement data supports the proposed dose.

Two validated, flow cytometry-based assays were used to quantify circulating lymphocytes (T, B, and NK cells) and proliferating T cell subsets from 59 patients with UC during the Study 1108. Increases in average proliferating CD8+ T-cell quantities on Day 10 (mean ± standard error of the mean [SEM]: 110% ± 27%) and 15 (mean ± SEM: 67% ± 15%) were observed following administration of a dose of 10 mg/kg as shown in **Figure 2**. These increases were significantly elevated above the mean of the range of variability (RV) for the proliferating T-cell assay (calculated as the mean percent change between serial samples tested prior to durvalumab administration) using a one sample T-test (Day 10: $p = 0.003$; Day 15: $p = 0.01$). Similar trends were observed for proliferating CD4+ T cells on Day 10 (mean ± SEM: 64% ± 18%); although, the magnitude of the increase was not significantly elevated above the RV ($p = 0.053$).

Figure 2. T Cells CD8 Ki67 Absolute Cell Count



ABS = absolute cell counts.
Black dotted line denotes baseline value, red dashed line denotes RV, ** $p < 0.05$
Source: Module 5.3.5.3 G-BI-0110 report Figure 6.2-2

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

Yes. The proposed dose of 10 mg/kg Q2W is acceptable. The results of an expansion cohort included in Study 1108 provided the primary evidence for the effectiveness of durvalumab in patients with locally advanced or metastatic UC; however, a dose of 10 mg/kg Q2W was the only dosing regimen administered to patients with UC in this disease specific expansion cohort. A dose of 10 mg/kg is in the linear PK range. The E-R analysis conducted by the applicant didn't identify an exposure-efficacy relationship, which could be caused by the relative small sample size and the relative low event rate. Overall, the dose appears acceptable based on the ORR and safety profile.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. There is no need for alternative dosing regimen for subpopulations based on the intrinsic factors.

The population PK analysis evaluated the effects of body weight (34 to 149.1 Kg), serum albumin (20 – 57.11 g/L), sex , post-baseline ADA, performance status (0-3), sPD-L1 (67.1 – 3471 pg/mL), CLcr (26.6 – 270.5 mL/min), LDH level (18 – 5707 IU/L), tumor type, age (19 -96 years of age), race, and hepatic function (BIL: 0.1 – 3.9 mg/dL; AST: 0 – 322 IU/L; ALT: 0 – 245 IU/L) on durvalumab clearance and volume of distribution. The analysis results showed none of these covariates had a clinically important effect on durvalumab PK parameters, because the changes in the PK parameters differed by less than 30% compared to the PK parameter

estimates for the typical patient. No dose individualization is needed for patients with these intrinsic factors at baseline.

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

Food-drug interactions are not applicable as durvalumab is administered as an intravenous infusion. Cytochrome P450 mediated drug interactions were not evaluated for duvalumab, since it undergoes proteolytic catabolism and it has no clinically significant effect on cytokine levels.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

This method utilized an electrochemiluminescent assay format to measure the concentration of durvalumab in human serum. Standards, controls and test samples were incubated with durvalumab anti-idiotype antibody (clone AB0470011) biotin which had been immobilized on a Meso Scale Discovery (MSD) Streptavidin Coated Standard MA2400 96-Well Plate. After incubation, unbound material was washed away and durvalumab was detected with anti-TM (clone A8) sulfotag, visualized with MSD Read Buffer T (1X), and read on the MSD Sector™ Imager 2400. The assay provides a quantitative measurement of the durvalumab serum concentration. The assay has 10-point standard curve consisting of nine standards ranging from 1.25 ng/mL to 320 ng/mL prepared in human serum and three validation QCs (Low: 5 ng/mL; 20 ng/mL and 100 ng/mL). The assay appears acceptable to measure durvalumab plasma concentrations for samples collected as part of Study 1108. **Table 2 and Table 3** show the method validation data, and **Table 4 and Table 5** show the performance of the assay. The assay appears acceptable to measure durvalumab plasma concentrations in Study 1108; the assay precision is 96.3% - 98.5% and the accuracy is 100.8% - 107%. The long term stability samples were within 20% relative error of the nominal concentration for all the intervals tested for both -20°C ± 5°C and -70°C ± 10°C. Durvalumab is stable for 735 days at -20°C ± 5°C and 732 days at -70°C ± 10°C at the concentrations tested and these data suggests that long term storage stability at the appropriate storage conditions was demonstrated. Incurred sample reanalysis (ISR) assessment was considered as passing if two thirds of the samples analyzed had a % relative difference within ± 30%. Seventy-five percent (234/311) of samples analyzed for ISR were within 30% relative difference of the original result demonstrating that the method has passed the ISR acceptance criteria.

Table 2. Summary of the Intra and Inter-assay Precision and Bias

Standard Curve		Quality Control Samples			
Mean Intra-Assay % CV Range	Inter-Assay % CV Range	Mean Intra-Assay % CV Range	Inter-Assay %CV Range	Mean Intra-Assay %Relative Error Range	% Total Error Range
2.0 to 10.4	0.5 to 1.5	1.5 to 3.7	2.0 to 3.2	0.5 to 12.1	2.8 to 15.3

Source: 16.1.13 Clinical Bioanalytical Reports, AR4646 Validation Report.

Reference ID: 4065384

Table 3. Quality Control Samples: Mean Values and Target Ranges

Identity	Nominal Concentration (ng/mL)	Mean Concentration (ng/mL)	n	Target Range (ng/mL)
Low2	2.50	2.51	9	1.88-3.13
Low	5.00	5.04	9	4.00-6.00
Medium	20.00	21.15	9	16.00-24.00
High	100.00	107.38	9	80.00-120.00
High2	160.000	179.32	9	128.00-192.00

Source: 16.1.13 Clinical Bioanalytical Reports, AR4646 Validation Report.

Table 4. Summary of Standard Curve Data for the Quantitative Determination of Durvalumab Concentration in Human Serum

Mean	1.25	2.50	5.11	9.85	20.01	40.14	81.06	156.43	330.58
SD	0.03	0.07	0.10	0.18	0.26	0.59	2.22	8.62	19.98
%CV	2.7	2.8	2.0	1.8	1.3	1.5	2.7	5.5	6.0
n	248	249	249	254	254	253	256	256	236

Source: 4469 Analytical Interim Report Final_04Jan2017_signed, Table 2.

Table 5. Summary of Quality Controls Data for the Quantitative Determination of Durvalumab in Human Serum

Mean	99.92	20.06	4.78
SD	8.97	1.73	0.46
%CV	9.0	8.6	9.5
n	442	496	507

Source: 4469 Analytical Interim Report Final_04Jan2017_signed, Table 3.

Only the method validation reports were submitted for the ADA assay, neutralizing antibody assay and PD assay, the confirmatory and neutralizing antibody were inadequately developed and two PMCs will be issued by OBP to further develop these assays.

4.2 Clinical PK and PD Assessments

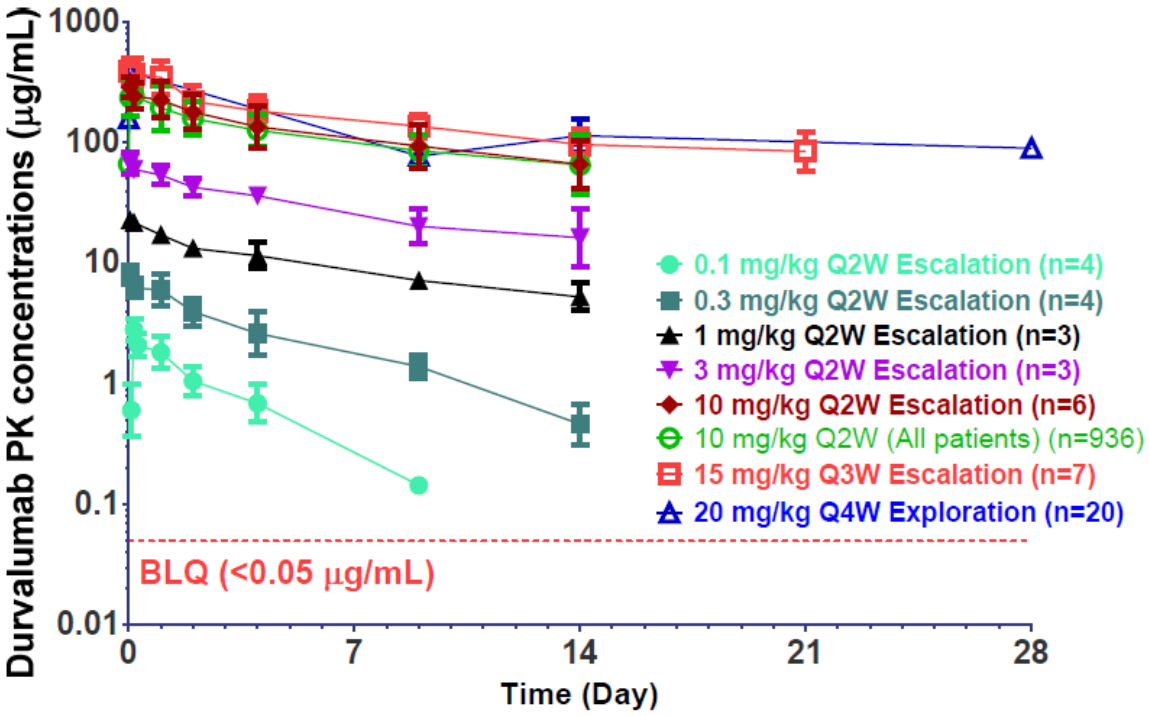
Pharmacokinetic

A single arm, open label, multicenter, first in human, dose escalation, dose exploration, and dose expansion study was conducted to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of durvalumab in adult patients with solid tumors (Study 1108). Patients received durvalumab at a dose of 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W or 20 mg/kg Q4W IV infused over 60 minutes.

Following the first IV dose, durvalumab exhibited nonlinear PK at doses less than 3 mg/kg Q2W likely due to saturable target-mediated clearance and exhibits linear PK at doses greater than or equal to 3 mg/kg Q2W. Mean (±SD) serum concentration-time profiles stratified by dose cohorts are presented in **Figure 3**. The estimated mean PK parameters are presented in **Table 6 and Table 7**. The $AUC_{0\text{-}14days}$ increased dose-proportionally at doses of 3 mg/kg to 20 mg/kg and more than dose-proportionally at doses of less than 3 mg/kg, likely due to saturable target-mediated clearance. C_{max} increased in a dose-proportional manner within the dose range examined. The steady state was achieved at approximately Week 16. Accumulation of durvalumab was observed following repeated dosing. Mean accumulation ratio ranged from 0.64 to 1.9 for C_{max} and from 3.2 to 4.9 for C_{trough}.

Reference ID: 4065384

Figure 2 Mean (±SD) Durvalumab Serum Concentration – Time Profile following IV Administration of 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W to 20 mg/kg Q4W (log scale)



BLQ = below the limit of quantification; IV = intravenous; PK = pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation.
Note: Escalation/exploration phases based on Study 1108 design.
Source: Module 5.3.5.2 Study 1108 CSR Figure 11.4.4.1-1.

Table 6. Mean Durvalumab Pharmacokinetic Parameters following the First Dose

Dose (mg/kg)	Schedule	Geometric Mean (n, geometric %CV)								
		T_{max1} (day)	C_{max1} (µg/mL)	$C_{max1}D$ (µg/mL/mg)	$C_{trough1}$* (µg/mL)	$C_{trough1}_D$** (µg/mL/mg)	AUC_{last} (µg·day/mL)	AUC_{last}_D (µg·day/mL/mg)	AUC_{0-14} (µg·day/mL)	AUC_{0-14}_D (µg·day/mL/mg)
0.1	Q2W	0.1695 (4, 1.80)	2.78 (4, 22.1)	0.341 (4, 27.9)	NC	NC	5.14 (4, 45.1)	0.632 (4, 39.8)	6.03 (4, 41.1)	0.741 (4, 39.7)
0.3	Q2W	0.0444 (4, 7.30)	7.97 (4, 23.0)	0.294 (4, 40.3)	0.431 (3, 49.9)	0.0168 (3, 57.0)	25.1 (4, 65.5)	0.926 (4, 80.2)	25.82 (4, 57.4)	0.952 (4, 71.6)
1	Q2W	0.0777 (3, 79.8)	22.77 (3, 11.3)	0.305 (3, 31.8)	5.106 (3, 34.1)	0.0685 (3, 9.40)	130.55 (3, 20.1)	1.749 (3, 23.9)	135.33 (3, 17.1)	1.818 (3, 18.1)
3	Q2W	0.129 (3, 518.3)	70.81 (3, 17.0)	0.397 (3, 13.3)	12.4 (3, 135.1)	0.0694 (3, 213.7)	399.86 (3, 21.7)	2.245 (3, 53.0)	401.66 (3, 22.0)	2.252 (3, 53.3)
10 (Escalation)	Q2W	0.0780 (5, 221.7)	293.54 (5, 23.4)	0.351 (5, 26.0)	53.795 (6, 92.3)	0.0637 (6, 99.1)	1780.15 (5, 39.1)	2.129 (5, 37.5)	1773.20(5, 38.5)	2.122 (5, 37.1)
10 (Escalation +Expansion)	Q2W	NC	224[a] (851, 35.7)	NC	57.7[a] (738, 49.0)	NC	NC	NC	NC	NC
15	Q3W	0.1026 (7, 168.4)	427.09 (7, 25.5)	0.351 (7, 38.4)	77.365* (7, 50.1)	0.0635* (7, 38.0)	2943.77 (7, 36.3)	2.420 (7, 34.5)	2321.16 (7, 34.4)	1.908 (7, 34.7)
20	Q4W	0.0443 (18, 86.3)	416.05 (18, 23.9)	0.268 (18, 37.6)	62.976** (19, 47.4)	0.0409** (19, 44.2)	4501.89 (18, 23.1)	2.897 (18, 29.5)	3290.72 (18, 21.3)	2.119 (18, 31.4)

n = sample size; AUC_{0-14} = area under the serum concentration-time curve from Day 1 to Day 15; AUC_{0-14}_D = dose-normalized area under the serum concentration-time curve from Day 1 to Day 15; AUC_{last} = area under the serum concentration-time curve up to the last measurable concentration; AUC_{last}_D = dose-normalized area under the serum concentration curve up to the last measurable concentration; C_{max1} = maximum serum concentration after the first dose; C_{max1}_D = dose-normalized maximum serum concentration after the first dose; $C_{trough1}$ = trough serum concentration in the first dosing interval; $C_{trough1}_D$ = dose-normalized trough serum concentration in the first dosing interval; NC = not calculated; $C_{trough1}$ includes Day 15 concentrations based on Q2W dosing; *$C_{trough1}$ and $C_{trough1}_D$ includes Day 22 concentrations based on Q3W dosing; **$C_{trough1}$ and $C_{trough1}_D$ includes Day 29 concentrations based on Q4W dosing; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; T_{max1}= time to maximum serum concentration after the first dose.

Note: All data are depicted as geometric mean (n, geometric CV%)

598 samples and 46 subjects composed the PK analysis dataset used for PK parameter estimation by non-compartmental analysis.

Source: Module 5.3.5.2 Study 1108 CSR Section 14, Table 14.2_8.1, Table 14.2_8.3.

Reference ID: 4065384

Table 7. Mean Durvalumab Pharmacokinetic Parameters at Steady State

Dose (mg/kg)	Schedule	Geometric mean (n, geometric%CV)				Accumulation ratio (n, geometric%CV)	
		C_{max_ss} (µg/mL)	$C_{max_ss}_D$ (µg/mL/mg)	C_{trough_ss} (µg/mL)	$C_{trough_ss}_D$ (µg/mL/mg)	ARC_{max} (Ratio)	ARC_{trough} (Ratio)
0.1	Q2W	1.85 (3, 37.6)	0.230 (3, 83.9)	NC	NC	0.639 (3, 54.0)	NC
0.3	Q2W	15.1 (2, 16.4)	0.511 (2, 13.3)	2.18 (2, 82.5)	0.0737 (2, 86.6)	1.68 (2, 26.0)	4.93 (2, 5.60)
1	Q2W	42.5 (3, 19.6)	0.579 (3, 5.00)	19.2 (3, 23.6)	0.262 (3, 1.20)	1.87 (3, 26.4)	3.77 (3, 9.90)
3	Q2W	NC	NC	NC	NC	NC	NC
10 (Escalation)	Q2W	324 (1, NC)	0.349 (1, NC)	91.9 (1, NC)	0.0988 (1, NC)	1.49 (1, NC)	4.32 (1, NC)
10 (Escalation +Expansion)	Q2W	409 (34, 35.7)	NC	182 (27, 57.3)	NC	1.83[b]	3.15[b]
15	Q3W	582 (3, 54.8)	0.504 (3, 48.9)	140 (3, 70.4)	0.121 (3, 79.1)	1.43 (3, 28.5)	2.05 (3, 67.5)
20	Q4W	489 (9, 32.7)	0.294 (9, 27.3)	99.6 (10, 50.1)	0.0611 (10, 32.1)	1.07 (9, 41.4)	1.44 (10, 47.6)

ARC_{max} = Accumulation index for C_{max}; ARC_{trough} = Accumulation index for C_{trough}; C_{max_ss} = maximum serum concentration at steady state; C_{trough_ss} = trough serum concentration at steady state; $C_{max_ss}_D$ = dose-normalized maximum serum concentration at steady state; $C_{trough_ss}_D$ = dose-normalized trough serum concentration at steady state; NC = not calculated; n = sample size; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

Note: Steady state was defined as the 8th dose (Day 98) for Q2W regimen, 6th dose (Day 105) for Q3W regimen, and 4th dose (Day 84) for Q4W regimen.

The PK analysis set included all subjects who received at least 1 dose of durvalumab per the protocol, for whom any post-dose PK data are available and do not deviate from the protocol that would significantly affect the PK analysis.

[a]. parameters are directly taken from pre-infusion and end of infusion data of dose 8 in Table 14.2_8.1. No non-compartmental analysis was performed for 10 mg/kg Q2W total (escalation + expansion).

[b]. ARC_{max} is calculated as the ratio of $C_{max.ss}/C_{max}$; ARC_{trough} is calculated as the ratio of $C_{trough.ss}/C_{trough}$

All parameters are rounded to 3 significant digits

Source: Module 5.3.5.2 Study 1108 CSR Section 14, Table 14.2_8.1, Table 14.2_8.3.

Pharmacodynamic:

The available data demonstrate a pharmacodynamic effect consistent with the mechanism of action of durvalumab.

Target engagement was assessed by measuring sPD-L1 in serum. Dose-dependent suppression in free serum sPD-L1 was observed following IV administration of durvalumab. Free serum sPD-L1 levels were below the study patient-based limit of detection (< 67.1 pg/mL) in the majority of patients at all time points following ≥ 0.3 mg/kg Q2W doses. Following 10 mg/kg Q2W durvalumab, approximately 93.3% patients demonstrated complete sPD-L1 suppression throughout the dosing interval.

Two validated, flow cytometry-based assays were used to quantify circulating lymphocytes (T, B, and NK cells) and proliferating T cell subsets from 59 UC patients during the study. Increases in average proliferating CD8+ T-cell quantities on Days 10 (mean ± standard error of the mean [SEM]: 110% ± 27%) and 15 (mean ± SEM: 67% ± 15%) were observed following administration of 10 mg/kg durvalumab. These increases were significantly elevated above the mean of the range of variability (RV) for the proliferating T-cell assay (calculated as the mean percent change between serial samples tested prior to durvalumab administration) using a one

sample t-test (Day 10: p = 0.003; Day 15: p = 0.01). Similar trends were observed for proliferating CD4+ T cells on day 10 (mean ± SEM: 64% ± 18%); although, the magnitude of the increase was not significantly elevated above the RV (p = 0.053). No other lymphocyte populations demonstrated mean changes from baseline that exceeded the RV during the first 100 days of the study.

4.3 Population PK Analyses

4.3.1 Results of Applicant's Population PK Analysis

Objectives

- To characterize the PK and associated between-patient variability of durvalumab as a single-immunomodulatory agent in cancer patients
- To identify the factors influencing the variability in PK exposure of durvalumab based on a pool of patients with advanced solid tumors

Data

Data from study 1108 and ATLANTIC were included in this analysis. The design features of the two studies are shown in **Table 8**. The population PK datasets consist of 7312 PK samples from 1324 patients including 892 patients from study 1108 and 432 patients from study ATLANTIC.

Table 8. Summary of Studies included in the Population PK Analysis

Study No.	Study design	Dose(s)	Approximate Number of subjects planned	Serum sampling schedule PK planned	Serum sampling schedule ADA planned	Study status at time of writing the document
CD-ON-MEDI4736-1108	A Phase 1/2 study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors	Ranging from 0.1 to 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W	185 patients with UC; 949 patients at 10 mg/kg IV Q2W	**Dose 1 D1** (pre-dose, 2h post start of infusion, EOI, 2-3 hr post-infusion) **Dose 1 D2, D3, D5, D10, and D15** **Dose 2 D1** (pre-dose, EOI, 3 hr post-infusion) **Dose 2 D8** **Dose 3 D1** **Dose 4 D1** **Dose 5 D1** **Dose 6 D1** (pre-dose, EOI) **Dose 7 D1** (pre-dose) **Dose 8 D1** (pre-dose and EOI) **Dose 9 D1** (pre-dose) **Dose 10 D1** **Dose 12 D1** **Dose 14 D1** (pre-dose, and EOI) **Dose 15 D1** (pre-dose) **Dose 16 D1** **Dose 18 D1** **Dose 20 D1** (pre-dose, and EOI) **Dose 21 D1** (pre-dose) **Dose 22 D1** **Dose 24 D1** **Dose 26 D1** (pre-dose, and EOI) **Dose 27 D1** (pre-dose) EOT, 14-day FU, 30-day FU,	Dose 1 D1 Dose 2 D1 Dose 3 D1 Dose 4 D1 Dose 5 D1 Dose 6 D1 Dose 7 D1 Dose 8 D1 Dose 9 D1 Dose 10 D1 Dose 12 D1 Dose 14 D1 Dose 15 D1 Dose 16 D1 Dose 18 D1 Dose 20 D1 Dose 21 D1 Dose 22 D1 Dose 24 D1 Dose 26 D1 Dose 27 D1 (pre-dose) EOT, 30-day FU, 3-month FU, 6-month FU	Ongoing

Study No.	Study design	Dose(s)	Approximate Number of subjects planned	Serum sampling schedule PK planned	Serum sampling schedule ADA planned	Study status at time of writing the document
				2-month FU, 3-month FU **Retreatment: Dose 1 D1** **Dose 2 D1** (pre-dose, EOI) **Dose 3, 9, 15, 21** (pre-dose) EOT, 30-day FU	Retreatment: Dose 1 D1 Dose 3 D1 Dose 9 D1 Dose 15 D1 Dose 21 D1 (pre-dose) EOT, 30-day FU, 6-month FU	
D4191C00003 (ATLANTIC)	A Phase 2, non-comparative, open-label, multi-centre, international study of MEDI4736, in patients with locally advanced or metastatic non-small cell lung cancer (Stage IIIB-IV) who have received at least two prior systemic treatment regimens including one platinum-based chemotherapy regimen	10 mg/kg Q2W up to 12 months	444 patients at 10 mg/kg IV Q2W	Week 0 (pre-dose and EOI) Week 4 (pre-dose) Week 16 (pre-dose) Week 28 (pre-dose) Week 40 (pre-dose) Week 52 (pre-dose) 30-day FU 3-month FU	Week 0 (pre-dose) Week 4 (pre dose) Week 16 (pre-dose) Week 28 (pre-dose) Week 40 (pre-dose) Week 52 (pre-dose) 30-day FU 3-month FU	Ongoing

ADA = antidrug antibody status; D = day; EOI = end of infusion; EOT = end of treatment; FU = follow up; PK = pharmacokinetic; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; UC = urothelial carcinoma.

Note that for Study 1108, a different PK and ADA sampling schedule applied for UC patients (please refer to protocol).

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Table 6.1.2-1 on page 30.

Methods and Software

A two-compartment structural model with parallel linear and nonlinear elimination from the central compartment was implemented in NONMEM. The nonlinear clearance component was modeled using a Michaelis-Menten function. The stochastic components of the PK model were assumed to follow a log-normal distribution. Different residual error structures including a combined additive and proportional residual error model were tested.

The stepwise covariate model building procedure was used for the covariate model building process. Covariates including performance status Eastern Cooperative Oncology Group at baseline (ECOG), tumor type (TUMTYP), body weight (WT), sex (SEXN), age (AGE), race (RACEN), alanine aminotransferase (ALT), aspartate aminotransferase (AST),total bilirubin (BIL), serum albumin (ALB), serum creatinine (CRE), creatinine clearance (CLcr), lactate dehydrogenase (LDH), soluble PD-L1 (SPDL1) level at baseline, and positive post-baseline ADA were tested in the model.

Goodness-of-fit plots and visual predictive check (VPC) were performed for model evaluation.

The population PK analysis was performed in NONMEM version 7.2 or higher. Data management and processing were performed using R version 3.3.1 or higher.

Results

Base model

Individual concentration-time profiles of durvalumab were best described by a two-compartment model with linear CL and nonlinear CL in parallel. The best stochastic model supported by the

Reference ID: 4065384

data was with inclusion of a random variable on CL, V1, and V2. The residual error was best-described by a combined additive and proportional residual error model.

Covariate model

After the final step of the backward elimination of the stepwise covariate model building procedure process, the following covariate-PK relationship were found to be statistically significant and were incorporated in the final model: ALB on CL, body weight on CL and V1, sex on CL, V1, and V2, LDH on CL, ECOG status on CL, post-baseline ADA on CL, tumor type on CL, CLcr on CL, and SPDL1 on CL.

Final model

PK parameter estimates from the final model are summarized in **Table 9**. Mean values of all PK parameters were precisely estimated (asymptotic RSE < 35%, apart for K_m (RSE=92.2%), the additive term of the error model (RSE=76.5%), and the covariate effect parameter of the ADA impact on CL relationship (RSE=42.6%). All PK parameters were typical for a fully human IgG1 antibody for the linear part (dose ≥ 3mg/kg). Durvalumab CL of the typical patient was estimated at 0.226 L/day and inter-compartmental clearance was 0.465 L/day. The between-patient variability of durvalumab was moderate, with population CV% estimates of 29.3%, 21.2%, and 39.9% for CL, V1, and V2 respectively. The K_m estimate was 0.533 mg/L (95% CI: 0.072 – 1.58 mg/L). Vmax was 0.931 mg/day.

Table 9. Summary of PK Parameter Estimates form the Final Model

Parameters	Estimates (Bootstrap 95% CI)	Between-subject variability ω estimates (CV%) (Bootstrap 95% CI)	SCOVARIANCE (RSE%)
Clearance (CL; L/day)	0.226 (0.218 – 0.233)	29.3% (27.2% – 31.1%)	CL = 1.52% ; ω^2_{CL} = 3.34%
Central volume (V_1; L)	3.51 (3.44 – 3.58)	21.2% (19.1% – 23.3%)	V_1 = 1.03% ; ω^2_{V1} = 4.92%
Peripheral volume (V_2; L)	3.51 (3.29 – 3.76)	39.9% (34.7% – 45.8%)	V_2 = 1.23% ; ω^2_{V2} = 7.57%
Inter-compartmental clearance (Q; L/day)	0.465 (0.396 – 0.558)	---	3.86%
Michaelis-Menten constant K_m (mg/L)	0.533 (0.0722 – 1.58)	---	92.2%
Maximum elimination rate V_{max} (mg/day)	0.931 (0.638 – 1.31)	---	16.6%
Correlation CL.V_1	0.257 (0.198 – 0.296)	---	8.89%
Correlation CL.V_2	-0.123 (-0.355 – 0.0234)	---	30.9%
Correlation V_1.V_2	0.553 (0.490 – 0.577)	---	7.91%
Covariate 1: ALB on CL (power)	-1.00 (-1.14 – -0.831)	---	7.66%
Covariate 2: WT on CL (power)	0.371 (0.254 – 0.481)	---	14.0%
Covariate 3: ADA on CL	0.188 (0.0303 – 0.356)	---	42.6%
Covariate 4: CRCL on CL (linear)	0.00147 (0.000704 – 0.00224)	---	28.6%
Covariate 5: ECOG (0 score) on CL	-0.0784 (-0.118 – -0.0468)	---	22.2%
Covariate 6: LDH on CL (power)	0.0915 (0.0593 – 0.122)	---	17.0%
Covariate 7: SPDL1 on CL (power)	0.0844 (0.0303 – 0.132)	---	30.8%
Covariate 8: TUMTYP2 (UC subgroup) on CL	0.180 (0.0818 – 0.286)	---	22.6%
Covariate 9: SEXN (female) on CL	-0.134 (-0.175 – -0.100)	---	13.8%
Covariate 10: SEXN (female) on V_1	-0.164 (-0.192 – -0.135)	---	9.33%
Covariate 11: WT on V_1 (power)	0.402 (0.321 – 0.477)	---	9.38%
Covariate 12: SEXN (female) on V_2	-0.234 (-0.296 – -0.163)	---	8.74%
Proportional residual error σ (CV%)	21.7% (20.9% – 22.5%)	---	1.91%

Additive error standard deviation σ (µg/mL)	0.259 (0.0849 – 0.466)	---	76.5%

ADA = antidrug antibody status; ALB = serum albumin; CI = confidence interval; CRCL = creatinine clearance; CV% = coefficient of variation in percent; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PK = pharmacokinetic; RSE% = relative standard error in percent; SE = standard error; SPDL1 = soluble PD-L1 level at baseline; UC = urothelial carcinoma; WT = weight; ω^2 = variance of omega; ω = standard deviation of omega; σ = standard deviation of sigma

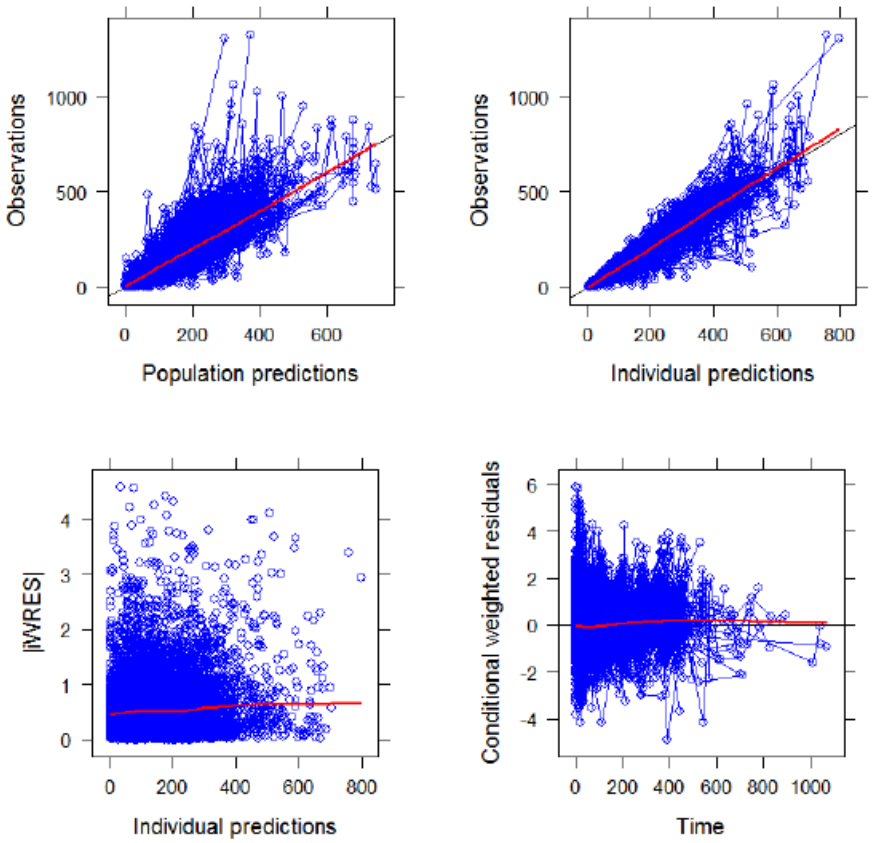
The parameter estimates are shown along with the bootstrap 95% CI of the estimate, based on 859 successful runs out of 1000 bootstrap replicates stratified by dose, to enable an adequate representation of the analysis data set in each replicate; note that parameters were reported based on 3 significant figures.

The RSEs were obtained from asymptotic SE in NONMEM ($COVARIANCE sandwich matrice $[R^{-1}SR^{-1}]$). For omega and sigma, RSEs are reported on the approximate standard deviation scale (SE/variance estimate)/2. Condition number of run65 is 240. η-shrinkage estimates of run65 were 15.9%, 20.6%, and 33.2% for CL, V_1, and V_2, respectively. ε-shrinkage estimate was 13.8%.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Table 6.4.1-1 on page 112.

Goodness-of-fit plots of the final model are presented in **Figure 4**.

Figure 3. Goodness-of-fit Plots of the Final Model

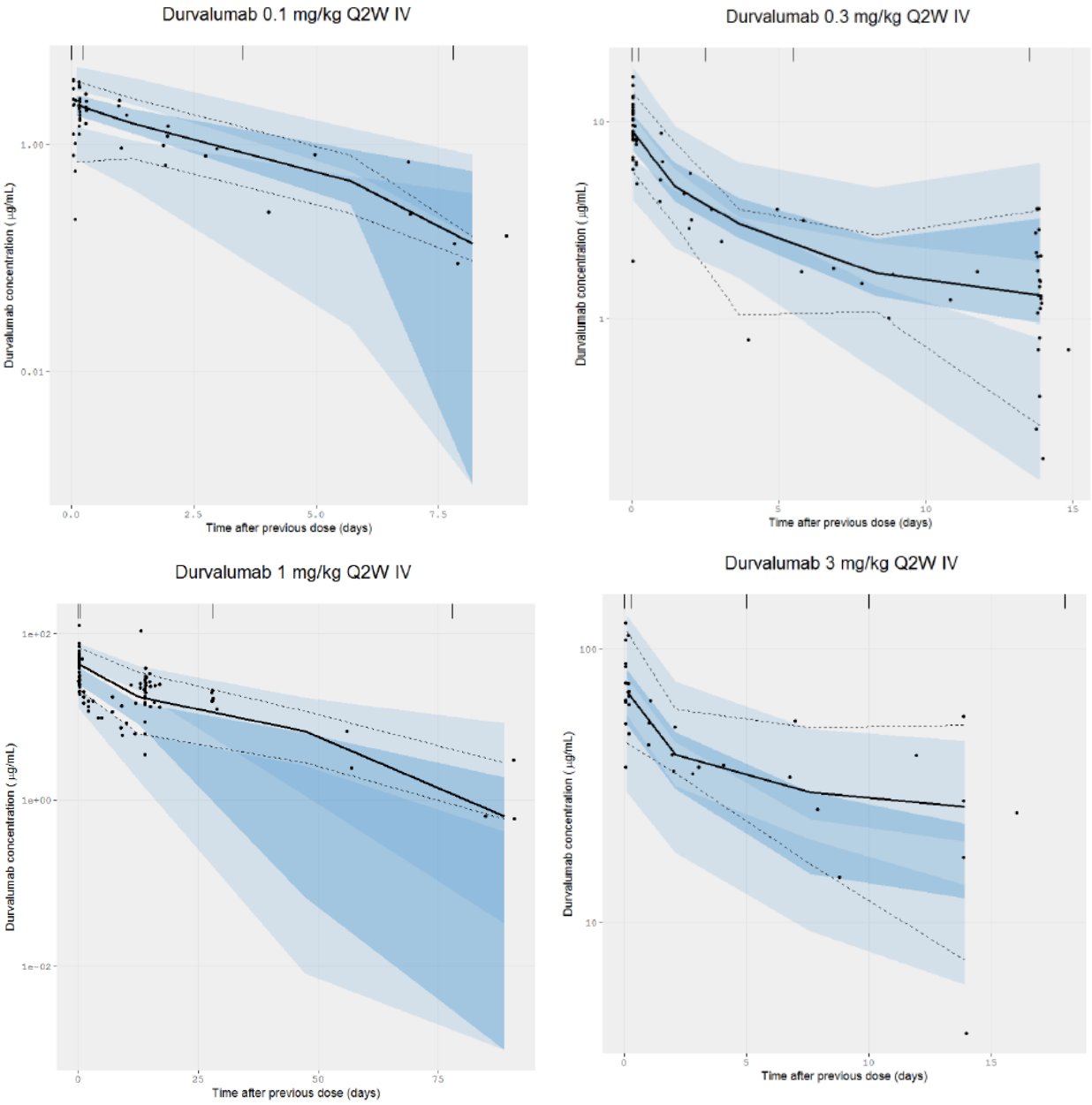


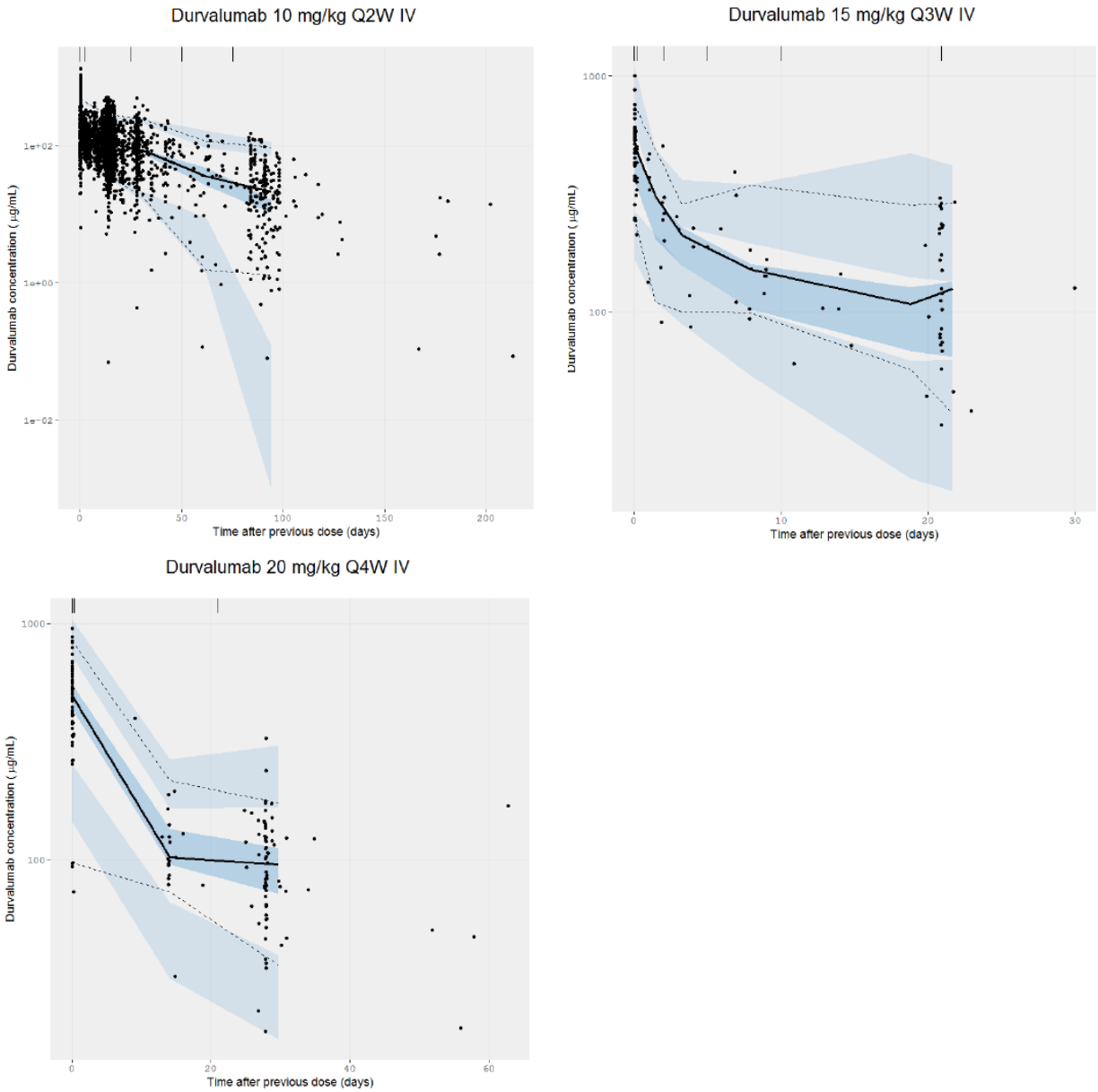
Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.1-1 on page 114.

Reference ID: 4065384

VPC results of the final model are presented in **Figure 5**.

Figure 4. VPC Plots of the Final PK Model (stratified by dose on log scales)





Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.3-1 on page 136-142.

Evaluation of impact of covariates on PK

The clinical significance of the 12 covariate-PK relationships incorporated in the final PK model was further evaluated. **Table 10** shows that none of the covariate relationships yielded a difference in PK parameters compared to a typical patient of 30% for the extreme of the continuous covariate distributions (taken as the 10^{th} and 90^{th} percentiles) or for the subgroup of interest of categorical covariates. The effect of covariates on durvalumab exposure parameters including AUC_{ss}, $Cmax_{ss}$, and $Cmin_{ss}$ is demonstrated in **Figure 6**. None of the covariates were found to be of clinical relevance based on individual impact evaluations of covariates on exposure metrics of durvalumab at steady state.

Table 10. Effect of Covariates on Durvalumab PK Exposure

PK parameters and baseline covariates	Percentile of covariate	Covariate value	Estimate	Percent change from typical (%) [a]
Clearance for a typical patient (CL; L/day)	---	---	**0.226**	---
Covariate 1: ALB on CL	10th percentile	30.0 g/L	0.286	+26.7%
	90th percentile	43.0 g/L	0.199	-11.6%
Covariate 2: WT on CL	10th percentile	51.0 Kg	0.202	-10.7%
	90th percentile	93.4 Kg	0.252	+11.8%
Covariate 3: ADA on CL	---	Positive	0.268	+18.8%
Covariate 4: CRCL on CL	10th percentile	57.0 mL/min	0.216	-4.5%
	90th percentile	134 mL/min	0.241	+6.9%
Covariate 5: ECOG on CL	---	ECOG=0	0.208	-7.8%
Covariate 6: LDH on CL	10th percentile	151 U/L	0.216	-4.1%
	90th percentile	604 U/L	0.246	+8.8%
Covariate 7: SPDL1 on CL	10th percentile	67.1 pg/mL	0.214	-5.1%
	90th percentile	204 pg/mL	0.235	+4.2%
Covariate 8: TUMTYP2 on CL	---	UC subgroup	0.266	+18.0%
Covariate 9: SEXN on CL	---	Female	0.195	-13.4%
V_1 for a typical patient (L)	---	---	**3.51**	---
Covariate 10: SEXN on V_1	---	Female	2.93	-16.4%
Covariate 11: WT on V_1	10th percentile	51.0 Kg	3.10	-11.5%
	90th percentile	93.4 Kg	3.96	+12.8%
V_2 for a typical patient (L)	---	---	**3.51**	---
Covariate 12: SEXN on V_2	---	Female	2.68	-23.4%

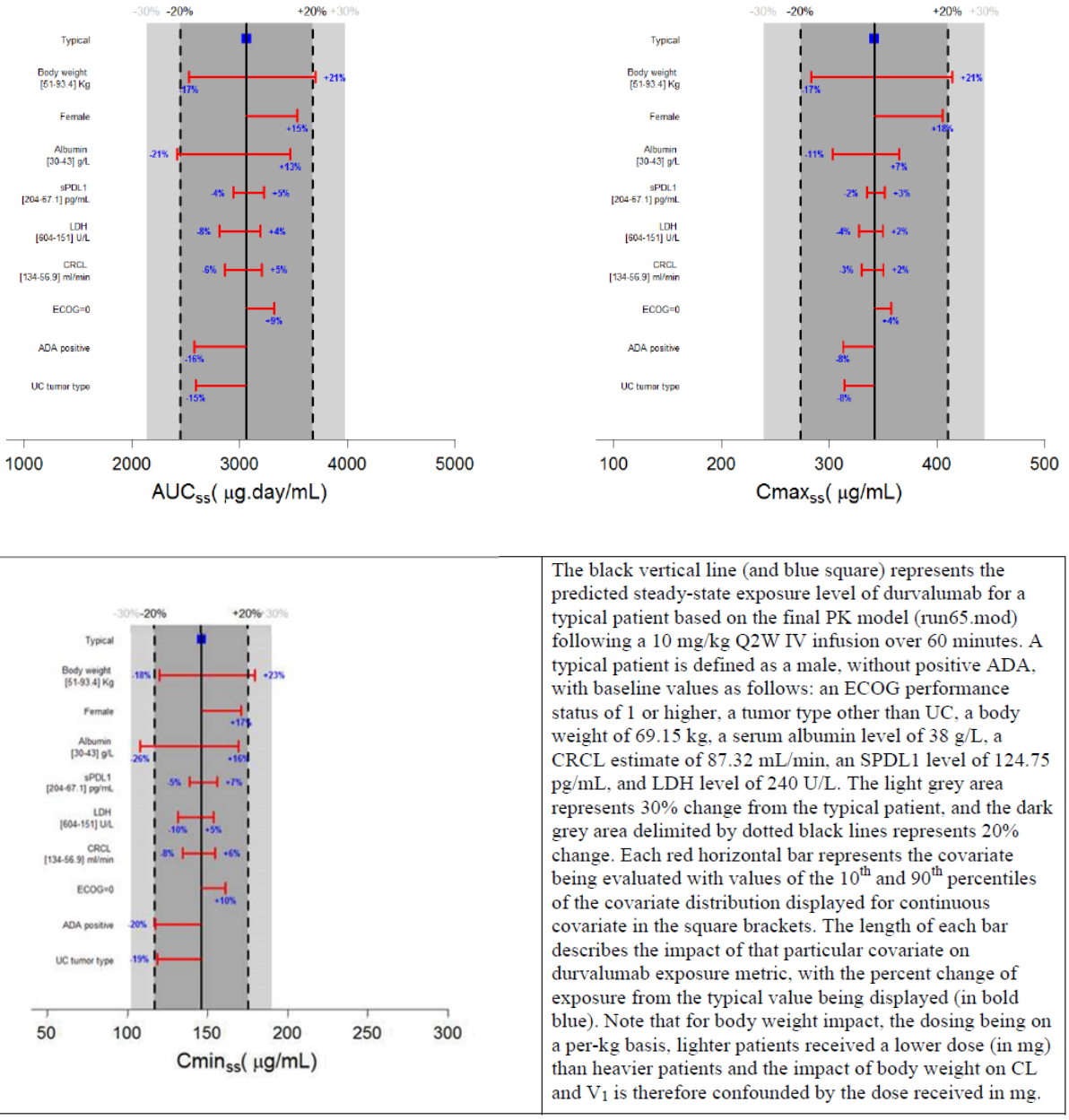
ADA = antidrug antibody status; ALB = serum albumin; CRCL = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PK = pharmacokinetic; SPDL1 = soluble PD-L1 level at baseline; V_1 = central volume; V_2 = peripheral volume; UC = urothelial carcinoma; WT = weight.

A typical patient is defined as a male, without positive ADA, with baseline values as follows: an ECOG performance status of 1 or 2, a tumor type other than UC, a body weight of 69.15 kg, a serum albumin level of 38 g/L, a CRCL estimate of 87.32 mL/min, a SPDL1 expression level of 124.75 pg/mL, and LDH level of 240 U/L.

[a] Estimates in the table were not rounded to 3 significant figures.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Table 6.4.2-1 on page 120.

Figure 5. Effect of Covariates on Exposure Parameters



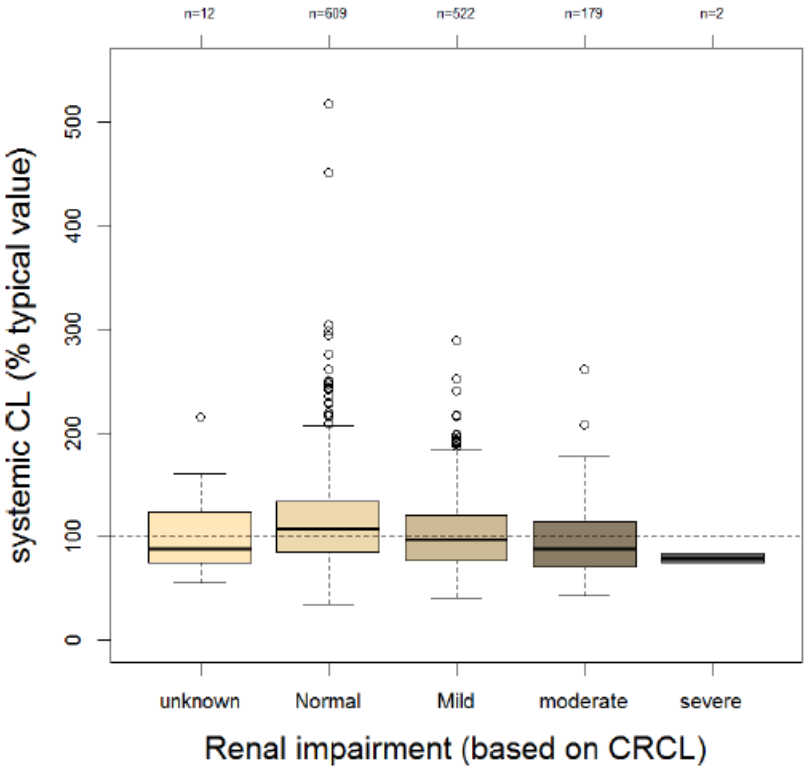
The black vertical line (and blue square) represents the predicted steady-state exposure level of durvalumab for a typical patient based on the final PK model (run65.mod) following a 10 mg/kg Q2W IV infusion over 60 minutes. A typical patient is defined as a male, without positive ADA, with baseline values as follows: an ECOG performance status of 1 or higher, a tumor type other than UC, a body weight of 69.15 kg, a serum albumin level of 38 g/L, a CRCL estimate of 87.32 mL/min, an SPDL1 level of 124.75 pg/mL, and LDH level of 240 U/L. The light grey area represents 30% change from the typical patient, and the dark grey area delimited by dotted black lines represents 20% change. Each red horizontal bar represents the covariate being evaluated with values of the 10th and 90th percentiles of the covariate distribution displayed for continuous covariate in the square brackets. The length of each bar describes the impact of that particular covariate on durvalumab exposure metric, with the percent change of exposure from the typical value being displayed (in bold blue). Note that for body weight impact, the dosing being on a per-kg basis, lighter patients received a lower dose (in mg) than heavier patients and the impact of body weight on CL and V_1 is therefore confounded by the dose received in mg.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.2-1 on page 122.

Effect of renal function on durvalumab PK

Based on the population PK analysis performed on patients with normal (n=609, 46.4%, CLcr ≥ 90 mL/min), mild (n=522, 39.8%, CLcr=60-89 mL/min), moderate (n=179, 13.6%, CLcr = 30-59 mL/min), and severe renal impairment (n=2, 0.2%, CLcr=15-29 mL/min), the effect of CLcr was not identified as having a clinically relevant impact on durvalumab PK since it did not change PK parameters (Figure 8) and exposure parameters (**Figure 7**) by more than 30% from a typical patient (defined with median CLcr of 87.32 mL/min). Data are not sufficient to draw definite conclusion on severely renal impaired patients.

Figure 6. Effect of Renal Function on Durvalumab Clearance

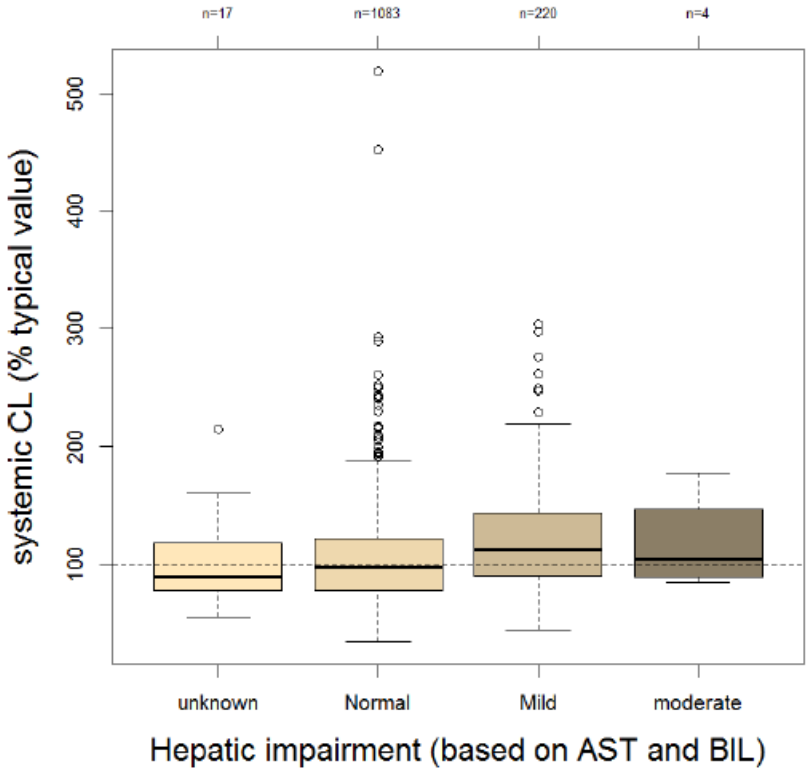


Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.2-3 on page 127.

Effect of hepatic function on durvalumab PK

Based on the population PK analysis performed on patients with normal hepatic function (n=1083, 82.9%, BIL ≤ ULN and AST ≤ ULN), mild hepatic impairment (n=220, 16.8%, BIL ≤ ULN and AST > ULN or BIL > 1 to 1.5 x ULN and any AST), moderate hepatic impairment (n=4, 0.3%, BIL > 1.5 to 3 x ULN and any AST), no clinically relevant effect of hepatic function was noticeable on the PK of durvalumab (**Figure 8**). This is corroborated by the covariate analysis of the PK model of durvalumab that showed no statistically significant impact of hepatic enzymes (AST, ALT, and BIL) on CL, V1, nor V2 of durvalumab. Data are, however, not sufficient to draw definite conclusions on moderate hepatic impairment patients (n=4) and severe hepatic impairment patients (none who received durvalumab).

Figure 7. Effect of Hepatic Function on Durvalumab Clearance



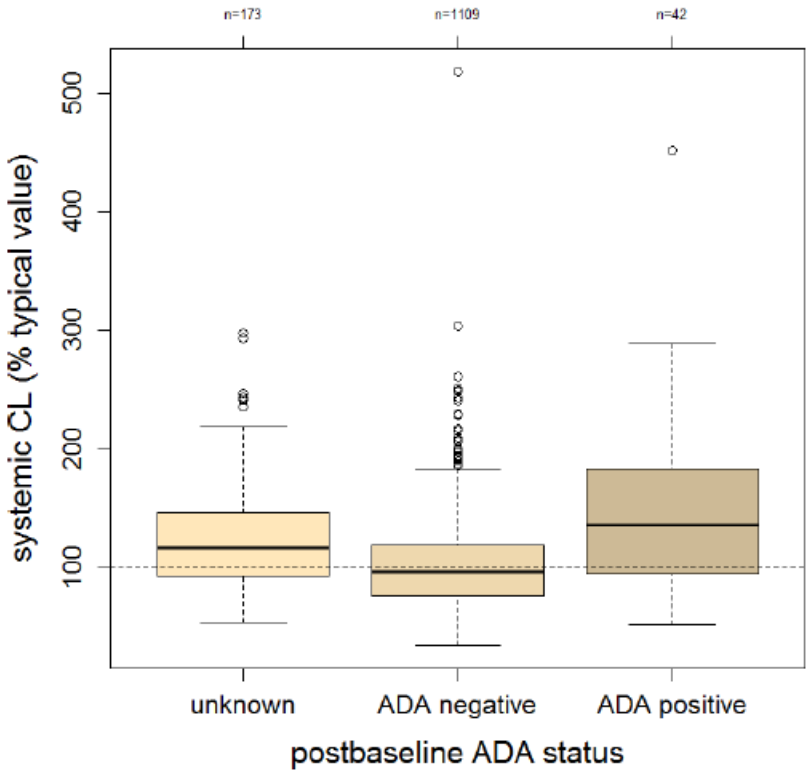
Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.2-4 on page 128.

Impact of Immunogenicity on Durvalumab PK

Durvalumab was confirmed with immunogenic potential only in a small proportion of patients who tested positive for post-baseline ADA (3.65% based on dataset-1, with n=42 patients whose samples tested positive for ADA post-first dose of durvalumab out of n=1109 patients whose samples tested negative and n=173 patients with no ADA data as. The percentage of patients whose samples tested positive for post-baseline ADA was similar across studies (3.27% for 1108 and 4.40% for ATLANTIC).

Despite a statistically significant enhanced CL of durvalumab for patients who tested ADA positive, as found in the final PK model, the CL of durvalumab for patients whose samples tested positive for post-baseline ADA was not found to be clinically different from the CL of durvalumab for patients whose samples tested negative (**Figure 9**). This confirms that despite a statistically significant impact of post-baseline ADA on the PK of durvalumab, immunogenicity would not warrant a dose-adaptation scheme.

Figure 8. Effect of Immunogenicity on Durvalumab Clearance



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 population PK modeling and simulation report Figure 6.4.2.1-2 on page 134.

Reviewer's Comments:

The applicant's population PK model seems to be able to describe the durvalumab concentration-time profiles reasonably well. However, potential time-varying clearance of durvalumab was not evaluated in the applicant's model, which could be important for labeling the clinical pharmacology section. Since time-varying PK has been well established for other previously approved PD-1/PD-L1 mAbs including nivolumab, atezoliaumab and pembrolizumab, it's highly likely that durvalumab also has a time-varying clearance. Therefore, the FDA reviewer refined the applicant's population PK model by incorporating the time-varying clearance component. The refined model with a time-varying clearance converged successfully and resulted in an OFV decrease of 791 comparing to the applicant's final model.

Although statistically significant covariates including ALB, body weight, sex, LDH, ECOG, post-baseline ADA, tumor type, CLcr, and sPDL1 were retained in the final model, none of the covariates were found to be of clinical relevance based on individual impact on exposure metrics of durvalumab at steady state (<30% change from a typical patient). Therefore, the FDA reviewer agrees with the applicant's conclusion that no dose adjustment is needed based on baseline patient characteristics including mild to moderate renal impairment and mild hepatic impairment.

4.3.2 Reviewer's Analysis

Introduction

It is well accepted that PD-1/PD-L1 targeting treatments exhibit time-varying PK phenomenon, as documented in labels of TECENTRIQ (atezoliaumab) BLA 761041, OPDIVO (nivolumab) BLA 125544, and KEYTRUDA (pembrolizumab) BLA 125514. Therefore, it's highly likely that durvalumab, as a PD-L1 targeting mAb, also has a time-varying PK profile. The FDA reviewer conducted population PK analysis to evaluate the potential time-varying PK of durvalumab.

Objectives

- To confirm Applicant's population PK analysis results.
- To assess the potential time-varying clearance in the population PK model.

Methods

Data sets

Data sets used in this analysis are summarized in **Table 11**.

Table 11. Summary of data sets used in the reviewer's population PK analysis

Name	Link to EDR
pknm1co.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing Reviews\Durvalumab_BLA761069_XW\PPK PM Analyses\ pknm1co.csv
pknm1co_gt3mgkg.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing Reviews\Durvalumab_BLA761069_XW\PPK PM Analyses\Time-varing PK run\ pknm1co_gt3mgkg.csv

Software

NONMEM and R were used for the reviewer's analysis.

Modeling Method

A time-varying clearance component was incorporated in the population PK model using the following model structure:

$$CL_{TDPKi} = TVCL \cdot e^{\frac{(T_{max}+\eta_{T_{max}})\cdot Time^{\gamma}}{T50+Time^{\gamma}}} \cdot Cov \cdot e^{\eta_i}$$

In addition, the following refinements were made to stabilize the model and solve the rounding error issue.

- Update of the dataset by excluding patients on doses less than or equal to 3 mg/kg (durvalumab exhibits nonlinear PK at doses less than 3 mg/kg)
- Deletion of the Michaelis-Mention clearance component
- Deletion of ETA on V2

Reference ID: 4065384

Results

The updated population PK model incorporating the time-varying PK component converged successfully and resulted in an OFV decrease of 791 comparing to the applicant's final model. Parameter estimates are shown in **Table 12**. Assessment of goodness-of-fit plots suggests that the updated model with time-varying PK can adequately describe the durvalumab concentration-time profiles (**Figure 10**). Based on the updated modeling results, the following labeling statement was proposed by the FDA reviewer and accepted by the applicant:

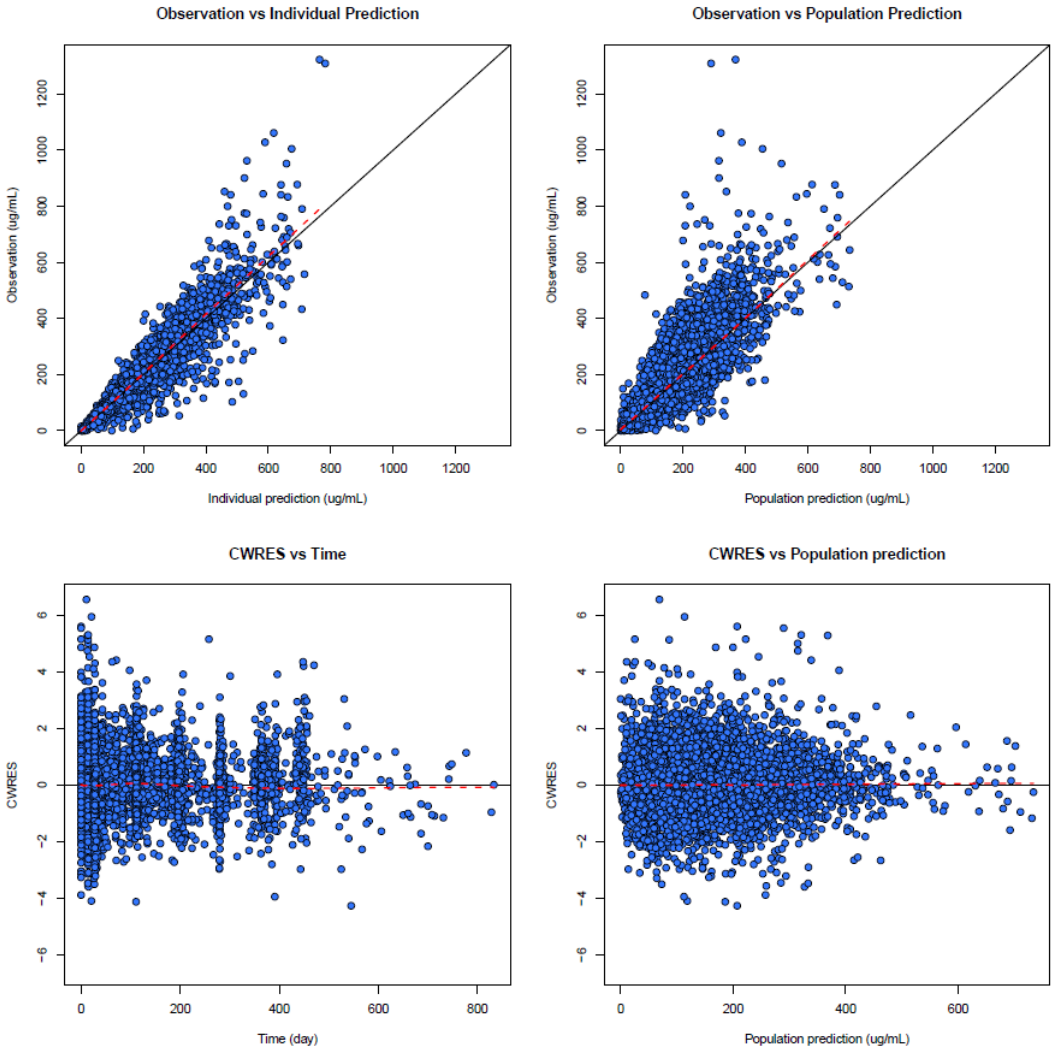
"Durvalumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.24 mL/h (37.3%); the decrease in CLss is not considered clinically relevant."

Table 12. Summary of Parameter Estimates of the Updated Population PK Model

Parameters	Estimates	Between-patient variability	RSE%
Clearance (CL; L/day)	0.266	27.2%	CL = 15.2%; ω^2_{CL} = 3.7%
Central volume (V_1; L)	3.51	22.1%	V1 = 1.2%; ω^2_{V1} = 4.7%
Peripheral volume (V_2; L)	2.64		16.8%
Inter-compartmental clearance (Q; L/day)	0.455		11.6%
Log maximum magnitude change in CL (T_{max}; L/day)	-0.269	28.1%	Tmax = 46.5%; ω^2_{Tmax} = 34.2%
Time when half T_{max} is achieved (TC50; days)	113		56.2%
Sigmoid factor of time-varying CL (γ)	1.66		62%
Covariate 1: ALB on CL (power)	-0.906		12.8%
Covariate 2: WT on CL (power)	0.302		16.9%
Covariate 3: ADA on CL	0.238		35%
Covariate 4: CLcr on CL (linear)	0.0015		32.7%
Covariate 5: ECOG (0 score) on CL	-0.0701		178.3%
Covariate 6: LDH on CL (power)	0.0729		65.2%
Covariate 7: SPDL1 on CL (power)	0.086		46%
Covariate 8: TUMTYP2 (UC subgroup) on CL	0.159		45.7%
Covariate 9: SEXN (female) on CL	-0.14		120.7%
Covariate 10: SEXN (female) on V_1	-0.157		14.3%
Covariate 11: WT on V_1 (power)	0.432		9.2%

Covariate 12: SEXN (female) on V_2	-0.226	147.8%
Proportional residual error σ (CV%)	4.55%	4.3%
Additive error standard deviation σ (µg/mL)	24.1	26.3%

Figure 9. Goodness-of-fit Plots of the Updated Population PK Model



4.4 Exposure-Response Analyses

4.4.1 Applicant's Exposure-Efficacy Analyses

Objective

To assess the potential relationships between durvalumab exposure metrics (observed maximum serum drug concentration after first dose [$C_{max,1}$], observed trough concentration levels after second dose [$C_{min,2}$] and at steady state [$C_{min,ss}$]), and efficacy parameters (objective response rate

Reference ID: 4065384

[ORR], best percentage change in target lesion from baseline, and duration of response [DoR]) in patients with UC.

Data and Methods

Data from study 1108 UC cohort at 10 mg/kg Q2W dose level was used for the exposure-efficacy analyses.

Observed individual $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$ values were used as the exposure metrics for the exposure-efficacy analyses. The efficacy metrics included ORR, DoR, and best percentage change in target lesion from baseline as assessed by a Blinded Independent Central Review (BICR) according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. For exposure-ORR analysis, each patient was classified as responder or non-responder. Responders are defined as patients who had complete response (CR) or partial response (PR) according to RECIST 1.1. Graphically exploration and logistic regression were employed to evaluate the potential relationship between these exposure and efficacy metrics.

Data processing and analyses were performed using R version 3.2.2 under R studio.

Results

A total of 96 UC patients with PK exposure data (out of 103 UC patients in the efficacy population) from study 1108 UC cohort were included in the analysis. $C_{max,1}$ values were available in 94 UC patients and 3 out of 94 $C_{max,1}$ values were exclude from the analysis as aberrant high or low $C_{max,1}$ values. $C_{min,2}$ and $C_{min,ss}$ values were available in 81 UC patients and 37 UC patients, respectively. **Table 13** lists the summary of PK exposure metrics used in the exposure-efficacy analyses.

Table 13. Summary Statistics of PK Exposure Metrics in Exposure-Efficacy Population

PK exposure	$C_{max,1}$ (µg/mL)	$C_{min,2}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
N	91	81	37
Mean ± SD	212 ± 54.8	93.3 ± 53.2	171 ± 84.4
25th percentile	177	55.4	128
Median	204	90.2	145
75th percentile	235	120	194
CV %	25.8	57.0	49.4

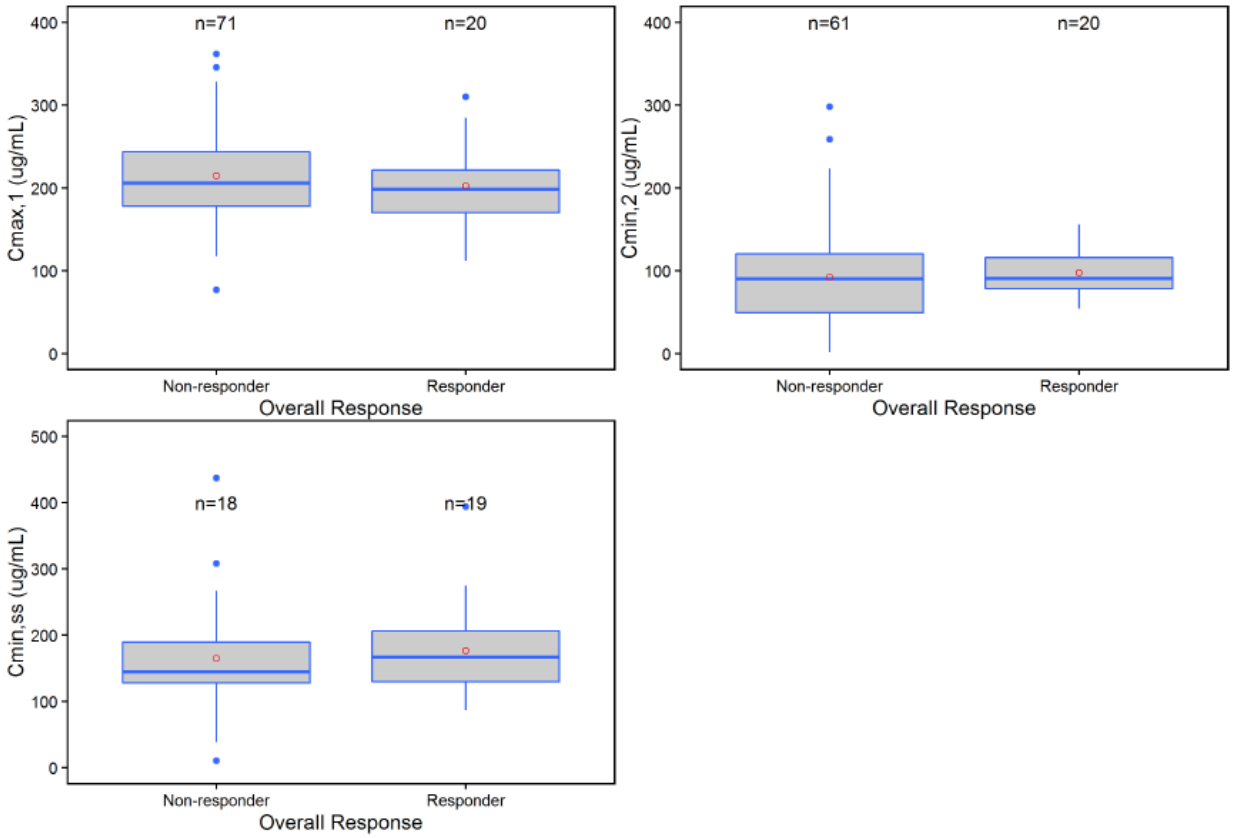
SD = Standard deviation.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Table 7.1.1-1 on page 21.

Exposure-ORR Analysis Results

No significant relationship between observed durvalumab exposure metrics ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) and ORR was identified within the exposure range at 10 mg/kg Q2W dosing regimen using both graphical exploration and logistic regression, as shown in **Figure 11 and Figure 12.**.

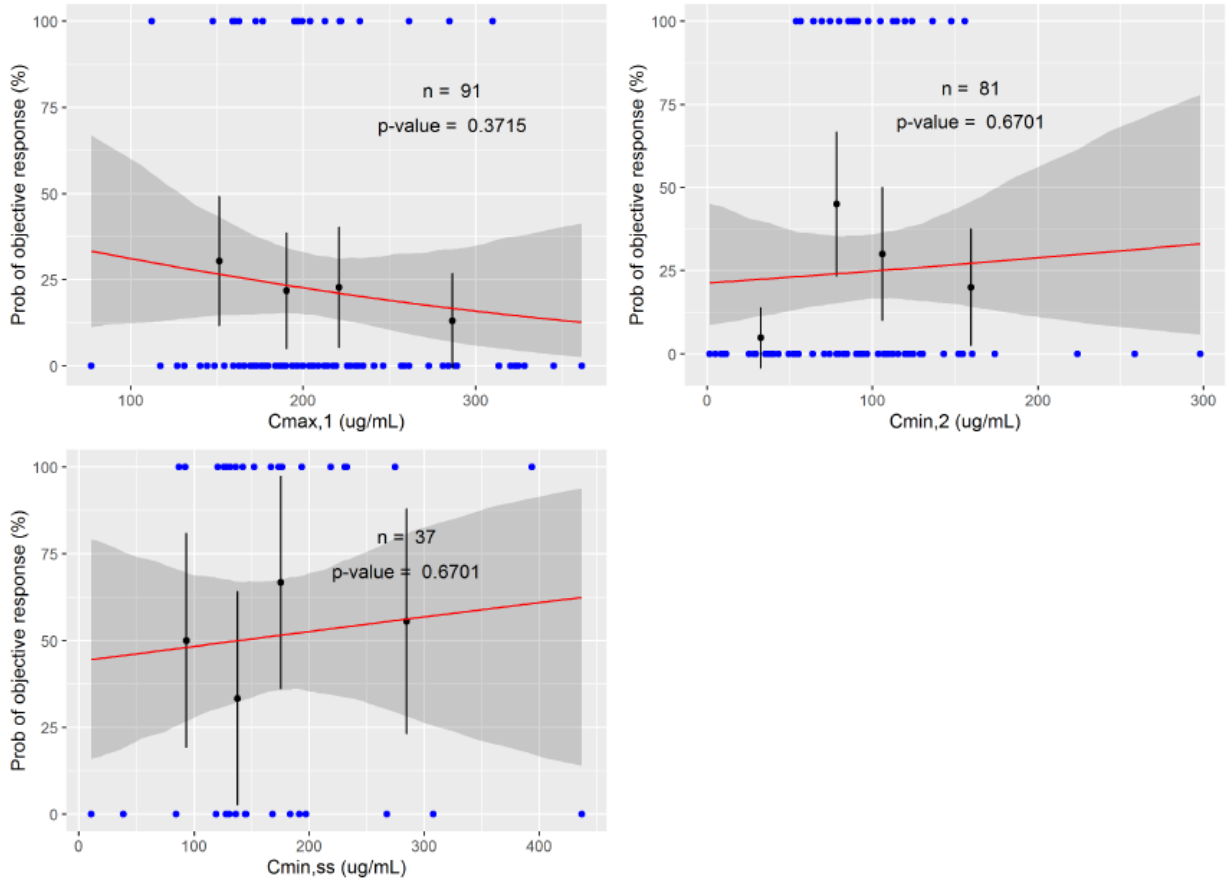
Figure 10, Boxplots of Durvalumab PK Exposures versus ORR



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.1.2-1 on page 22.

Reference ID: 4065384

Figure 11. Logistic Regression of Probability of Objective Response versus PK Exposures



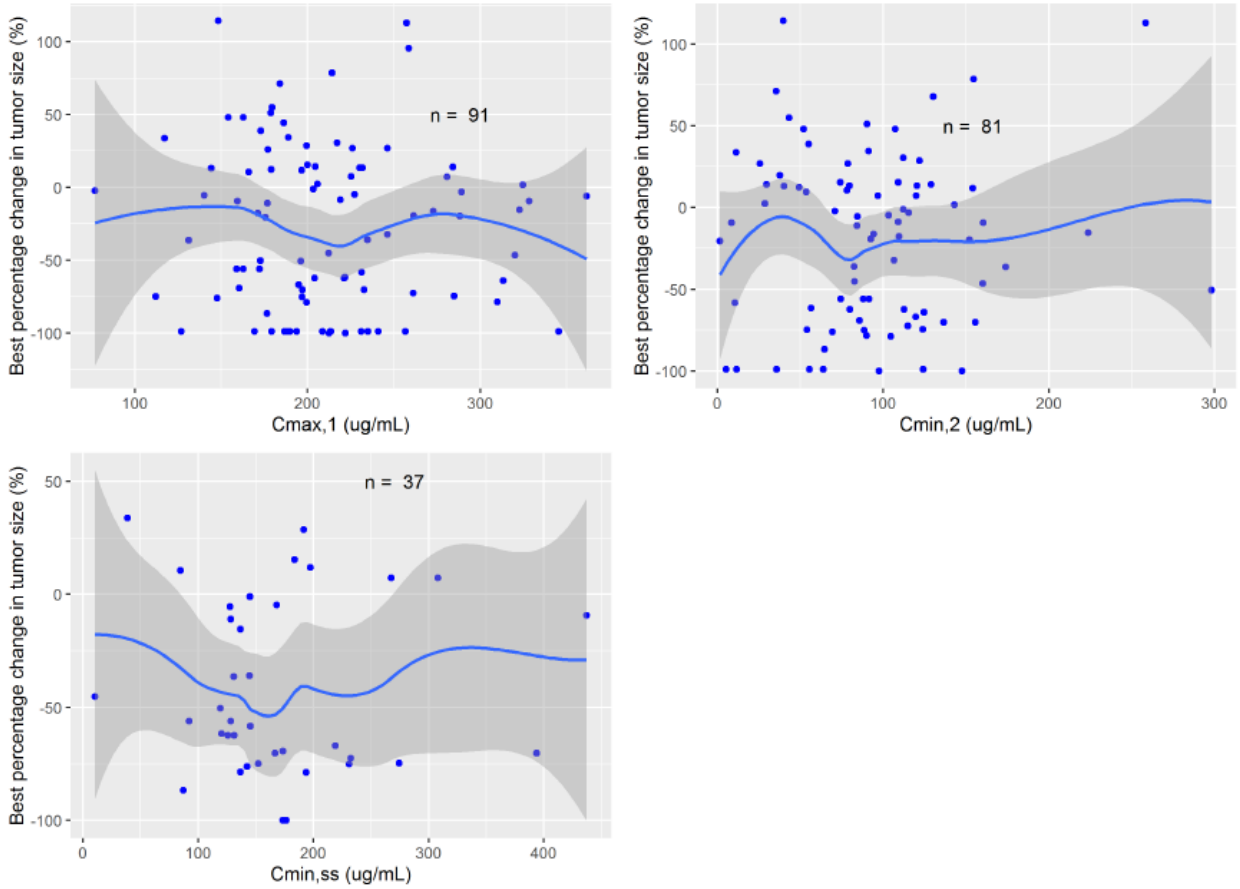
Note: Solid line and shaded area represent the model prediction with 95% prediction interval (PI); dots are incidence rate at exposure quartile with standard error bar; blue circles are observed exposure with the event (0%: Nonresponder; 100%: Responder)

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.1.2-2 on page 23.

Exposure-Best Percentage Change in Target Lesion from Baseline Analysis Results

No apparent relationship between durvalumab exposure metrics ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) and best percentage change in target lesion from baseline was identified by graphical exploration, as shown in **Figure 13.**

Figure 12. Durvalumab Exposure versus Best Percentage Change in Target Lesion from Baseline



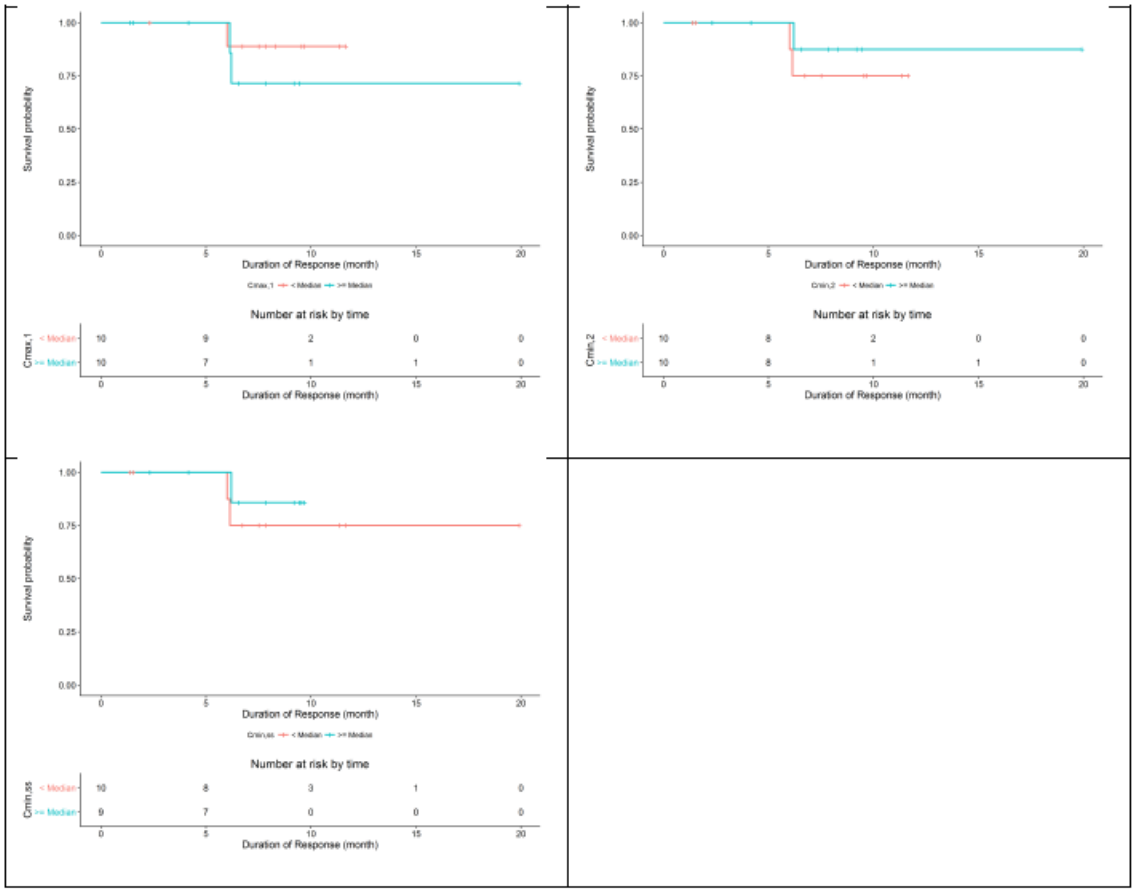
Note: Solid line and shaded area represent LOESS regression line with 95% prediction interval (PI); dots represent observed data.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.1.3-1 on page 24.

Exposure-DoR Analysis Results

Limited data was available for the exposure-DoR analysis. At the time of the DCO (data cut-off), 20 out of the 21 responders had exposure data. 17 out of the 20 responders with exposure data had ongoing response at the time of DCO. The exposure-DoR relationship was only explored graphically using Kaplan-Meier plots of DoR stratified by median of $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$, respectively. Due to such limited data, median DoR for each exposure subgroup has not been reached. Therefore, no conclusion on the exposure-DoR relationship can be made.

Figure 13. Kaplan-Meier Estimate of Duration of Response by BICR Stratified by Exposure Median



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.1.4-1 on page 25.

Conclusion

No exposure response relationship was observed between durvalumab exposure metrics ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) and efficacy endpoints including ORR, DoR, and best percentage change in target lesion from baseline.

Reviewer's Comments:

The exposure-efficacy analysis results should be interpreted with caution due to limitations of ER analysis based on data from a single arm immunotherapy study in cancer patients. Potential interaction between patient response status and late exposure metric, as well as potentially imbalanced risk factors are likely to confound the analysis. Therefore, the exposure-efficacy relationship for durvalumab is considered inconclusive with currently available data.

4.4.2 Applicant's Exposure-Safety Analyses

Objective

To assess the potential relationships between durvalumab exposure metrics ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$), and the occurrence of treatment-emergent adverse events (AEs) (any grade, Grade 2+,

Grade 3+ AE (any type); any grade, Grade 2+, Grade 3+ drug-related AE (any type); any grade, Grade 2+, Grade 3+ treatment-emergent adverse events of special interest AESI (any type); any grade, Grade 2+, Grade 3+ drug-related AESI (any type) and AE leading to discontinuation of treatment).

Data and Methods

Data from study 1108 and study ATLANTIC were used for the exposure-safety analyses.

Observed individual $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$ values were used as the exposure metrics to explore the potential relationship between durvalumab exposure and safety endpoints including AEs (any type of any grade, Grade 2+, Grade 3+), drug-related AEs (any type of any grade, Grade 2+, Grade 3+), AESIs (any type of any grade, Grade 2+, Grade 3+), drug-related AESIs (any type of any grade, Grade 2+, Grade 3+), and AE leading to discontinuation of treatment. The exposure-safety analysis was performed with 3 different datasets, including the cohort of UC patients in study 1108 dosed with 10 mg/kg Q2W IV dose, the study 1108 dataset including all solid tumors but only focusing on the 10 mg/kg Q2W IV dose and the ATLANTIC study dataset with all cohorts at 10 mg/kg Q2W IV dose level.

Potential confounding issues by factors such as Baseline Eastern Cooperative Oncology Group (ECOG), anti-drug antibodies (ADA) (ADA positive at post-baseline), sPD-L1 level at baseline, PDL1 status at baseline, baseline aspartate aminotransferase (AST), baseline alanine aminotransferase (ALT), baseline serum creatinine (CRE), baseline creatinine clearance (CLcr), lactate dehydrogenase at baseline (LDH), baseline total bilirubin(BIL), and baseline albumin (ALB) were also explored.

All data processing and analyses were performed using R version 3.2.2 under R studio.

Results

Exposure-safety analysis results (Study 1108; UC patients)

Observed individual $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$ values were used as the exposure metrics to assess the relationship between durvalumab exposure and various safety endpoints with data from the study 1008 UC cohort using logistic regression. Summary statistics of the exposure metrics are presented in **Table 14**. Logistic regression results show that increasing PK exposure levels ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) were not associated with an increased risk of Grade 3+ AEs, Grade 3+ drug-related AE, Grade 3+ AESI, Grade 3+ drug-related AESI and AEs leading to discontinuation (**Figure 15, Figure 16, and Figure 17**).

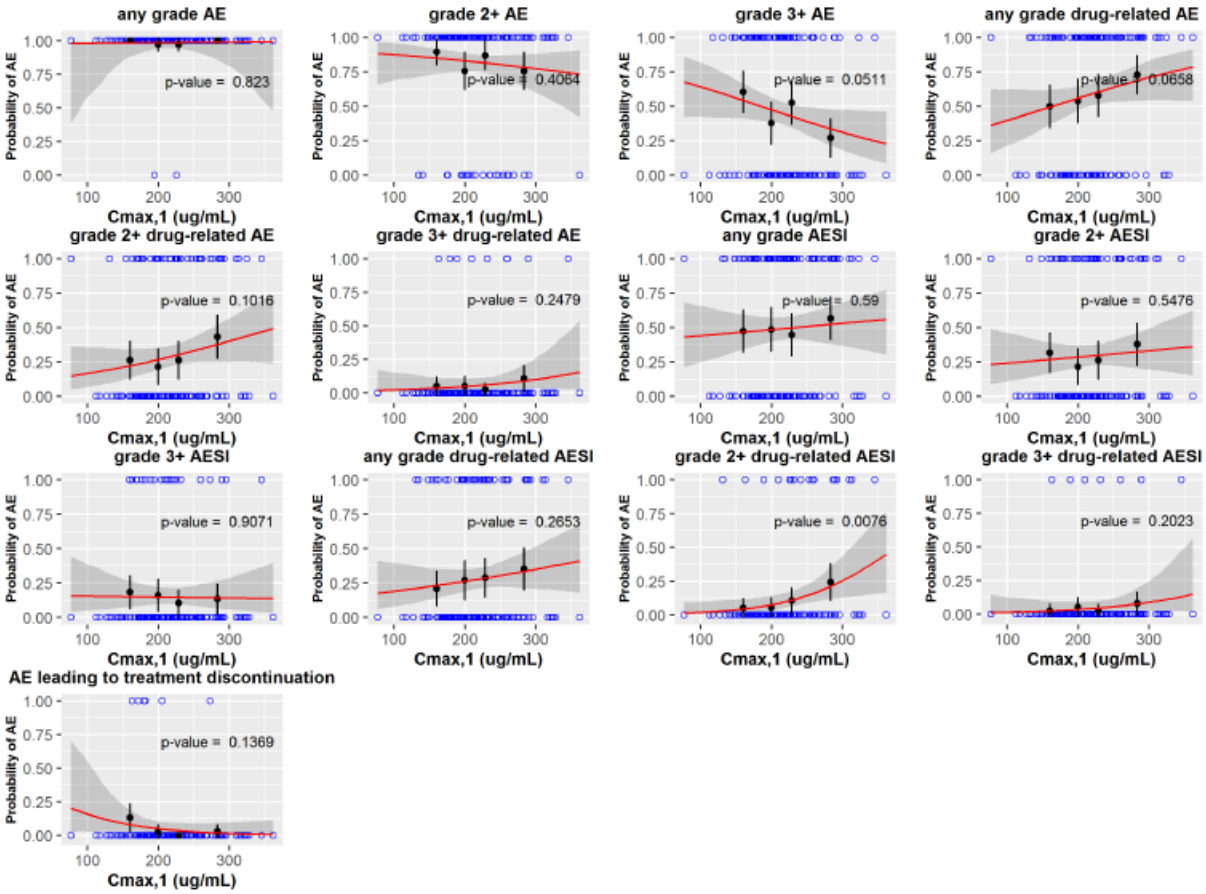
Table 14. Summary Statistics of PK Exposure (Study 1108; UC patients)

PK exposure	$C_{max,1}$	$C_{min,2}$	$C_{min,ss}$
N	150	111	37
Mean ± SD	218 ± 49.1	96.4 ± 50.0	171 ± 84.4
25th percentile	182	63.7	128
Median	214	94.2	145
75th percentile	246	123	194
CV%	22.5	51.9	49.4

CV% = Coefficient of variation.

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Table 7.2.1.1-1 on page 26.

Figure 14. Logistic Regression of AE Incidence versus $C_{max,1}$ (Study 1108; UC patients)

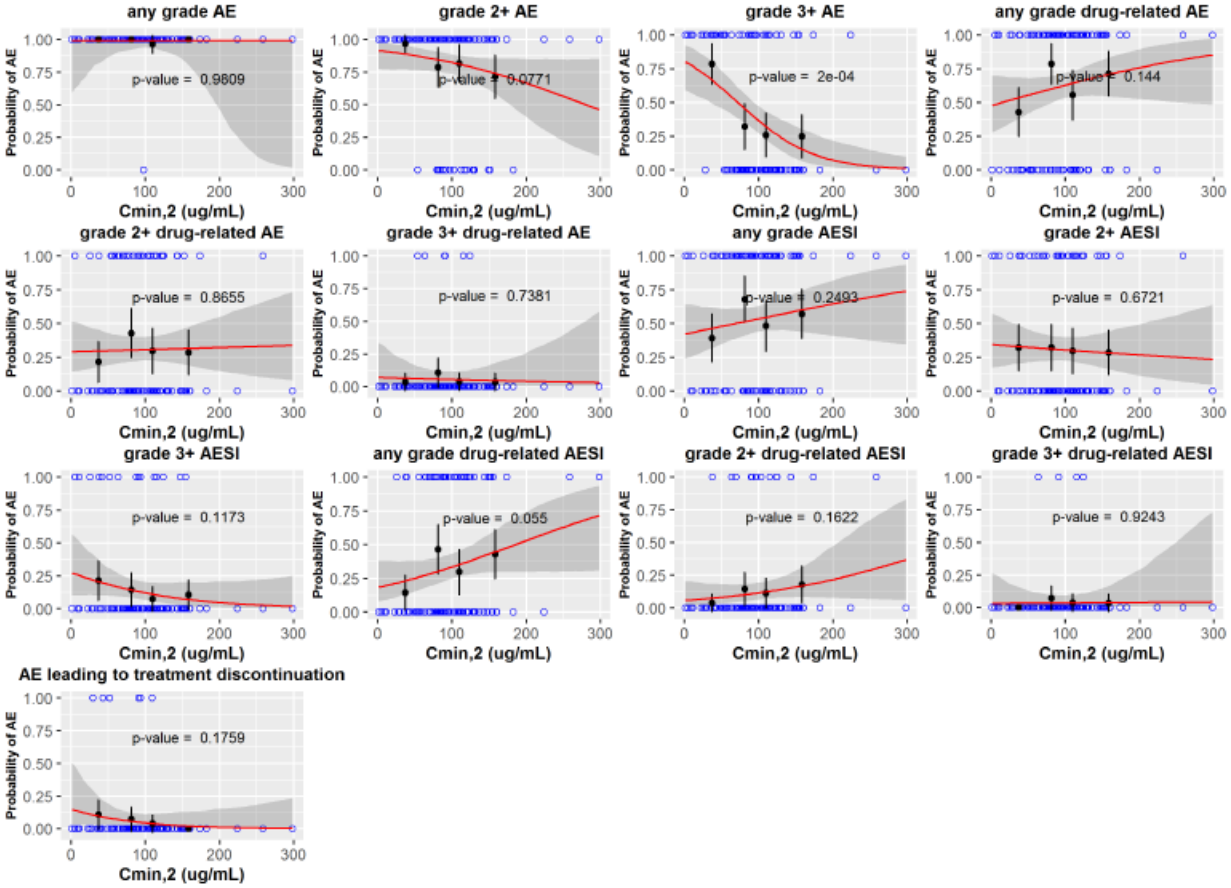


Solid line and shaded area represent the model prediction with 95% PI; dots are incidence rate at exposure quartile with standard error bar; blue circles are observed exposure with the event (0: No AE; 1: AE occurred)

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.1.2-4 on page 30.

Reference ID: 4065384

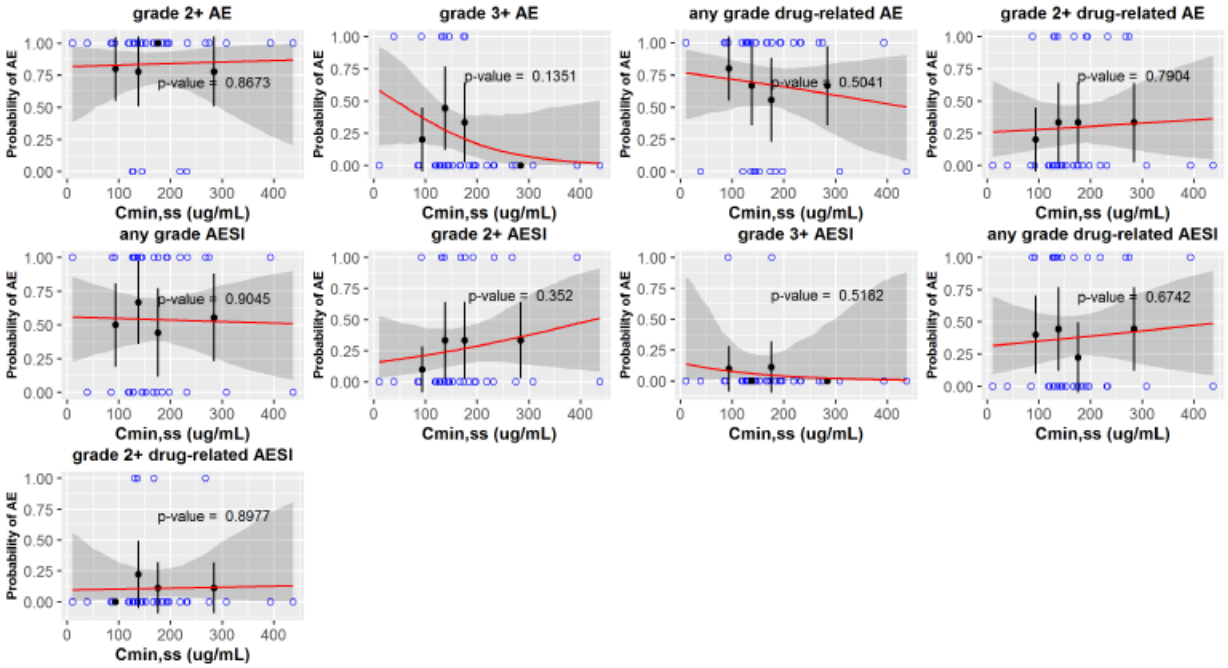
Figure 15. Logistic Regression of AE Incidence versus $C_{min,2}$ (Study 1108; UC patients)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.1.2-5 on page 31.

Reference ID: 4065384

Figure 16. Logistic Regression of AE Incidence versus $C_{min,ss}$ (Study 1108; UC patients)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.1.2-6 on page 32.

Exposure-safety analysis results (Study 1108; all patients)

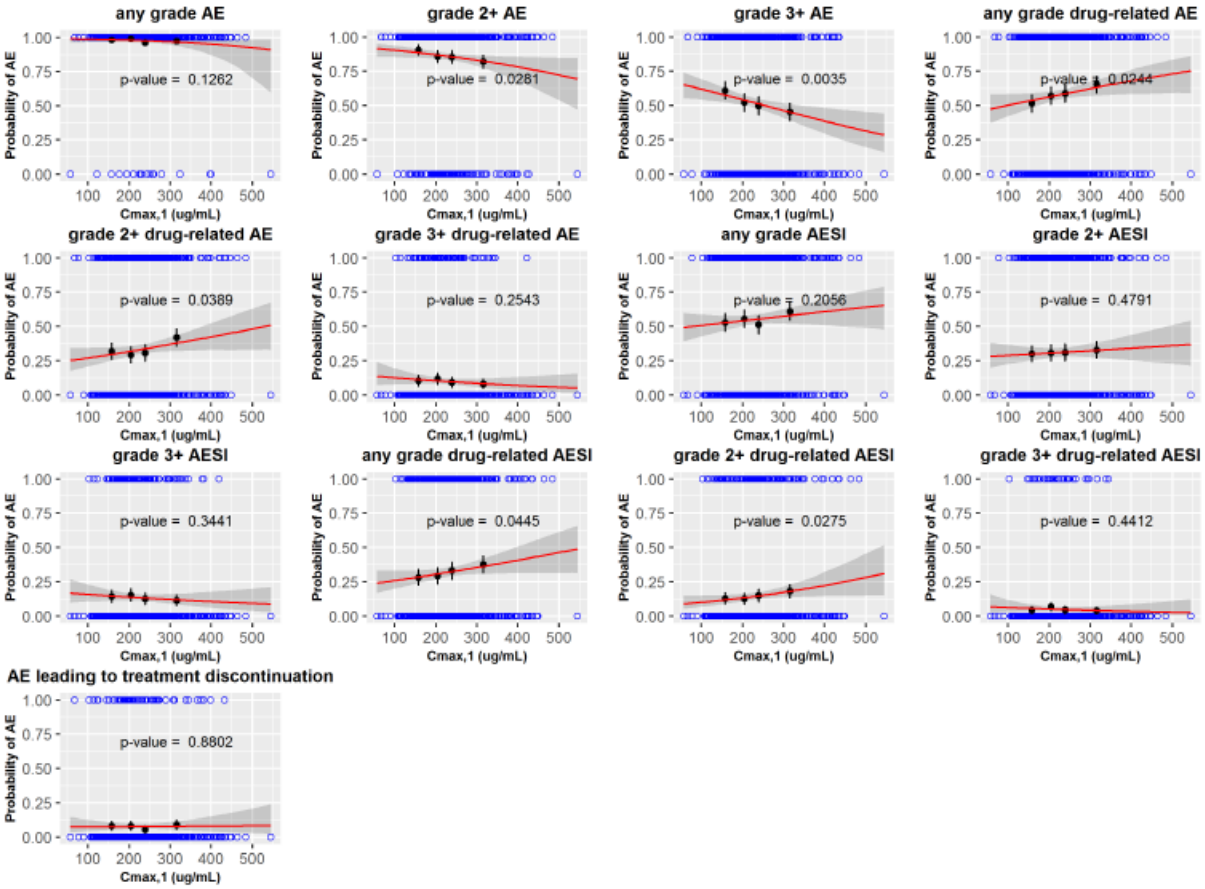
Observed individual $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$ values were used as the exposure metrics to assess the relationship between durvalumab exposure and various safety endpoints with data from all patients in study 1008 using logistic regression. Summary statistics of the exposure metrics are presented in **Table 15**. Logistic regression results show that increasing PK exposure levels ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) were not associated with an increased risk of Grade 3+ AEs, Grade 3+ drug-related AE, Grade 3+ AESI, Grade 3+ drug-related AESI and AEs leading to discontinuation (**Figure 18, Figure 19 and Figure 20**).

Table 15. Summary Statistics of PK Exposure (Study 1108; all patients)

PK exposure	$C_{max,1}$	$C_{min,2}$	$C_{min,ss}$
n	838	819	334
Mean ± SD	229 ± 65.1	86.5 ± 42.8	176 ± 83.7
25th percentile	185	56.6	121
Median	222	81.4	162
75th percentile	260	112	217
CV %	28.4	49.5	47.6

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Table 7.2.2.1-1 on page 36.

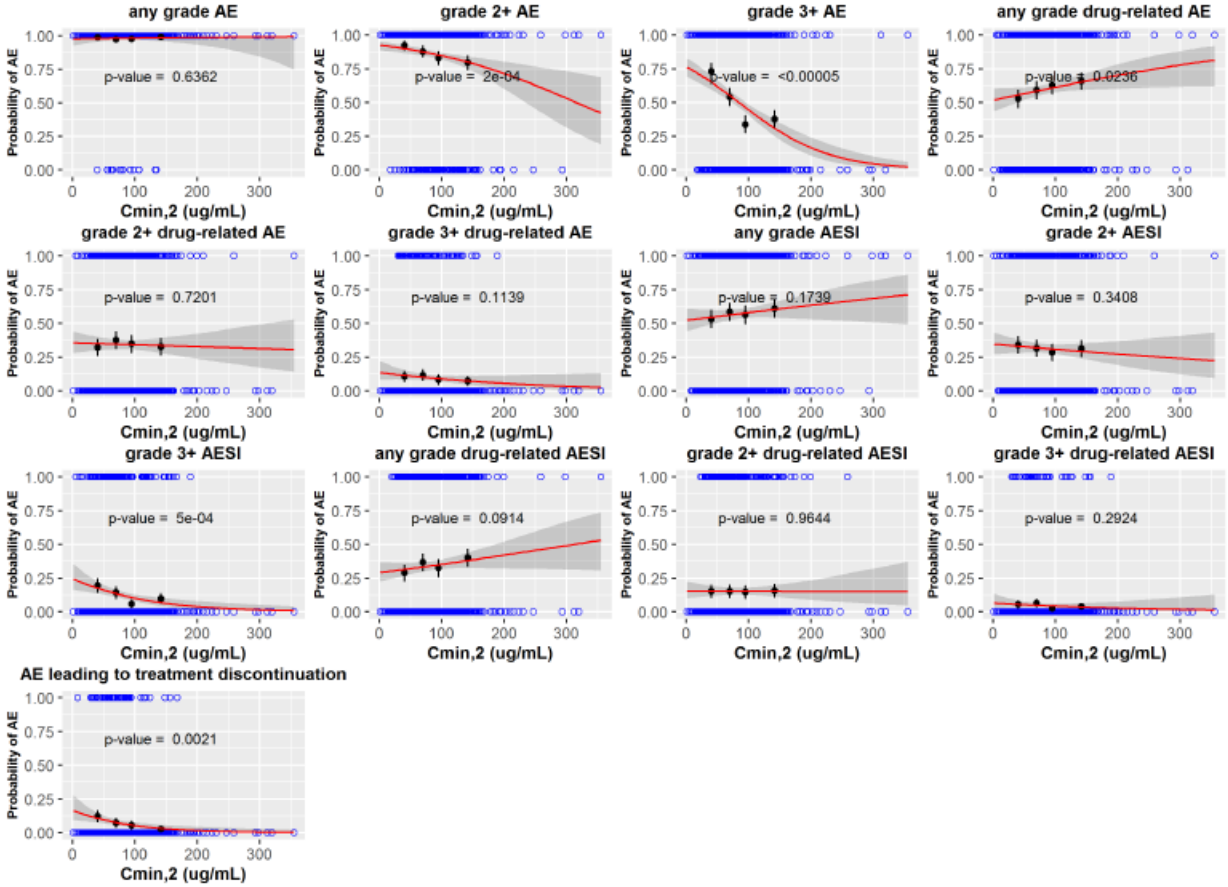
Figure 17. Logistic Regression of AE Incidence versus $C_{max,1}$ (Study 1108; all patients)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.2.2-4 on page 40.

Reference ID: 4065384

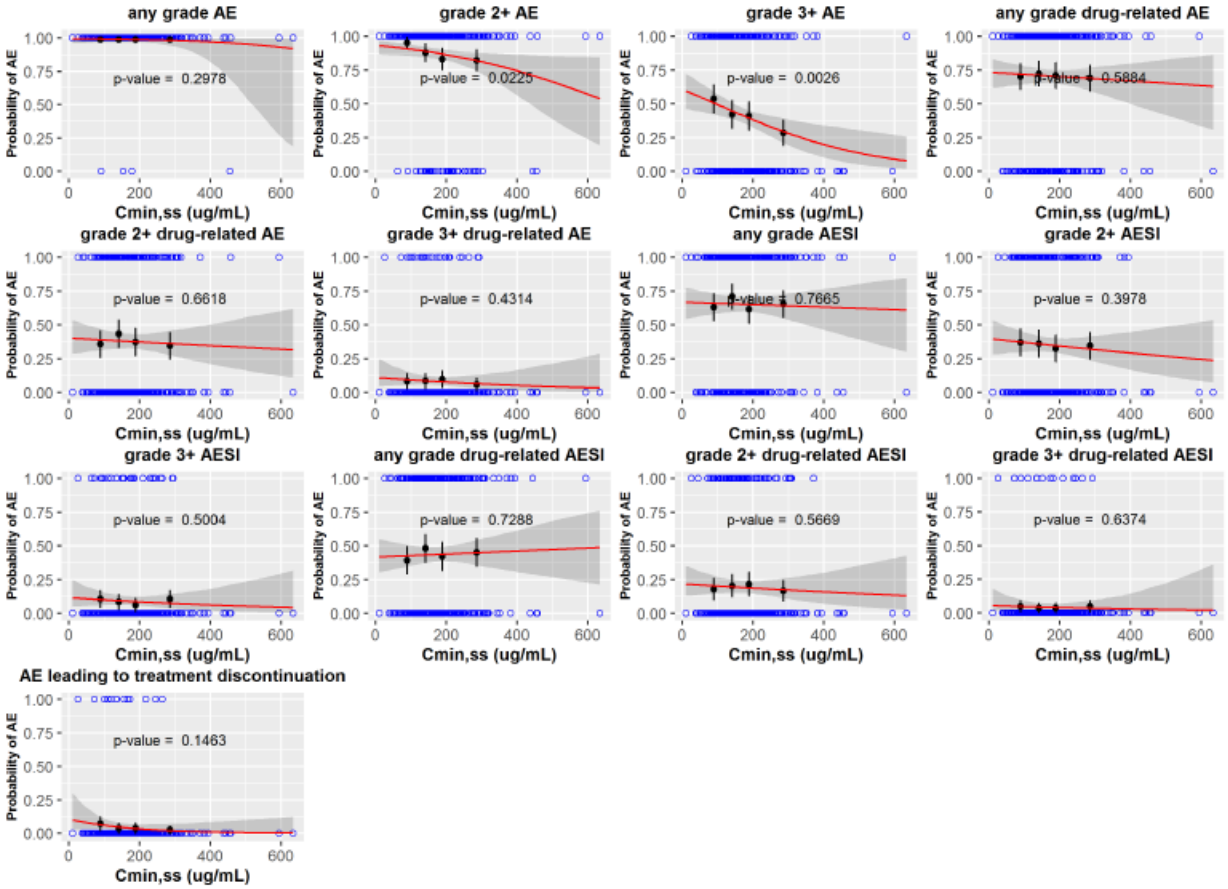
Figure 18. Logistic Regression of AE Incidence versus $C_{min,2}$ (Study 1108; all patients)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.2.2-5 on page 41.

Reference ID: 4065384

Figure 19. Logistic Regression of AE Incidence versus $C_{min,ss}$ (Study 1108; all patients)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.2.2-6 on page 42.

Exposure-safety analysis results (Study ATLANTIC)

Observed individual $C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$ values were used as the exposure metrics to assess the relationship between durvalumab exposure and various safety endpoints with data from study ATLANTIC using logistic regression. Summary statistics of the exposure metrics are presented in **Table 9**. Logistic regression results show that increasing PK exposure levels ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) were not associated with an increased risk of Grade 3+ AEs, Grade 3+ drug-related AE, Grade 3+ AESI, Grade 3+ drug-related AESI and AEs leading to discontinuation (**Figure 23**, **Figure 24**, and **Figure 25**).

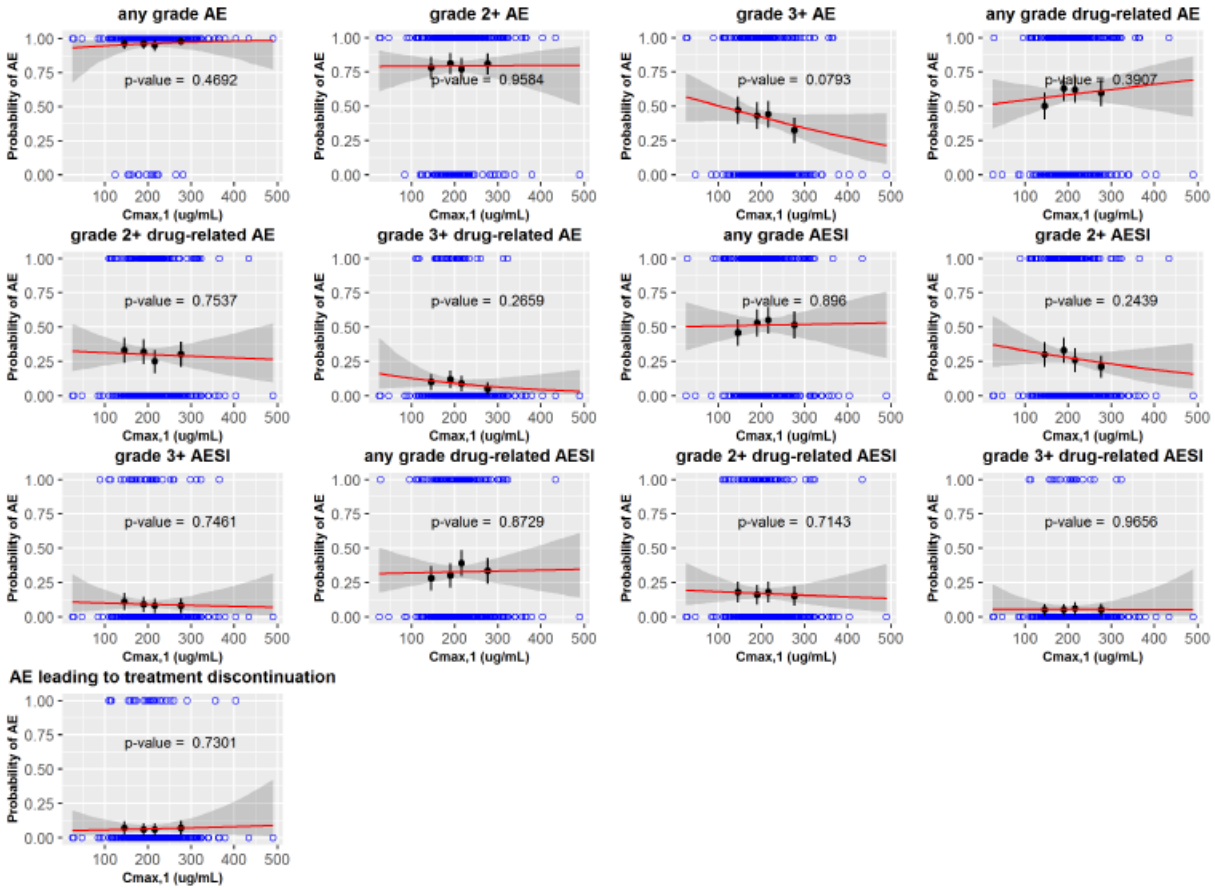
Reference ID: 4065384

Table 2 Summary Statistics of PK Exposure (Study ATLANTIC)

PK exposure	$C_{max,1}$	$C_{min,2}$	$C_{min,ss}$
n	399	355	193
Mean ± SD	207 ± 54.9	87.6 ± 39.4	168 ± 76.9
25th percentile	173	68.9	116
Median	204.7	86.9	165
75th percentile	229	107	204
CV %	26.5	44.9	45.7

Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Table 7.2.3.1-1 on page 53.

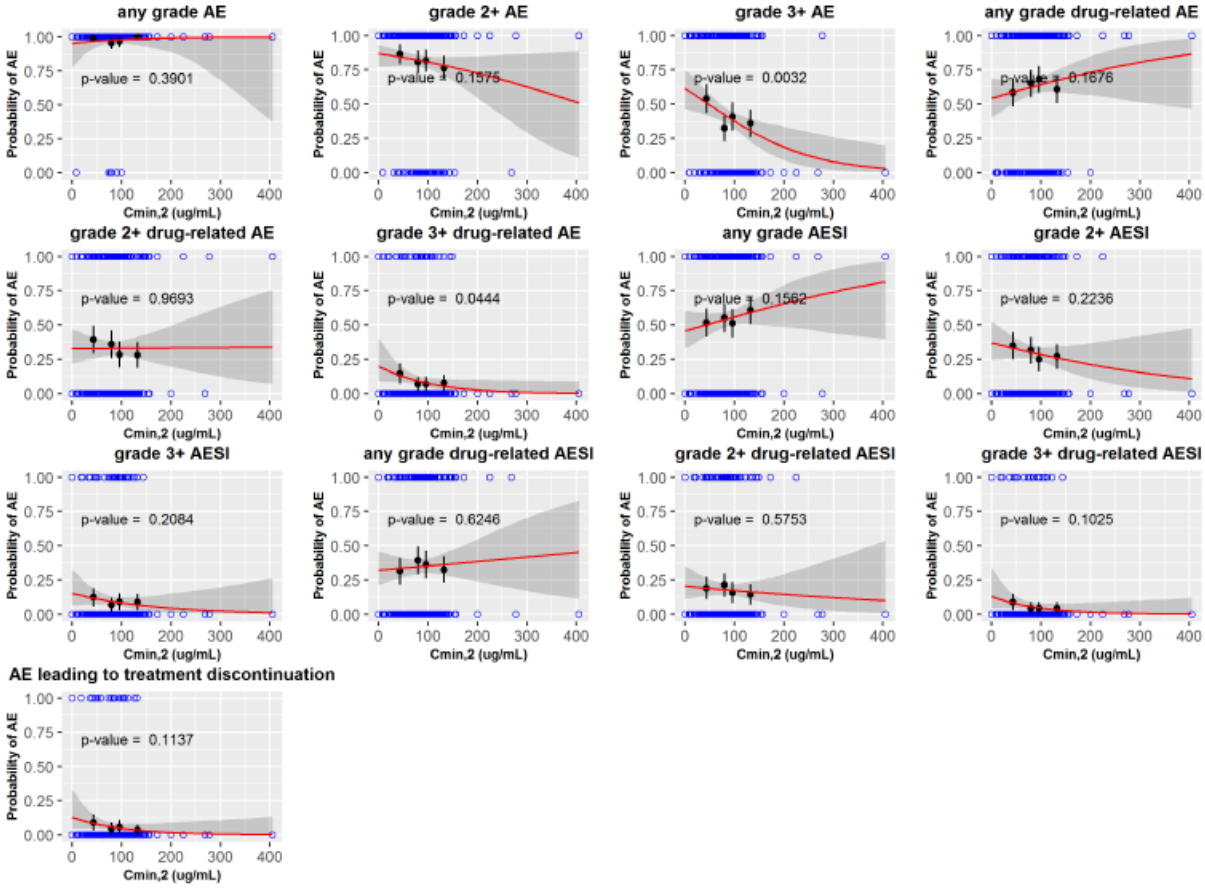
Figure 20. Logistic Regression of AE Incidence versus $C_{max,1}$ (Study ATLANTIC)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.3.2-4 on page 57.

Reference ID: 4065384

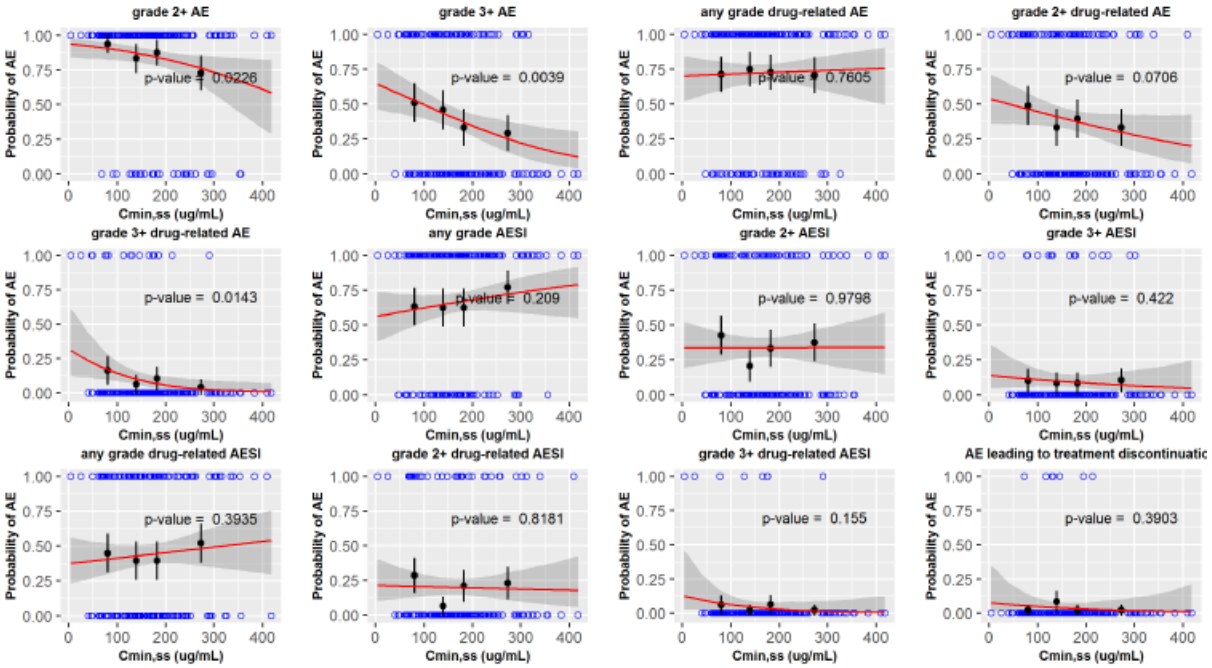
Figure 21. Logistic Regression of AE Incidence versus $C_{min,2}$ (Study ATLANTIC)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.3.2-5 on page 58.

Reference ID: 4065384

Figure 22. Logistic Regression of AE Incidence versus $C_{min,ss}$ (Study ATLANTIC)



Source: Sponsor's CD-ON-MEDI4736-1108 and D4191C00003 exposure-response analysis study report Figure 7.2.3.2-6 on page 59.

Conclusion

No relationship of PK exposure with safety was observed following 10 mg/kg Q2W IV regimen.

Reviewer's Comments:

The applicant's exposure-safety analyses appear reasonable. No evident exposure-safety relationship was identified following 10 mg/kg Q2W IV regimen. Logistic regression results across analyses using three different datasets (study 1108 UC cohort, study 1108 all patients, and study ATLANTIC) demonstrate that increasing durvalumab exposure levels ($C_{max,1}$, $C_{min,2}$, and $C_{min,ss}$) were not associated with an increased risk of selected safety endpoints including Grade 3+ AEs, Grade 3+ drug-related AE, Grade 3+ AESI, Grade 3+ drug-related AESI and AEs leading to discontinuation.

Inverse relationship was observed between certain durvalumab exposure metrics and AE endpoints, e.g. inverse relationship between Grade 3+ AE versus $C_{min,2}$ in the analysis using study 1108 UC cohort data, etc. However, the inverse exposure-safety relationship is not considered clinically relevant since it is likely due to limited sample size or potential confounding by other risk factors including. ECOG status (Higher AE incidence rate was observed in the ECOG = 1 group compared to the ECOG = 0 group) and baseline albumin levels (Baseline albumin levels were correlated with Grade 3+ AE and Grade 3+AESI, with a higher AE incidence rate in patients with lower baseline albumin levels.)

Increasing trends between certain durvalumab exposure and AE endpoints were observed in the analysis using data from study 1108, including Grade 2+ drug-related AE with $C_{max,1}$, Grade 2+ drug-related AESI with $C_{max,1}$, Any grade drug-related AE with $C_{max,1}$and $C_{min,2}$, Any grade drug-related AESI with $C_{max,1}$. However, such increasing trends were not observed in the analysis using data from study ATLANTIC. Therefore, these observed increasing treads should be

Reference ID: 4065384

interpreted with caution due to inconsistency between studies and may need to be confirmed with additional data.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4065384

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUHONG CHEN
03/06/2017

XIAOFENG WANG
03/06/2017

SARAH E DORFF
03/06/2017

ROSANE CHARLAB ORBACH
03/06/2017
“Formatting issues to be corrected"

JINGYU YU
03/06/2017

STACY S SHORD
03/06/2017

NAM ATIQUR RAHMAN
03/06/2017
I support the recommendation of the review team.