CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA	761034
Submission Date	January 12, 2016
Brand Name	TECENTRIQ™
Generic Name	Atezolizumab
Dosage Form / Strength	Infusion: 60 mg/mL solution in a single use 20 mL vial
Related IND	120827
Applicant	Genentech, Inc.
OCP Reviewer	Wentao Fu, Ph.D.
Pharmacometrics Reviewer	Chao Liu, Ph.D.
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Genomics Team Leader	Rosane Charlab Orbach, Ph.D.
OCP Division	Division of Clinical Pharmacology V
ORM Division	Division of Oncology Products 1
Submission Type; Code	Original BLA; New Biologic Entity
Dosing Regimen	1200 mg as an intravenous infusion over 60 minutes every 3 weeks.
Indication	Locally advanced or metastatic urothelial carcinoma

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1 EXECUTIVE SUMMARY

Atezolizumab is a humanized, IgG1 monoclonal antibody targeting the programmed death-ligand 1 (PD-L1). The applicant seeks the approval of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- •Have disease progression during or following platinum-containing chemotherapy (b) (4)
- • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

The proposed atezolizumab dosage is 1200 mg administered as an intravenous infusion every 3 weeks (q3w).

The Phase 2 open-label, single-arm trial in patients with locally advanced or metastatic urothelial carcinoma demonstrated a confirmed overall objective response rates (ORRs) of 14.8% (95% CI: 11.1, 19.3) for all patients. Patient subgroup with PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥ 5% of the tumor area) had an ORR of 26.0% (95% CI: 17.7, 35.7) compared to 9.5% (95% CI: 5.9, 14.3) for patients with PD-L1 expression of <5% (PD-L1 stained tumor-infiltrating ICs covering 0 - < 5% of the tumor area). Most common adverse reactions in the Phase 2 trial were fatigue, decrease appetite, nausea, pyrexia, diarrhea, vomiting, dyspnea, rash, arthralgia, pruritus, and abdominal pain.

Atezolizumab demonstrated linear pharmacokinetics (PK) at a dose range of 1-20 mg/kg. With the proposed dosing regimen, steady-state concentration of atezolizumab was reached after 6 to 9 weeks (2 to 3 cycles) of repeated dosing based on a population PK analysis. The population PK analysis estimated clearance, volume of distribution at steady state, and terminal elimination half-life of atezolizumab as 0.20 L/day, 6.9 L, and 27 days, respectively. Based on the population PK analysis, dose adjustments are not needed for gender, body weight, tumor burden, serum albumin level and anti-therapeutic antibody (ATA) status. Based on the population PK analysis, dose adjustments are not needed for mild or moderate renal impairment and mild hepatic impairment.

There is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization.

The incidence of positive ATA was 41.9% (161/384), 31.7% (139/439) and 16.7% (1/6) in Phase 2 pivotal study IMvigor 210, Phase 1a supportive study PCD4989g, and Phase 1 supportive study JO28944, respectively. The presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology recommends approval of the BLA761034 from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosage is 1200 mg administered as an intravenous infusion every 3 weeks (q3w).	☒ Yes ☐ No Refer to **Section 2.2.2** **Section 2.2.5**	The proposed dose is acceptable based on the efficacy and safety observed in clinical trials.
No dosing adjustment is recommended for any intrinsic or extrinsic factor	☒ Yes ☐ No Refer to **Section 2.3.2**	Age , body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab.

1.2 POST-MARKETING REQUIREMENTS

None.

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1.3 CLINICAL PHARMACOLOGY SUMMARY

Atezolizumab is a humanized, IgG1 monoclonal antibody.

Mechanism of Action: Atezolizumab is a monoclonal antibody 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.

Dose Selection: The proposed dosing regimen of atezolizumab (1200 mg every 3 weeks) is the same as the regimen used in the Phase 2 trial IMvigor 210. This dosing regimen is acceptable based on atezolizumab safety and efficacy data. In addition, the selected dosing regimen can reach a projected target steady-state C_{min} (6 μg/mL) based on nonclinical tissue distribution data in tumor-bearing mice and receptor occupancy in the tumor.

Pharmacokinetics: Atezolizumab demonstrated linear pharmacokinetics (PK) at a dose range of 1-20 mg/kg. Based on data from 472 patients who received 1-20 mg/kg of atezolizumab every 3 weeks, the population PK mean estimates were as follows:

- Clearance, 0.20 L/day
- Volume of distribution at steady-state, 6.9 L
- Half-life, 27 days
- Time to reach steady state concentrations, 6 to 9 weeks (2 to 3 cycles) after 1200 mg every 3 weeks and the systemic accumulation of area under the curve (AUC), approximately 1.9-fold

Population Pharmacokinetic Analysis: Population PK analyses (n=472) showed that the following factors have no clinically important effect on the PK parameters of atezolizumab administrated at 1200 mg every 3 weeks: gender, body weight, tumor burden, serum albumin level, anti-therapeutic antibody (ATA) status, mild and moderate renal impairment, and mild hepatic impairment. Therefore, no dose adjustments based on above covariates are needed.

Exposure/Dose-Response Relationship for Efficacy and Safety at 1200 mg q3w: Steady-state exposure ($AUC_{,ss}$) of atezolizumab was not a significant predictor of either probability of ORR or probability of Adverse Events (AE) in patients.

Immunogenicity: The percentages of evaluable patients tested positive ATA were 41.9% (161/384), 31.7% (139/439) and 16.7% (1/6) in Phase 2 pivotal study IMvigor 210, Phase 1 supportive study PCD4989g, and Phase 1 supportive study JO28944, respectively. The presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.

Drug-Drug interaction (DDI) potential: No DDI studies have been conducted.

QT prolongation: IRT-QTc review team concluded that there is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 144 kDa (without heavy chain C-terminal lysine residues). It is composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 amino acid residues.

The physico-chemical properties of atezolizumab are summarized below (Table 1):

Table 1. Atezolizumab General Properties

Property	Molecule Details
Molecular Formula	$C_{6434}H_{9878}O_{1996}N_{1702}S_{42}$ (peptide chains only, without heavy chain C-terminal lysine residues)
Molecular Mass	Approximately 144,356 Da (peptide chains only, without heavy chain C-terminal lysine residues)
Extinction Coefficient	1.62 mL mg^{-1} cm^{-1} at 278 nm
Isoelectric Point	8.8
Immunoglobulin Subclass	IgG1 with V_HIII and $V\kappa$I variable region subgroups
Glycosylation	Nonglycosylated: the conserved N-glycosylation site (heavy chain Asn 298) is substituted with Ala 298 by design
Biological Activity	Inhibits PD-L1/PD-1 and PD-L1/B7.1 interactions leading to the reactivation of PD-1-expressing T cells
Binding Affinity	*In vitro* binding affinity to the recombinant human PD-L1: K_d = 0.433 nM by equilibrium binding assay

Source: Table S.1.3-1 of General Properties of BLA761034 (Section 3.2.S.1.3)

TECENTRIQ™, the drug product, is supplied in a single-dose 20-mL vial containing preservative free ready for infusion liquid concentrate, at a concentration of 60 mg/mL. Each vial of TECENTRIQ contains a total of 1200 mg atezolizumab. Vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Indication: Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy (b) (4)
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Mechanism of action: Atezolizumab is a monoclonal antibody 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.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of atezolizumab is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The proposed dosing regimen of atezolizumab is the same as that was used in the pivotal Phase 2 trial. The results of a pivotal Phase 2 trial (IMvigor 210 (GO29293)) and two supportive Phase 1 trials (PCD4989g (GO27831); JO28944 for PK only) were used to support the approval (Table 2). In the cohort 2 of pivotal Phase 2 trial, patients (N=311) with locally advanced or metastatic urothelial carcinoma were received atezolizumab as second-line plus treatment. The study demonstrated a confirmed ORR of 15.1% (95% CI: 11.3, 19.6) for all 311 patients with a median length of follow-up of 7.1 months. Patient subgroup with PD-L1 expression of ≥ 5% had an ORR of 27.0% (95% CI: 18.6, 36.8) compared to 9.5% (95% CI: 5.9, 14.1) for patients with PD-L1 expression of < 5%. In an updated analysis with a median length of follow-up of 14.4 months, the confirmed ORR per IRF-RECIST v1.1 was 26.0% (95% CI: 17.7, 35.7; 26/100 patients) in patients with PD-L1 expression ≥ 5%, 9.5% (95% CI: 5.9, 14.3; 20/210 patients) in patients with PD-L1 expression < 5%, and 14.8% (95% CI: 11.1, 19.3; 46/310 patients) in all patients.

A population PK model for atezolizumab was built based on pooled PK data from 472 cancer patients in two Phase 1 clinical studies (Table 2) with dose levels ≥ 1 mg/kg. The population PK model provided the characterization of atezolizumab PK across different dose levels, assessment of factors associated with PK variability, and support for a fixed dosage. The population PK model was validated using PK data in the Phase 2 trial IMvigor 210 (GO29293) (Table 2).

The immunogenic effects of atezolizumab were evaluated by measuring ATAs to atezolizumab using a screening assay that used a bridging ELISA format. Positive samples in the screening assay were then run in a confirmatory assay for specificity testing, and verified positive samples were subsequently titered. These ATA methods were validated. The percentages of evaluable patients tested positive ATA were 41.9% (161/384), 31.7% (139/439) and 16.7% (1/6) in studies IMvigor 210, PCD4989g and JO28944, respectively. The impact of the presence of ATAs on the PK, safety, and efficacy were evaluated.

No DDI studies have been conducted. Atezolizumab as a large targeted protein has a low likelihood of direct ion channel interactions. IRT-QTc review team concluded that there is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization

Table 2. Clinical Trial with Atezolizumab Clinical Pharmacology Data and Analyses

Study No.	Phase	N treated	N PK evaluable	Population	Assessment	Dosage q3w
PCD4989g (GO27831)	1	All cohorts: 481 mUC cohort: N=92	472 but only 466 patients with dose levels ≥ 1 mg/kg mUC cohort: N=90	Patients with locally advanced or metastatic sold malignancies or hematologic malignancies Patients with mUC	PK, PPK, QT prolongation potential, E-R for safety (mUC cohort only), immunogenicity	0.01 to 20 mg/kg and 1200 mg 15 mg/kg and 1200 mg (mUC cohort)
JO28944	1	6	6	Japanese patients with solid tumors	PK, PPK, immunogenicity	10 and 20 mg/kg
IMvigor 210 (GO29293)	2	All cohorts: 429 Cohort 1 (1L): N=118 Cohort 2 (2L+): N=311	423 Cohort 1: N=117 Cohort 2: N=306	Patients with mUC	PPK validation, E-R for safety, E-R for efficacy (cohort 2 only), immunogenicity	1200 mg

Abbreviations: mUC: locally advanced or metastatic urothelial carcinoma; PK: pharmacokinetics; PPK: population pharmacokinetics; q3w: every 3 weeks; 1L: first-line treatment; 2L+: second-line plus treatment

2.2.2 What is the basis of the dose selection?

The pivotal Phase 2 trial IMvigor 210 used the fixed (non-weight-based) dosage of 1200 mg dose every three weeks. This fixed dosage was selected based on clinical studies of atezolizumab administered as a single agent in cancer patients.

In dose escalation part of Phase 1 study PCD4989g, atezolizumab was dosed on a weight-based basis (mg/kg) at doses ranging from 0.01 to 20 mg/kg. A maximum tolerated dose was not achieved during this escalation. In dose expansion part of the Phase 1 study PCD4889g, atezolizumab was dosed on a weight-based basis (mg/kg) dose of 15 mg/kg as well as a fixed (non-weight-based) dose of 1200 mg. A population PK analysis based on PK data from studies PCD4989g and JO28944 did not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. The lack of safety concern in addition to an assessment of the PK characteristics of atezolizumab in relation to the target serum concentration of 6 μg/mL led to an adoption of a 1200 mg fixed (equivalent to an average body weight-based dose of 15 mg/kg) dosage q3w for later clinical trials, including the pivotal Phase 2 trial IMvigor 210.

The serum atezolizumab concentration of 6 μg/mL was set as a target serum concentration based on the nonclinical tissue distribution data in tumor-bearing mice and receptor occupancy in the tumor. In Phase 1 studies PCD4989g, patients received ≥ 10 mg/kg atzolizumab, including the fixed 1200 mg dose, maintained geometric mean steady-state trough serum concentration > 6 μg/mL. In pivotal Phase 2 trial used the fixed 1200 mg dosage q3w, steady-state trough serum concentrations for all patients were above the targeted serum concentration of 6 μg/mL.

2.2.3 What are the clinical endpoints used to assess efficacy in the clinical efficacy studies? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoints of the pivotal Phase 2 trial IMvigor 210 and Phase 1 trial PCD4989g were confirmed ORR per independent review facility (IRF) using Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessment and confirmed ORR per investigator-modified RECIST assessment (IMvigor 210 cohort 2 only). The ORR was defined as complete (CR) or partial response (PR). High concordance rates in ORR were observed between IRF-assessed and investigator-modified RECIST. IRF-assessed ORR was used as primary efficacy outcome for atezolizumab label insert and exposure-response analysis for efficacy. Additional secondary efficacy endpoints included duration of response (DOR) assessed by IRF per RECIST v1.1. DOR was first occurrence of a documented PR or CR (whichever occurred first) to the time of first radiographic progression or death, whichever occurred first.

In the cohort 2 of Phase 2 trial IMvigor 210, patients (N=311) with locally advanced or metastatic urothelial carcinoma were received atezolizumab as second-line plus treatment. Based on a median length of follow-up for all patients of 7.1 months (data cutoff date: 05/05/2015), the study demonstrated an IRF-assessed ORR of 15.1% (95% CI: 11.3, 19.6; 47/311 patients) for all 311 patient. IRF-assessed ORR of 27.0% (95% CI: 18.6, 36.8; 27/100 patients) was observed for patients subgroups had a PD-L1 expression of ≥ 5% determined by a Ventana PD-L1 (SP142) CDx Assay. IRF-assessed ORR of 9.5% (95% CI: 5.9, 14.1; 20/211 patients) was observed for patients subgroups had a PD-L1 expression of < 5. Based on the median length of follow-up for all patients of 7.1 months, the median DOR was not reached. The 47 patients with responses had durations ranging from 2.1+ to 8.3+ months, of which 43 (91.5%) had an ongoing response at the time of clinical data cutoff. The median DOR for all patients was not reached on an updated data analysis with a median length of follow-up of 14.4 months. In the updated analysis, the confirmed ORR per IRF-RECIST v1.1 was 26.0% (95% CI: 17.7, 35.7; 26/100 patients) in patients with PD-L1 expression of ≥ 5%, 9.5% (95% CI: 5.9, 14.3; 20/210 patients) in patients with PD-L1 expression of < 5%, and 14.8% (95% CI: 11.1, 19.3; 46/310 patients) in all patients. See genomics review (Section 2.3.2.9) by Dr. Sarah Dorff for more information related to PD-L1 expression.

In Phase 1 trial PCD4989g, 87 patients were evaluable for ORR with at least 12 weeks follow-up. 67 out of the 87 patients had a known PD-L1 expression. The IRF-assessed ORR was 36.8% (95% CI: 16.3, 61.6; 7/19 patients) in patients with PD-L1 expression of ≥ 5% tumor infiltrating immune cells, 18.8% (95% CI: 9.0, 32.6; 9/48 patients) for patients who had PD-L1 expression of < 5% tumor infiltrating immune cells, and 27.6% (95% CI: 18.54, 38.21; 24/87 patients) for all evaluable patients. Median DOR per IRF-RECIST v1.1 in all responders was not reached on an updated data analysis with a median length of follow up of 12 months.

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Serum concentrations of atezolizumab were appropriately measured by ELISA methods to assess PK parameters.

See Section 2.6.

2.2.5 Exposure-response

2.2.5.1 Can exposure-response relationships be established for the efficacy and safety in the pivotal Phase 2 trial?

Yes. PK data from the cohort 2 of pivotal Phase 2 trial (306 out of 311 patients receiving atezolizumab as second-line plus treatment, Table 2) were used to establish the exposure-response relationship for ORR. PK data from the pivotal Phase 2 trial (423 out of 429 patients, Table 2) in combination with PK data from Phase 1 study PCD4989g (90 out 92 patients in locally advanced and urothelial carcinoma cohort, Table 2) were used to establish the exposure-response relationship for Safety. There appeared to be no significant exposure-efficacy relationship for ORR and no significant exposure-safety relationships within the exposure range following atezolizumab administration of 1200 mg q3w.

See pharmacometrics review (Section 4) by Dr. Chao Liu for more information.

2.2.5.2 Does atezolizumab prolong the QT or QTc interval?

In the QTc sub-study of supportive Phase 1 study PCD4989, 417 patients dosed at 10, 15 and 20 mg/kg or at 1200 mg. No clinically meaningful change in QTc interval (i.e., > 10 ms) at atezolizumab concentrations up to the geometric mean C_{max} following 4 doses of atezolizumab 20 mg/kg administered q3w in the QTc sub-study. The predicted ΔQTcF (upper bound of two-sided 90% CI) at the observed geometric mean C_{max} was 0.71 (1.75) ms for the 10 mg/kg, 1.14 (2.33) ms for the 15 mg/kg dose cohort and 2.57 (4.68) ms for the 20 mg/kg dose cohort. IRT-QTc review team concluded that there is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization.

Please see IRT-QTc review by Dr. Dhananjay D. Marathe (dated March 22, 2016 in DARRTs) for more information.

2.2.5.3 Is the fixed dosing regimen acceptable? Are there any unresolved dosing or administration issues?

Yes, the fixed dosing, without regard to body weight, is acceptable in patients with locally advanced or metastatic urothelial carcinoma. There were no clinically meaningful differences in atzolizumab serum exposures from fixed administration of 1200 mg q3w and from administration of 15mg/kg q3w. The selection of atezolizumab dosing regimen is supported by atezolizumab pharmacokinetics, safety, and efficacy data. There are no outstanding unresolved dosing or administration issues from a clinical pharmacology perspective.

Please also see 2.3.2.2 and the pharmacometrics review (Section 4) by Dr. Chao Liu.

2.2.6 Pharmacokinetic characteristics of atezolizumab in humans

2.2.6.1 What are the pharmacokinetic parameters of atezolizumab across studies?

Atezolizumab PK data were obtained for doses ranging from 0.1-20 mg/kg in Phase 1 dose escalation study PCD4989g. In study PCD4989g where PK parameters were obtained for patients receiving atzolizumab dose ≥ 1 mg/kg, the estimated mean values for CL, Vss and $t_{1/2}$ ranged from 0.288 - 0.420 L/day, 2.66 - 5.20 L, and 18.0 - 26.6 days, respectively (Table 3). Atezolizumab exposures were less than dose proportional for the tested dose level < 1 mg/kg. In study JO28944, the estimated mean values for CL, Vss and $t_{1/2}$ ranged from 0.207 - 0.232 L/day, 3.62 – 3.78 L, and 11.6 – 13.0 days, respectively (Table 4).

PK data from patients receiving atzolizumab dose ≥ 1 mg/kg in studies PCD4989g (N=466) and JO28944 (N=6) were used for a population PK analysis. The population PK analysis using a two-compartment linear model with first-order elimination from the central compartment described serum atezolizumab PK in the dose range 1.0 to 20.0 mg/kg. The population elimination clearance (CL), the central compartment volume (V1), volume of distribution of peripheral compartment (V2), and terminal elimination half-life were estimated as 0.20 L/day, 3.3 L, 3.6 L and 27 days, respectively.

Table 3. Summary of Atezolizumab Serum PK Parameters in Study PCD4989g Cycle 1

Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 (GM, %CV)				
	C_{max} (μg/mL)	C_{max}/D (μg/mL/mg)	C_{min} (μg/mL)	C_{min}/D (μg/mL/mg)	$t_{1/2}$ [A] (days)
0.01 mg/kg (n = 1)	NA	NA	NA	NA	NA
0.03 mg/kg (n = 1)	0.37	0.16	NA	NA	NA
0.1 mg/kg (n = 1)	0.96	0.14	NA	NA	NA
0.3 mg/kg (n = 3)	6.49 (19) n = 3	0.33 (8.3) n = 3	NA	NA	NA
1 mg/kg (n = 3)	25.8 (17) n = 3	0.35 (26) n = 3	3.80 (160) n = 3	0.05 (120) n = 3	26.6 n = 1
3 mg/kg (n = 3)	75.6 (26) n = 3	0.27 (24) n = 3	12.2 (62) n = 3	0.04 (67) n = 3	21.8 n = 1
10 mg/kg (n = 36)	265 (16) n = 36	0.30 (24) n = 36	54.1 (25) n = 34	0.06 (33) n = 34	22.7 (56) n = 10
15 mg/kg (n = 235)	332 (53) n = 232	0.29 (57) n = 232	67.1 (73) n = 214	0.06 (76) n = 214	18.0 (39) n = 29
20 mg/kg (n = 145)	472 (35) n = 145	0.31 (37) n = 145	91.1 (36) n = 132	0.06 (43) n = 132	23.7 (36) n = 28
1200 mg (n = 45)	405 (50) n = 40	0.34 (50) n = 40	95.5 (51) n = 30	0.08 (51) n = 30	NA

C_{max} = maximum serum concentration; C_{max}/D = dose-normalized C_{max}; C_{min} = trough or minimum serum concentration; C_{min}/D = dose-normalized C_{min}; CV (%) = (percent) coefficient of variation (geometric mean); GM = geometric mean; NA = PK parameter is not available due to insufficient data; PK = pharmacokinetic.

[A] The terminal half-life (t1/2) was calculated only for patients with 3 or more consecutive end-of-treatment samples after 3 or more cycles of therapy and reported as harmonic mean ± pseudo standard deviation. $t_{1/2}$ was estimated for patient data ranging from Cycle 3 to 36.

Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 (GM, %CV)				
	$AUC_{0\text{-}21}$ (day*µg/mL)	$AUC_{0\text{-}21}$/D (day*µg/mL/mg)	$AUC_{0\text{-}inf}$[B] (day*µg/mL)	CL[B] (L/day)	V_{ss}[B] (L)
0.1 mg/kg (n=1)	1.62	0.240	1.62	4.23	5.30
0.3 mg/kg (n=3)	31.5 (8.1) n=3	1.59 (12) n=3	33.0 (7.9) n=2	0.603 (15) n=2	2.79 (13) n=2
1 mg/kg (n=3)	201 (8.5) n=3	2.73 (27) n=3	225 (2.8) n=2	0.296 (19) n=2	2.66 (53) n=2
3 mg/kg (n=3)	601 (34) n=3	2.19 (25) n=3	651 (22) n=2	0.420 (10) n=2	5.20 (7.4) n=2
10 mg/kg (n=36)	2240 (17) n=29	2.46 (28) n=29	2780 (22) n=9	0.329 (33) n=9	4.28 (39) n=9
15 mg/kg (n=235)	2730 (27) n=29	2.23 (22) n=29	3280 (35) n=17	0.365 (23) n=17	4.89 (22) n=17
20 mg/kg (n=145)	3870 (21) n=32	2.59 (27) n=32	4860 (23) n=10	0.288 (30) n=10	3.89 (30) n=10

AUC = area under the curve; $AUC_{0\text{-}21}$ = AUC from Day 1 to Day 21; $AUC_{0\text{-}21}$/D = dose-normalized AUC from Day 1 to Day 21; $AUC_{0\text{-}inf}$ = AUC from time zero to infinity; CL = clearance; CV (%) = (percent) coefficient of variation; GM = geometric mean; PK = pharmacokinetic; V_{ss} = volume at steady-state.

Note: PK parameters were not calculated for the 0.01-, 0.03- and 1200-mg dose groups due to insufficient data.

[B] Given the 18.0 – 26.6 day $t_{1/2}$ and that $AUC_{0\text{-}inf}$ was calculated using only up Day 21 data in Cycle 1, $AUC_{0\text{-}inf}$, CL and V_{ss} estimates are considered to be approximate in nature.

Source: Table 2 of Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

Table 4. Summary of Atezolizumab Serum PK Parameters in Study JO28944 Cycle 1

Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 (GM, %CV)			
	C_{max} (µg/mL)	C_{max}/D (µg/mL/mg)	C_{min} (µg/mL)	$t_{1/2}$[A] (days)
10 mg/kg (n=3)	219 (10.3)	0.413 (22.4)	36.8 (3.63)	11.6 (8.51)
20 mg/kg (n=3)	534 (9.14)	0.319 (30.4)	113 (10.1)	13.0 (10.2)
	$AUC_{0\text{-}21}$ (day*µg/mL)	$AUC_{0\text{-}inf}$[A] (day*µg/mL)	CL[A] (L/day)	V_{ss}[A] (L)
10 mg/kg (n=3)	1670 (2.96)	2290 (4.49)	0.232 (23.3)	3.62 (29.3)
20 mg/kg (n=3)	4480 (8.76)	6610 (10.4)	0.207 (29.3)	3.78 (18.8)

$AUC_{0\text{-}21}$ = area under the serum concentration-time curve from Day 1 to Day 21; $AUC_{0\text{-}inf}$ = area under the serum concentration-time curve from Day 1 to infinity; CL = clearance; C_{max} = maximum serum concentration; C_{max}/D = dose-normalized C_{max}; C_{min} = trough or minimum serum concentration; CV (%) = (percent) coefficient of variation (geometric mean); GM = geometric mean; PK = pharmacokinetic; $t_{1/2}$ = half-life; V_{ss} = volume of distribution at steady-state.

[A] Given that $t_{1/2}$ was calculated using up Day 21 data in Cycle 1 only, $AUC_{0\text{-}inf}$, CL, and V_{ss} estimates are considered to be approximate in nature.

Source: Table 6 of Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.2.6.2 How does the PK of atezolizumab in healthy volunteers compare to that in patients?

It is unknown whether the PK of atezolizumab in healthy volunteers differs from that in patients, as atezolizumab has only been tested in patients with advanced tumors (locally advanced or metastatic solid malignancies or hematologic malignancies). Tumor burden was identified as a statistically significant covariate by population PK analysis. However, the tumor burden effects on atezolizumab exposure (AUC,ss, Cmax, ss and Cmin,ss) were not clinical relevant.

Please also see section 2.3.1.

2.2.6.3 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?

Atezolizumab exhibited linear PK in a dose range of 1.0-20 mg/kg, including 1200 mg fixed dose, in studies PCD4989g (N=466) and JO28944 (N=6). The population PK analysis for PK data from these two studies using a two-compartment linear model with first-order elimination from the central compartment well described serum atezolizumab PK in the dose range 1.0 to 20.0 mg/kg. However, at the dose < 1.0 mg/kg, atezolizumab exposure was less than does proportional.

See Section 2.2.6.1.

Dose proportionality following the first dose of atezolizumab

Using C_{max} and $AUC_{Day0-21}$ in the first treatment cycle in Phase 1 dose escalation trial PCD4989g, a power model was applied to test the dose proportionality (Figure 1). The slope of the power model on logarithmic scale was 0.93 for C_{max} with a 95% confidence interval of (0.81, 1.05), and was 0.95 for $AUC_{Day0-21}$ with a 95% confidence interval of (0.87, 1.03). Therefore, the systemic exposure of atezolizumab increased with dose in a proportional manner over a dose range from 1 mg/kg to 20 mg/kg. The dose level less than 1 mg/kg was not included in the analyses due to obvious nonlinearity.

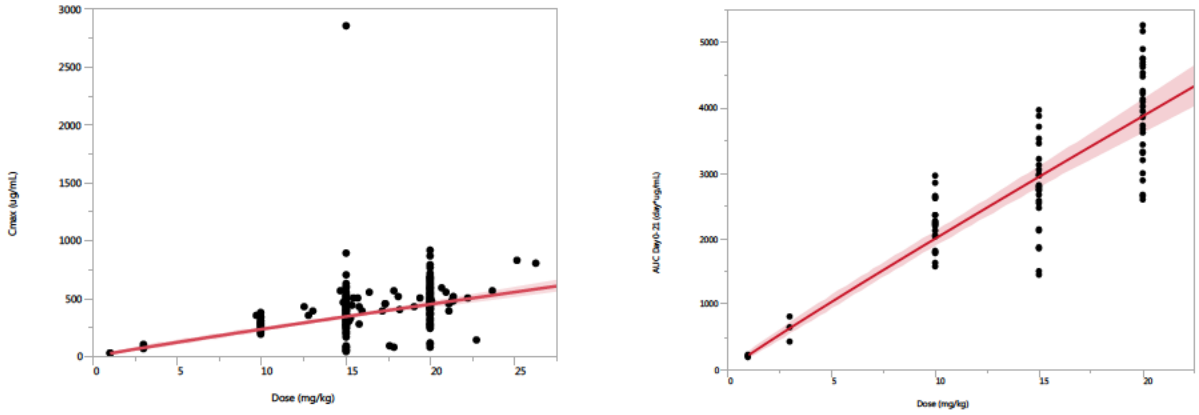


Figure 1: Relationship between Dose and Atezolizumab C_{max} (left) and $AUC_{Day0-21}$ (right) in Cycle 1 (Day 0 -21) of Study PCD4989

The shaded area is the 95% confidence interval of the slope. The dots represent the observed C_{max} form 459 patients and calculated $AUC_{Day0-21}$ from 96 patients in Phase 1 trial PCD4989g.

Steady-state following multiple doses

For patients receiving 1 mg/kg or higher atezolizumab dose q3w in study PCD4989g, accumulation ratios for C_{min} and C_{max} both appear to rise for successive cycles until the 4th and 5th cycle of dosing. In Cycles 4 to 8, the geometric mean accumulation ratio for C_{min} and C_{max}, ranged from 2.07 to 2.39 and from 1.21 to 1.41, respectively (Table 5 and Figure 2). Steady-state exposure was achieved in Cycles 4 to 6 in study JO28944 (Figure 2), the reported mean accumulation ratios for C_{min} and C_{max}, ranged from 2.53 to 3.06 and from 1.25 to 1.47, respectively.

Table 5. Atezolizumab Accumulation Ratio Based on C_{min} and C_{max} at Each Treatment Cycle (Patients Receiving 1 mg/kg or Higher) in Study PCD4989g

	C_{min} (GM, %CV)	C_{max} (GM, %CV)
Cycle 2	1.52 (42) n=333	1.15 (38) n=384
Cycle 3	1.82 (42) n=290	1.29 (34) n=307
Cycle 4	2.07 (42) n=165	1.32 (44) n=277
Cycle 5	2.04 (61) n=81	1.41 (56) n=55
Cycle 6	2.39 (52) n=133	1.38 (43) n=70
Cycle 7	2.39 (68) n=100	1.36 (58) n=34
Cycle 8	NA	1.21 (70) n=15

C_{max}=maximum serum concentration; C_{min}= trough or minimum serum concentration; CV=coefficient of variation; GM=geometric mean.
NA=pharmacokinetic data at the end of cycle 8 is not available.
The reference concentration for C_{min} is Cycle 1 Day 21 (predose for Cycle 2).
The reference concentration for C_{max} is Cycle 1 Day 1, 30-minute postdose timepoint.

Source: Table 3 of Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

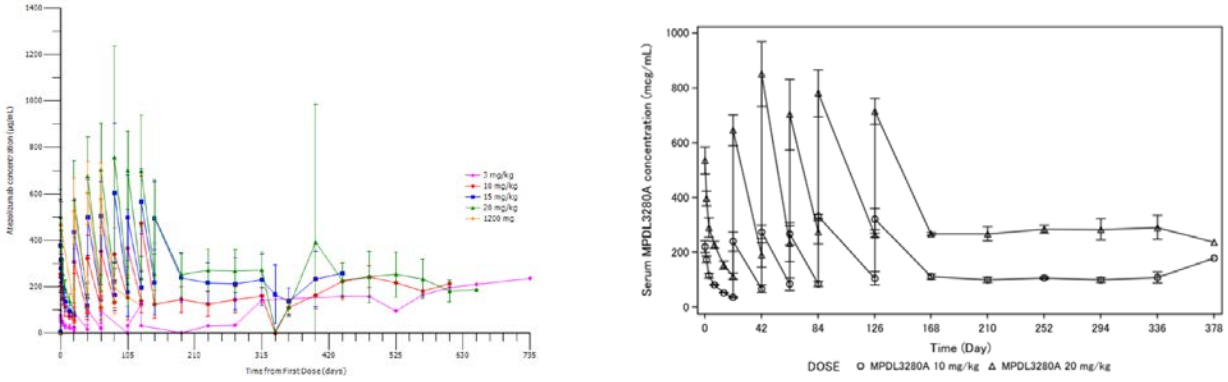


Figure 2: Mean (±SD) serum atezolizumab (MPDL3280A) concentration vs time profile for all Cycles by dose group for Study PCD4989g (left) and Study JO28944 (right)

Source for left figure: Figure C of 2016-02-26 Clinical Response to FDA Request for Information of BLA 761034 (SDN0022); Source for right figure: Figure 3 of Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.2.6.4 What is the inter- and intra-subject variability of PK parameters in patients, and what are the major causes of variability?

Variability in atezolizumab PK parameters in patients with advanced solid tumors was estimated in the population PK analysis. Inter-individual variability (IIV) was estimated to be 29%, 18% and 34%, for CL, V1 and V2, respectively.

Population PK analysis identified serum albumin concentration, ATA status, body weight, tumor burden were covariates for CL. Albumin concentration, body weight and gender were covariates for V1. Gender was covariate for V2. (Table 6).

Table 6. Parameter Estimates for Final Population PK Model

Table 4-9. Final Population PK Model Parameter Estimates for Atezolizumab

Parameters	Estimate	RSE (%)	Shrinkage (%)	Residual Error or IIV
CL (L/day)	0.200	2		
V1 (L)	3.28	2		
V2 (L)	3.63	4		
Q (L/day)	0.546	8		
Albumin on CL	-1.12	10		
ATAG on CL	0.159	25		
Tumor burden on CL	0.125	17		
Body weight on CL	0.808	8		
Albumin on V1	-0.350	21		
Body weight on V1	0.559	8		
Gender (female) on V1	-0.129	16		
Gender (female) on V2	-0.272	16		
σ^2 Proportional residual error	0.0433	7	9	21%
σ^2 Additive residual error	16.6	39	9	4 µg/mL
ω^2 CL	0.0867	9	9	29%
ω^2 V1	0.0328	18	17	18%
ω^2 V2	0.114	25	33	34%
Correlation CL.V1	0.341			
Correlation CL.V2	-0.236			
Correlation V1.V2	0.434			
Objective function	40748			

CL=clearance; IIV=inter-individual variability; Q=inter-compartmental clearance; RSE=relative standard error; V1=volume of distribution of central compartment; V2=volume of distribution of peripheral compartment; ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight (normalized to a 77-kg body weight); Albumin=normalized to 40 g/L; Tumor burden normalized to 63 mm; ω^2=variance of omega; σ^2=variance of sigma

Source: Table 4-9 of Population PK Report 1066935

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, gender, race, body weight, height, body surface area (BSA), disease, genetic polymorphism, pregnancy, renal or hepatic dysfunction on atezolizumab PK.

Population PK analysis evaluated the impact of covariates related to: demographics (age, gender, body weight); cancer (performance status, tumor burden, number of metastatic sites, liver metastases, brain metastases and visceral metastases); liver function (aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALBU) and bilirubin (BIL)); kidney function

(creatinine clearance (CRCL) and estimated glomerular filtration rate (eGFR)); Anti-Therapeutic Antibodies (ATA) status. Additional covariates, that may be confounded with demographics or pathophysiological status, were assessed graphically at the last stage of the analysis after the incorporation of statistically significant demographics or pathophysiological covariates in the model. The additional covariates evaluated were PD-L1 status, formulation, race and region.

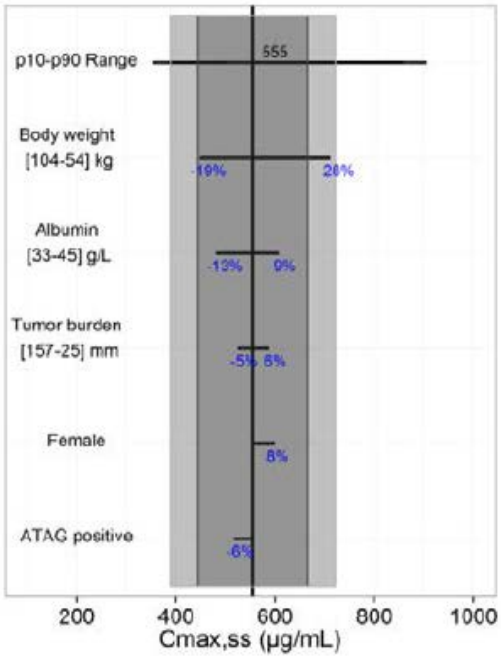
Body weight, gender, ATA status, serum albumin concentration, tumor burden have a statistically significant effect on atezolizumab PK. No covariate induced more than 27% change from typical for extreme values (i.e. 10^{th} and 90^{th} percentile of covariate distributions). The magnitude of their effects on atezolizumab PK parameters (CL, V1 and V2; Table 7) and exposure parameters ($AUC_{,ss}$, $C_{max,ss}$ and $C_{min,ss}$; Figure 3) was not clinical relevant.

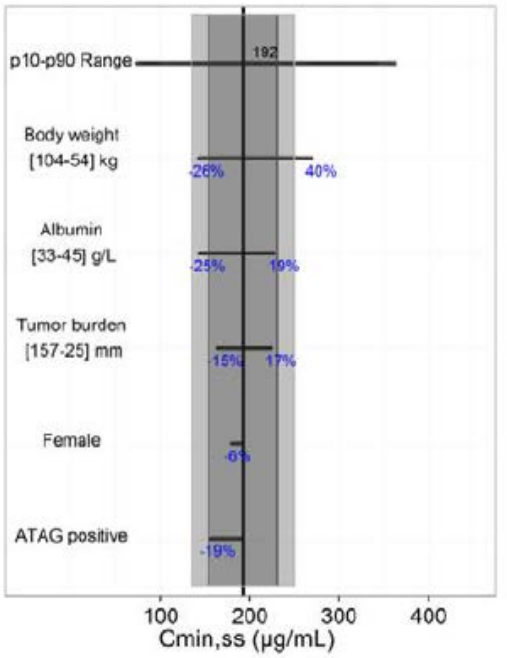
Table 7. Effect of Covariates on Atezolizumab PK Parameters

PK Parameters and Baseline Covariates		Covariate Value	Estimate	Percent Change from Typical (%)
CL (L/day) for a typical patient			**0.200**	
Albumin (g/L)	10^{th} percentile	33	0.248	+24%
	90^{th} percentile	45	0.175	-12%
ATAG		positive	0.232	16%
Body weight (kg)	10^{th} percentile	54	0.150	-25%
	90^{th} percentile	104	0.255	+27%
Tumor burden (mm)	10^{th} percentile	25	0.178	-11
	90^{th} percentile	157	0.224	+12%
V1 (L) for a typical patient			**3.28**	
Albumin (g/L)	10^{th} percentile	33	3.51	+7%
	90^{th} percentile	45	3.15	-4%
Body weight (kg)	10^{th} percentile	54	2.69	-18%
	90^{th} percentile	104	3.88	+18%
Gender		female	2.86	-13%
V2 (L) for a typical patient			**3.63**	
Gender		female	2.64	-27%

For a typical patient defined as a male patient with negative ATAG, a body weight of 77 kg, an albumin level of 40 g/L, and a tumor burden of 63 mm; CL=clearance; V1=volume of distribution of central compartment; V2=volume of distribution of peripheral compartment; ATAG=Post-baseline status of anti-therapeutic antibodies

Source: Table 4-10 of Population PK Report 1066935





Final model estimate, as represented by the black vertical line and value, refers to the predicted steady-state exposure of atezolizumab at 1200 mg q3w in a typical patient with covariates equal to medians. The typical patient is a male without positive ATAG, weighing 77 kg, with an albumin level of 40 g/L and a tumor burden of 63 mm. Grey areas, light and dark represent 30% and 20% of change from the base, respectively. The top bar shows the 10th and 90th percentile ([p10-p90]) exposure range across the population receiving 1200 mg q3w. Each horizontal bar represents the influence of a single covariate on the exposure metric. The label at left end of the bar represents the covariate being evaluated with values of the 10th and 90th percentiles ([p10-p90]) of the covariate distribution. The length of each bar describes the potential impact of that particular covariate on atezolizumab exposure, with the percent change of exposure from the base (blue values).

Figure 3: Impact of Covariates on Exposure Parameters: $AUC_{,ss}$, $C_{max,ss}$ and $C_{min,ss}$

$AUC_{,ss}$ = Steady state AUC; $C_{max,ss}$ = Steady state maximum serum concentration; $C_{min,ss}$ = steady state minimum serum concentration

Source: Figure 4-8 of Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosing regimen adjustments, if any, are recommended for each of these groups? If dosing regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the clinical pharmacology data, no dose adjustments are recommended for specific patient populations.

2.3.2.1 Pediatric patients

Safety and effectiveness of atezolizumab have not been established in pediatric patients.

2.3.2.2 Body size

Higher body weight may be related with increased atezolizumab clearance and subsequent lower systemic exposure (Figure 3). Patients with body weight lower than 54 kg would have up to a 32%, 28%, 40% higher AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$, respectively, than the typical patient (body weight 77 kg).

2.3.2.3 Gender

Gender was identified as statistically significant covariate on both V1 and V2, but not on CL in population pharmacokinetic analysis with data from 196 females and 276 males. Gender did not have a remarkable effect on drug exposure (Figure 3).

2.3.2.4 Elderly

Age was not identified as a significant covariate in population pharmacokinetic analysis. No significant difference was observed in the pharmacokinetics of atezolizumab between patients < 65 years (n=274), patients between 65 to75 years (n=152), and patients > 75 years (n=46).

2.3.2.5 Hepatic impairment

No formal hepatic impairment trials have been conducted. The 472 patients in population analysis were categorized as normal hepatic function (N=401, bilirubin ≤ upper limit of normal (ULN), AST ≤ ULN) and mild hepatic impairment (N=71, bilirubin between 1–1.5 × ULN or AST > ULN and bilirubin ≤ ULN). Assessment in patients with moderate or severe hepatic impairment was not possible in the current population. The cut offs for ULN were 34 U/L and 1.9 mg/dL (17.1×1.9 μmol/mL) for AST and bilirubin, respectively. A population PK model-derived CL values in patients with mild hepatic impairment were similar to those in patients with normal hepatic function (Table 8). No dose adjustment in patients with mild hepatic impairment is required.

Table 8. Comparison of Bayesian post-hoc Atezolizumab Covariate-normalized CL for Hepatic Function Categories (Mean, 90% CI of the Mean).

	HEPATIC FUNCTION	
Characteristics	**Normal N=401**	**Mild N=71**
Normalized CL (L/day)	0.208 (0.203; 0.213)	0.210 (0.200; 0.221)

CL=clearance; N=Number of patients; normal hepatic function=bilirubin ≤ ULN, AST ≤ ULN, mild = bilirubin between 1–1.5 × ULN or (AST > ULN and bilirubin ≤ ULN), moderate=bilirubin between 1.5–3 × ULN, any AST, and severe=bilirubin > 3 × ULN, any AST
ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight (normalized to a 77-kg body weight); Albumin=normalized to 40 g/L; Tumor burden normalized to 63 mm;
e.g. for NMID 4, Individual CL=0.19 L/day, Albumin =45 g/L, BWT=59.4 kg, tumor burden=43 mm, ATAG=1;
Normalized CL=0.192/(((((45/40)^-1.12)((59.4/77)^0.808)*((43/63)^0.125))*(1+1*0.159))=0.245 L/day.*

Source: Table 4-13 of Population PK Report 1066935

2.3.2.6 Renal impairment

No formal renal impairment trials have been conducted. Based on population PK analysis which included patients with varying degrees of renal impairment categories based on their estimated eGFR (Normal (N=140): eGFR ≥ 90 mL/min/1.73 m2, Mild (N=208): eGFR ≥ 60 and < 90 mL/min/1.73 m2, Moderate (N=116): eGFR ≥ 30 and <60 mL/min/1.73 m2, and Severe (N=8): eGFR <30 mL/min/1.73 m2), the effect of mild and moderate renal impairment on CL of atezolizumab was minor (Table 9). Data is not sufficient for drawing a conclusion on severely renal impaired patients.

Also see the Pharmacometrics review (Section 4) by Dr. Chao Liu.

Table 9. Comparison of Bayesian post-hoc Atezolizumab Covariate-normalized CL for Renal Function Categories (Mean, 90% CI of the Mean)

	RENAL FUNCTION			
Characteristics	**Normal N=140**	**Mild N=208**	**Moderate N=116**	**Severe N=8**
eGFR (mL/min/1.73 m^2)	112 (109; 115)	75.1 (74.1; 76.1)	48.8 (47.7; 50.0)	25.7 (20.4; 31.1)
Normalized CL (L/day)	0.212 (0.204; 0.220)	0.210 (0.203; 0.217)	0.202 (0.194; 0.210)	0.202 (0.169; 0.235)

CL=clearance; eGFR: estimated Glomerular Filtration Rate; N=Number of patients, Normal=eGFR ≥ 90 mL/min/1.73 m^2, Mild=eGFR ≥ 60 and < 90 mL/min/1.73 m^2, Moderate:=eGFR ≥ 30 and <60 mL/min/1.73 m^2, and Severe=eGFR <30 mL/min/1.73 m^2 ; ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight (normalized to a 77-kg body weight); Albumin=normalized to 40 g/L; Tumor burden normalized to 63 mm;
e.g. for NMID 4, Individual CL=0.19 L/day, Albumin =45 g/L, BWT=59.4 kg, tumor burden=43 mm, ATAG=1;
Normalized CL=0.192/(((((45/40)^-1.12)((59.4/77)^0.808)*((43/63)^0.125))*(1+1*0.159))=0.245 L/day.*

Source: Table 4-13 of Population PK Report 1066935

2.3.2.7 Race/Ethnicity

Race/ethnicity was not identified as a significant covariate in population pharmacokinetic analysis.

2.3.2.8 Immunogenicity

The immunogenicity atezolizumab was evaluated during the drug development.

2.3.2.8.1 How was the immunogenicity of atezolizumab evaluated?

The serum samples were collected at the following listed time points for ATA analysis.

- IMvigor 210: Cycle 1 Day 1, Predose; Day 1 on Cycles 2, 3, 4, and 8, Predose; Treatment discontinuation visit; 120 days (± 30 days) after last dose.
- PCD4989g: Cycle 1 Day1, Predose; Day 1 on Cycles 2 and 4, Predose; Study completion/early termination visit.
- JO28944: Cycle 1 Day 1, Predose; Cycle 1 Day 22; Day 22 on Cycles 2, 3, 4, and 6; Within 30 days after final infusion.

A "tiered strategy" was used for ATA sample analysis. Serum samples were first screened in a bridging enzyme-linked immunosorbent assay (ELISA) assay. Samples that screened positive were further analyzed by competitive binding with atezolizumab to confirm the positivity. Samples that were confirmed positive were then diluted further to obtain a value in titer units.

See 2.6.2 for more information on ATA bioassays.

2.3.2.8.2 What is the ATA incidence of atezolizumab?

The ATA incidence to atezolizumab was 31.7%, 16.7% and 41.9% in the Studies PCD4989g, JO28944 and IMvigor 210, respectively (Table 10).

Table 10. Summary of Immunogenicity Results for Atezolizmab

	PCD4989g Atezolizumab (All Cohorts) n=481	JO28944 Atezolizumab (All Cohorts) n=6	IMvigor 210 Atezolizumab (Cohorts 1 and 2) n=429
Baseline			
Evaluable patients	n=458	n=6	n=423
No. of patients positive for ATA	14 (3.1%)	0 (0.0%)	16 (3.8%)
No. of patients negative for ATA	444 (96.9%)	6 (100.0%)	407 (96.2%)
Post-Baseline			
Evaluable patients	n=439	n=6	n=384
No. of patients positive for ATA	139 (31.7%)	1 (16.7%)	161 (41.9%)
Treatment-induced[a] ATA	136	1	157
Treatment-enhanced[b] ATA	3	0	4
No. of patients negative for ATA	300 (68.3%)	5 (83.3%)	223 (58.1%)
Treatment-unaffected[c] ATA	10	0	10

ATA=anti-therapeutic antibody.

[a] Treatment-induced ATAs: Patients who had a baseline-negative ATA result who developed anti-atezolizumab antibodies at any time after initial drug administration.

[b] Treatment-enhanced ATAs: Patients who had a baseline-positive ATA result in whom the assay signal was enhanced (greater than baseline titer by≥0.60 titer units) at any time after initial drug administration.

[c] Treatment-unaffected ATAs: Patients who had a baseline-positive ATA result in whom the assay signal was not enhanced (not greater than baseline titer by≥0.60 titer units) at any time after initial drug administration. These patients are considered post-baseline negative for ATAs.

Note: Patients with treatment-induced ATA and Treatment-enhanced ATA were considered positive for ATA.

Source: Table 10 in the Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.3.2.8.3 Is the positive ATA incidence related to the inferior objective response rate (ORR)?

A review of IRF-assessed ORRs per RECIST v1.1 across Studies PCD4989g and IMvigor 210 for urothelial carcinoma patients dosed at 15 mg/kg or 1200 mg does not demonstrate that ATA positivity is consistently associated with a lower ORR (Table 11). In Trial PCD4989g, the ORR data in patients with urothelial carcinoma patient may show a trend of lower objective response for ATA-positive patients, but the number of patients was small and the ORR confidence intervals overlap for ATA-negative and ATA-positive patients. The ORR for ATA-negative and ATA-positive patients in Study IMvigor 210 Cohort 2 appeared to be similar in both IRF-assessed RECIST v1.1 (Table 11) and investigator-assessed modified RECIST ORRs (Table 12). Overall, ATA positivity did not seem to impact efficacy.

Table 11. IRF-assessed Objective Response Rate per RECIST v1.1 by ATA Positivity (Treated Patients with Urothelial Carcinoma)

	PCD4989g (urothelial carcinoma cohort), Efficacy Evaluable Patients with 12-Weeks Follow-Up		IMvigor 210 Cohort 2, Objective Response Evaluable Patients	
All Treated Patients	ATA-Negative (n=38)	ATA-Positive (n=42)	ATA-Negative (n=161)	ATA-Positive (n=114)
Responders	15	7	25	22
Non-responders	23	35	136	92
% ORR Responders	39.5%	16.7%	15.5%	19.3%
95% CI for Response Rates	(24.04, 56.61)	(6.97, 31.36)	(10.31, 22.06)	(12.51, 27.75)

ATA=anti-therapeutic antibody; CI=confidence interval; ORR=overall response rate; q3w=every three weeks.

Note: Patients with urothelial carcinoma in Study PCD4989g received doses 15 mg/kg (n=82) and 1200 mg (n=6) q3w.

Source: Table 11 in the Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

Table 12. Investigator-Assessed Objective Response Rate per Modified RECIST by ATA Status

	Cohort 2	
	ATA-Negative (n=161)	ATA-Positive (n=114)
Responders	30	27
Non-responders	131	87
% Responders	18.6%	23.7%
95% CI for Response Rates	12.94, 25.52	16.22, 32.56

ATA=anti-therapeutic antibody; CI=confidence interval; ORR=overall response rate; RECIST=response evaluation criteria in solid tumors.

Table is based on objective response evaluable population where a sample was available.

Note: ORR per modified RECIST is not applicable to Cohort 1.

Source: Table 12 in the Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.3.2.8.4 Is the positive ATA incidence related to safety?

Positive ATA did not appear to be related to safety in the pivotal Phase 2 Study IMvigor 210 and Phase 1 Study PCD4989g. The incidence of AESIs for atezolizumab was similar irrespective of post-baseline ATAs status (Table 13)

Table 13. Studies IMvigor 210 and PCD4989g: Incidence of AESIs by ATA Status

	IMvigor 210 Cohort 1		IMvigor 210 Cohort 2		PCD4989g urothelial carcinoma Cohort	
	ATA negative N=62 n (%)	ATA positive N=47 n (%)	ATA negative N=161 n (%)	ATA positive N=114 n (%)	ATA negative N=41 n (%)	ATA positive N=43 n (%)
AESIs	13 (21.0%)	12 (25.5%)	42 (26.1%)	35 (30.7%)	13 (31.7%)	13 (30.2%)

ATA anti-therapeutic antibodies; AESI adverse event of special interest

Source: Table 35 in the Summary of Clinical Safety of BLA761034 (Section 2.7.4)

2.3.2.8.5 Does ATA incidence affect the PK of Atezolizumab?

There was a trend to slightly lower C_{min} concentrations in ATA-positive patients compared to ATA negative patients in Studies IMvigor 210 (Table 14) and PCD4989g (Table 15). There was one ATA-positive patient out of three 10 mg/kg dosing group patients in Study JO28944. The serum atezolizumab concentration of the ATA-positive patients was not lower than that in the 2 ATA-negative patients in the same dosing group. A population PK analysis on 472 PK evaluable patients from Phase 1 Studies PCD4989g and JO28944 (population PK report 1066935) suggested that ATAG, which stands for positive post-baseline status of anti-therapeutic antibodies, is a statistically significant covariate on CL. In patients with positive ATAG, CL was estimated to be 16% higher than in patients with negative ATAG. Positive ATAG did not result in more than a 20% change in $AUC_{,ss}$, $C_{max,ss}$ or $C_{min,ss}$ from the typical patient (Figure 3). The relationship estimated in the Phase 1 population PK model adequately described trends in Study IMvigor 210.

Table 14. IMvigor 210: Summary Statistics for Atezolizumab C_{max} and C_{min} Following Multiple IV Doses of Atezolizumab 1200 mg Given q3w by ATA Status (All Cohorts)

Visit[1]	Nominal Time (day)	N[2]	AM (µg/mL)	AM SD (µg/mL)	GM (µg/mL)	GM %CV	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
ATA Positive (n = 161)									
C1D1	0	158[4]	0.000487	0.00612	NE	NE	0.00	0.00	0.0769[3]
C1D1	0.021	157	359	82.7	350	22.3	230	351	694
C1D21	21	155	68.4	27.5	60.7	62.6	4.32	68.3	168
C3D21	63	103	137	49.8	126	45.4	16.2	132	254
C7D21	147	55	166	68.3	151	48.3	34.8	151	364
ATA Negative (n = 223)									
C1D1	0	216[4]	0.00	0.00	NE	NE	0.00	0.00	0.00
C1D1	0.021	208	376	96.3	365	24.3	117	360	1080
C1D21	21	211	79.7	28.5	74.0	44.3	7.05	77.7	182
C3D21	63	141	155	57.6	144	43.6	31.6	149	390
C7D21	147	72	206	75.4	191	41.1	80.9	208	392

AM = arithmetic mean; ATA = anti-therapeutic antibody; C_{max} = maximum observed serum concentration; C_{min} = trough or minimum serum concentration; CV = coefficient of variation; GM = geometric mean; LLOQ = lower limit of quantitation, defined as 0.06 µg/mL; NE = not estimated; SD = standard deviation.

[1] Visit is denoted by Cycle abbreviated by "C" and Day abbreviated by "D". For example, C1D1 corresponds to Cycle 1, Day 1, etc. Predose Cycle 1 is C1D1 0 days. C_{max} is C1D1 0.021 days (or 30 minutes post end of infusion). Predose or C_{min} Cycle 2 is C1D21, predose or C_{min} Cycle 3 is C2D21 etc.

[2] N = number used to calculate statistics.

[3] At Cycle 1, Day 1 predose (Nominal Time = 0) samples, one patient in the ATA–positive group was above the LLOQ.

[4] 43 patients did not have a post-dose ATA sample.

Source: Table 8 in the Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

Table 15. PCD4989g: Geometric Mean (%CV) Serum Atezolizumab C_{min} and C_{max} Concentration across Treatment Cycles Stratified by ATA Status

Atezolizumab PK Parameters, stratified by ATA Status (GM, %CV)							
Dose	ATA Status	C_{max} C1 postdose (µg/mL)	C_{min} C2 predose (µg/mL)	C_{min} C4 predose (µg/mL)	C_{min} C5 predose (µg/mL)	C_{min} C8 predose (µg/mL)	C_{max} C8 postdose (µg/mL)
10 mg/kg	+	235 (20) n=12	47.4 (22) n=12	91.1 (62) n=10	118 (26) n=3	NR	NR
	-	260 (24) n=22	58.2 (23) n=22	105 (32) n=17	140 (13) n=4	112 (65) n=3	NR
15 mg/kg	+	297 (150) n=82	54.5 (110) n=87	95 (190) n=60	107 (280) n=35	176 (67) n=22	516 (24) n=9
	-	306 (240) n=128	77.4 (41) n=127	144 (46) n=93	146 (150) n=69	196 (55) n=33	386 (63) n=5
20 mg/kg	+	435 (21) n=26	70.9 (35) n=27	132 (53) n=23	168 (80) n=11	163 (130) n=13	388 n=1
	-	505 (24) n=104	97.2 (33) n=105	180 (48) n=90	206 (58) n=49	237 (59) n=30	614 n=1
1200 mg	+	392 (27) n=3	56.9 (45) n=3	144 n=1	143 n=1	NR	NR
	-	458 (22) n=26	101 (48) n=27	139 (43) n=7	142 n=1	NR	NR

ATA = anti-therapeutic antibody; C_{max} = maximum serum concentration; C_{min} = trough or minimum serum concentration; CV = coefficient of variation; GM = geometric mean; NR = not reported; PK = pharmacokinetic.

Source: Table 5 in the Summary of Clinical Pharmacology of BLA761034 (Section 2.7.2)

2.3.2.9 PD-L1 Expression

PD-L1 expression was prospectively assessed in tumor-infiltrating immune cells (ICs) in tumor tissue from all patients in the Phase 2 study IMvigor 210 (Cohort 2) and the Phase 1 study PCD4989g. An investigational use only (IUO) immunohistochemistry (IHC) assay was used to assess PD-L1 expression in an unselected (all-comers) patient population in study IMvigor 210. In PCD4989g, a prototype IHC assay was initially used to assess PD-L1 expression and enrich for patients with higher IC scores (e.g. IC2/3). PD-L1 expression was later assessed retrospectively in 74% of patients (69 / 93) using the IUO IHC assay. Patients were assigned to subgroups for pre-specified analysis based on IC score (percentage of tumor area covered by PD-L1-expressing ICs (any intensity)). IC score distributions for each study are indicated in Table 16.

Table 16. PD-L1 IC Staining Criteria and IC Score Distribution in Studies IMvigor 210 and PCD4989g

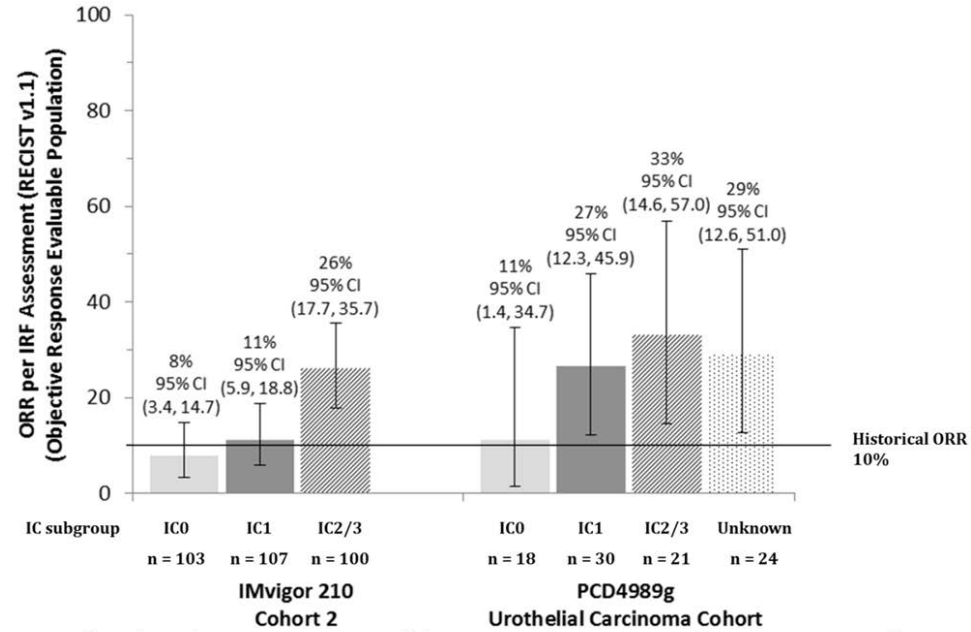
IC score	% of Tumor Area Occupied by PD-L1-Expressing ICs	IMvigor 210 Cohort 2 IUO Assay N = 310	PCD4989g TCC IUO Assay N = 93
IC3	≥10%	0	4 (4%)
IC2	≥5% and <10%	100 (32%)	17 (18%)
IC1	≥1% and <5%	107 (35%)	30 (32%)
IC0	<1%	103 (33%)	18 (19%)
Unknown	N/A	0	24 (26%)

IC: Tumor–Infiltrating Immune Cells; TCC: Transitional Cell Carcinoma;
IUO: Investigational Use Only Assay.

Source: Reviewer analyses of IMvigor 210 analysis dataset ADSL.xpt (14 September 2015 data cut) and PCD4989g analysis dataset ARS.xpt (7 Aug 2015 data cut)

As indicated in Figure 4, a trend toward higher independent review facility (IRF)-assessed ORR with higher IC scores was observed in patients in study IMvigor 210. A similar trend was observed in study PCD4989g, although responses in all IC categories were higher in study PCD4989g compared to IMvigor 210. Exploratory analyses of IRF-assessed ORR in patients with IC0 and IC1 scores in study IMvigor 210 suggest that ORRs in these subsets of patients are similar to historical control ORR (10%) [PMIDs: 24220220, 19687335, 22184381, 26926681, 12108893].

Figure 4: Objective Response Rate per IRF Assessment (RECIST v1.1) (Objective Response Evaluable Population)



IC score based on the IUO assay. CI: Confidence Interval; IC: Tumor-Infiltrating Immune Cells; IRF: Independent Review Facility; ORR: Objective Response Rate.

Source: Reviewer plot based on IMvigor 210 Supplemental Results Report (Data Cutoff: 27 November 2015) Table 1 and PCD4989g Supplemental Results Report (Data Cutoff: 7 August 2015) Table 2

Reviewer exploratory analyses of disease characteristics by IC score showed that patients with higher IC scores tended to have mixed histology, less visceral metastases, lung metastases, lymph node metastases, prior intravesical therapy, or prior therapy with cisplatin-based regimens. Patients with tumor responses (CR or PR) tended to have visceral metastases, liver metastases, lung metastases, brain metastases, lower baseline ECOG score, fewer Bellmunt risk factors, lower baseline alkaline phosphatase, serum hemoglobin < 10 g/dL, or previous tobacco use. IC score tended to be associated with tumor response in all relevant subgroups (Table 17). In a multivariable model adjusting for potentially confounding factors and the factors that predicted tumor response, IC score remained associated with tumor response in atezolizumab treated subjects (adjusted OR [95%CI] 1 vs. 0 = 1.04 [0.37, 2.91] , 2 vs. 0 = 2.69 [1.04, 6.91]).

Table 17. Effect of IC Score on ORR across Relevant Subgroups

		ORR n/N (%)			
Subgroup		Overall	IC0	IC1	IC2
Lymph Node Only Metastases	Yes	13/43 (30%)	1/4 (25%)	4/15 (27%)	8/24 (33%)
	No	33/267 (12%)	7/99 (7%)	8/92 (9%)	18/76 (24%)
Visceral Metastases	Yes	24/243 (10%)	6/91 (7%)	7/86 (8%)	11/66 (17%)
	No	22/67 (33%)	2/12 (17%)	5/21 (24%)	15/34 (44%)
Liver Metastases	Yes	5/96 (5%)	2/35 (6%)	0/34 (0%)	3/27 (11%)
	No	41/214 (19%)	6/68 (9%)	12/73 (16%)	23/73 (32%)
Lung Metastases	Yes	13/135 (10%)	4/50 (8%)	3/54 (6%)	6/31 (19%)
	No	33/175 (19%)	4/53 (8%)	9/53 (17%)	20/69 (29%)
Brain Metastases	Yes	3/8 (38%)	1/2 (50%)	2/3 (67%)	0/3 (0%)
	No	43/302 (14%)	7/101 (7%)	10/104 (10%)	26/97 (27%)
Number of Metastatic Sites	0	7/20 (35%)	1/6 (17%)	1/6 (17%)	5/8 (62.5%)
	1	16/81 (20%)	1/23 (4%)	6/28 (21%)	9/30 (30%)
	2	14/98 (14%)	3/40 (8%)	4/29 (14%)	7/29 (24%)
	3	4/66 (6%)	1/19 (5%)	1/27 (4%)	2/20 (10%)
	>4	5/45 (11%)	2/15 (13%)	0/17 (0%)	3/13 (23%)
Baseline ECOG	0	30/117 (26%)	5/34 (15%)	7/41 (17%)	18/42 (43%)
	1	16/177 (9%)	3/69 (4%)	5/66 (8%)	8/58 (14%)

IC: Tumor-Infiltrating Immune Cells; ORR: Objective Response Rate; ECOG: Eastern Cooperative Oncology Group.

Source: Reviewer exploratory analyses using IMvigor 210 analysis datasets ARS.xpt and ADSL.xpt (27 November 2015 data cut)

Reviewer comment: Although the data suggest a trend towards higher ORR in patients with higher IC scores, responses were observed across all IC score categories. According to the reviewer exploratory analysis, this trend generally persisted after adjusting for *potentially confounding factors. Given these findings, the use of a PDL-1 expression assay may be useful as a complementary diagnostic. A premarket approval (PMA) for the PD-L1 IHC assay has been submitted to CDRH.*

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

None of the extrinsic factors including drugs, herbal products, diet, smoking, and alcohol use were studied for their influence on atezolizumab exposure and/or response.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

No.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Unlikely.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Unlikely.

2.4.2.4 Are there metabolic/transporter pathways that may be important?

Unlikely. Metabolism studies are not generally performed for biological protein products. As proteins are degraded into amino acids that are subsequently recycled into other proteins, the classical biotransformation studies for small molecule drugs are not applicable.

2.4.2.5 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No.

2.4.2.6 What is the drug-drug interaction potential between atezolizumab and other chemotherapies?

No formal drug-drug interaction studies have been performed with atezolizumab.

2.4.2.7 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Unknown.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What moieties should be assessed in biocomparability studies?

Atezolizumab, the active ingredient of the drug product, should be assessed in biocomparability studies, based on the current knowledge.

2.5.2 What is the composition of the to-be-marketed formulation?

The commercial formulation of atezolizumab, the drug product, is supplied in a single dose 20-mL vial containing preservative free liquid concentrate, at a concentration of 60 mg/mL ready for infusion. Each vial contains a total of 1200 mg atezolizumab. The commercial Drug Product formulation (F03) is currently being used for clinical trials, including the Phase 2 pivotal clinical trial IMvigor 210. The composition (b) (4) is listed in Table 18.

Table 18. Overview of Atezolizumab Formulations

Component	Formulation	
	F01	F03
Active Ingredient (atezolizumab)	(b) (4)	60 mg/mL
L-Histidine		20 mM[b]
Glacial Acetic Acid		13 mM[b]
Sucrose		120 mM
Polysorbate 20		0.04% (w/v)
pH		5.8
Nominal Fill Volume		20.0 mL
Dose Strength		1200 mg
Dosage Form	Concentrate for solution for infusion	Concentrate for solution for infusion

(b) (4)
(b) (4)

Source: Table 4 in the Summary of Biopharmaceutics Studies and Associated Analytical Methods of BLA761034 (Section 2.7.1)

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess serum concentrations of atezolizumab?

An ELISA method was developed to quantify atezolizumab concentrations in human serum. This assay was validated and run at two sites (Genentech and (b) (4) in six clinical pharmacology studies (Table 19).

Table 19. Validation Performance Parameters for Pharmacokinetic Assays

PK Assay Validation and Sample Analysis Site, Method Number	Validation Report No.	Standard Curve Reporting Range (ng/mL)	MQC (ng/mL)	Accuracy (%Recovery)	Intra-Assay Precision (%CV)	Inter-Assay Precision (%CV)	Clinical Study No.
Genentech, Inc., BA.MET.MPDL.005	MPDL.005.AVR_1	0.6 to 24	60	81 to 112	2 to 5	2 to 11	PCD4989g
(b) (4) M08.MPDL3280A.huse.1	MPDL.005.AVR_1	0.6 to 20	60	93.2 to 125.0	1.57 to 4.12	2.21 to 4.59	PCD4989g, JO28944, IMvigor 210, FIR, POPLAR, BIRCH

CV = coefficient of variation; MQC = minimum quantifiable concentration; PK = pharmacokinetic.

Source: Table 5 in the Summary of Biopharmaceutics Studies and Associated Analytical Methods of BLA761034 (Section 2.7.1)

2.6.2 What bioanalytical methods are used to detect Anti-Therapeutic Antibody (ATA) to Atezolizumab?

The ATA analysis strategy used a tiered approach. ATAs to atezolizumab in human serum were detected using a validated screening assay. This semi-homogeneous assay used a bridging design. Serum samples from patients were incubated with atezolizumab conjugates that have been labeled with biotin and with digoxigenin. Immune complexes formed between labeled atezolizumab and ATAs were subsequently captured on high capacity streptavidin plates and detected. Samples that were positive in the ATA screening assay were further analyzed by competitive binding with atezolizumab to confirm the specificity of the positive response. Samples that were confirmed positive were then serially diluted to obtain a titer value. The ATA assays were validated at Genentech and at (b) (4) (Table 20).

Table 20. Validation Performance Parameters for ATA Assays

ATA Assay Validation and Sample Analysis Site, Method Number	Validation Report No.	Relative Sensitivity (ng/mL)	Atezolizumab Tolerance [a]	Intra-Assay Precision for Controls (%CV)	Inter-Assay Precision for Controls (%CV)	Clinical Study No.
Genentech, Inc., MPDL.006	MPDL.006.AVR_1	10.7	> 200 µg/mL	2 to 4	3 to 13	PCD4989g
(b) (4) (b) (4) M08.Anti-MPDL3280A.huse.1	MPDL.006.AVR_1	20.4	> 200 µg/mL	2.16 to 5.14	4.55 to 16.3	JO28944, IMvigor 210, FIR, POPLAR, BIRCH

ATA = anti-therapeutic antibody; CV = coefficient of variation; PK = pharmacokinetic.

[a] Atezolizumab tolerance = concentration of atezolizumab present in sample where 500 ng/mL anti-atezolizumab positive control antibody can still be detected.

Source: BLA 761034 Table 6 of Section 2.7.1 "Summary of biopharmaceutic studies and associated analytical methods"

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Underlines indicate the content that was added to the proposed label by the Agency and ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

PROPOSED LABELING	AGENCY'S SUGGESTIONS
6.2 IMMUNOGENICITY	
As with all therapeutic proteins, there is a potential for immune response to atezolizumab. Among 275 patients in Trial 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In Trial 1, the presence of ATAs did not appear to have a clinical (b) (4) significant impact on pharmacokinetics.	As with all therapeutic proteins, there is a potential for immune response to atezolizumab. Among 275 patients in (b) (4) Study 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In (b) (4) Study 1, the presence of ATAs did not appear to have a clinically (b) (4) significant impact on pharmacokinetics, safety or efficacy.
(b) (4)	
8.4 PEDIATRIC USE	
(b) (4)	The safety and effectiveness (b) (4) of TECENTRIQ (b) (4) have not been established in pediatric patients.
8.6 RENAL IMPAIRMENT	
8.6 Renal Impairment Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)].	8.6 Renal Impairment Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)].
8.7 HEPATIC IMPAIRMENT	
8.7 Hepatic Impairment	8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with mild hepatic impairment. TECENTRIQ has not been studied in patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3)].	Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with mild hepatic impairment. TECENTRIQ has not been studied in patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3)].
12.3 PHARMACOKINETICS	
(b) (4)	(b) (4) (b) (4) atients' exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose 1200 mg administered every 3 weeks. Based on a (b) (4) population analysis that included 472 patients (b) (4) (b) (4) in the dose range., tThe typical population clearance was 0.200 L/day, volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. The population PK analysis suggests steady state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) was 1.91, 1.46 and 2.75-fold, respectively. Specific Populations: (b) (4) (b) (4) (b) (4) Age (21–89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or race, mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST), level of PD-L1 expression, or ECOG status had no clinically significant effect on the systemic exposure of atezolizumab. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or moderate or severe hepatic impairment (bilirubin > ULN and AST > ULN or bilirubin ≥ 1.0 to 1.5 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown. *Drug Interaction Studies*

(b) (4)	The drug interaction potential of atezolizumab is unknown. (b) (4)

4 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

BLA Number	761034
Drug Name	TECENTRIQ® (atezolizumab)
Dose Regimen	Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks
Indication	Locally advanced or metastatic urothelial carcinoma (b) (4) [redacted]
Pharmacometrics Reviewer	Chao Liu, Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
Sponsor	Genentech, Inc.

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4.1 SUMMARY OF FINDINGS

The proposed dose of 1200 mg Q3W for atezolizumab is acceptable for the proposed indication. There appeared to be no significant exposure-efficacy relationship for the objective response rates (ORR) within the exposure range at 1200 mg Q3W dosing regimen for the proposed indication. Meanwhile, there appeared to be no significant exposure-safety relationships following 1200 mg Q3W dosing regimen based on the clinical safety data of Study IMvigor 210 and PCD4989g.

4.1.1 Key Review Questions

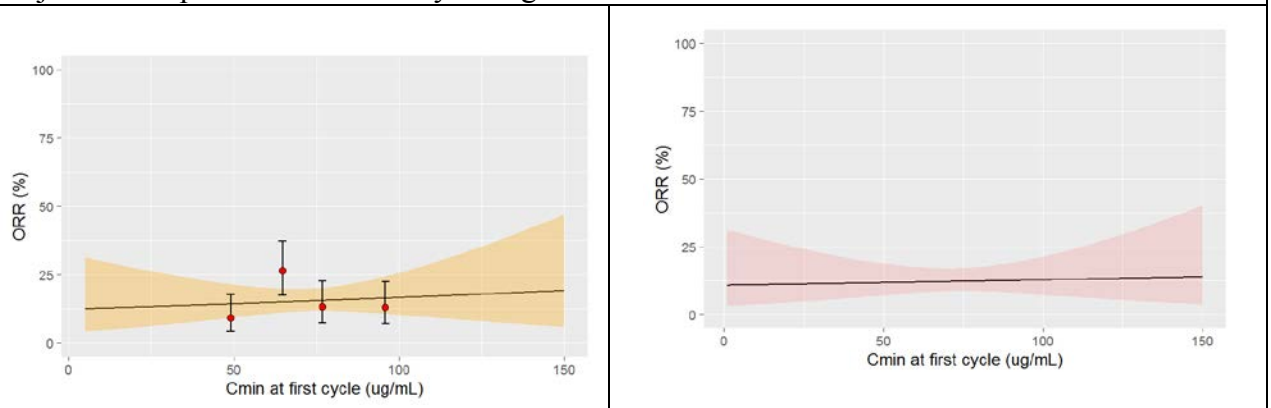
The purpose of this review is to address the following key questions.

4.1.1.1 What are the characteristics of exposure-efficacy relationship following atezolizumab Q3W treatment for the proposed indication?

There appeared to be no exposure-efficacy relationship for the objective response rates (ORR) across the exposure range following administration of 1200 mg Q3W for the proposed indication.

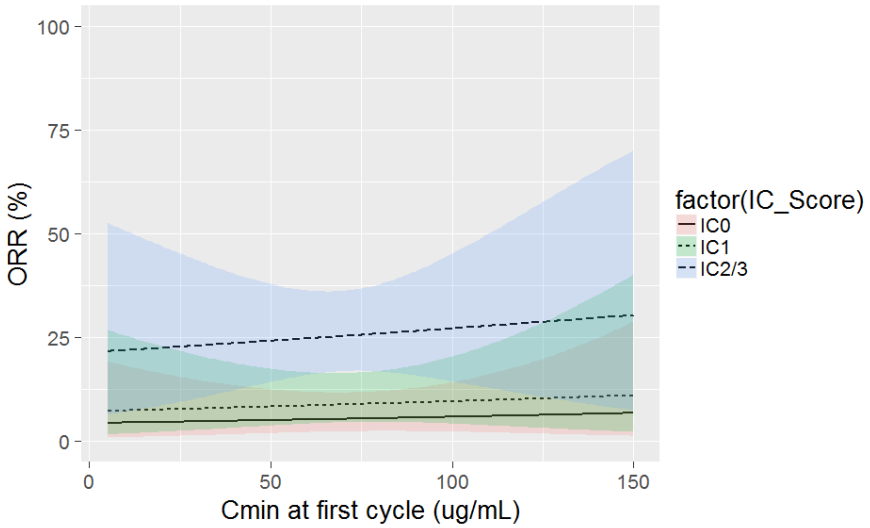
- In the study IMvigor 210, exposure-ORR relationship was flat across the trough concentration ($C_{min1)}$ range of 18-127 μg/mL for the first 1200 mg Q3W dose (**Figure 1**). In addition, ER relationship is flat for all three IC score groups (IC0, IC1, IC2/3) (**Figure 2**).
- Based on multivariate analysis, the statistically significant covariates identified for ORR were:
    - Baseline ECOG performance status: higher ECOG score is associated with lower probability to respond.
    - IC score: higher IC score is associated with higher probability to respond (Figure 2)
    - Number of metastatic sites at enrollment: greater number of metastatic sites is associated with lower probability to respond

Figure 1: Exposure-Response for the Trough Concentration of the First Dose (C_{min1}) versus Objective Response Rate for Study IMvigor 210



Left Panel: Solid line is the logistic regression of the predicted probability of response and the orange area is the 95% CI. Red circles are observed ORR. For each C_{min1} quartile, the observed ORR is plotted at the mean value of the quartile with the vertical bar as the 95% CI.
Right Panel: Solid line is predicted probability of response by multivariate logistic regression and the shaded area is the 95% CI.
Source: The two panels are from FDA reviewer's analysis based on dataset er.xpt for Study IMvigor 210.

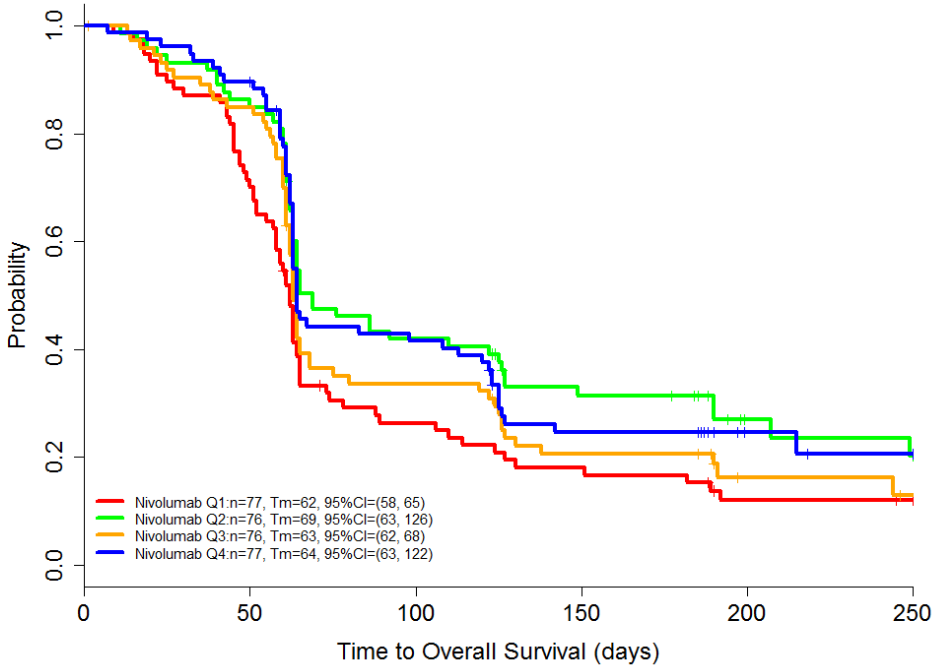
Figure 2: Exposure-Response for the Trough Concentration of the First Dose (C_{min1}) versus Objective Response Rate stratified by IC score group



Solid line is predicted probability of response by multivariate logistic regression and the shaded area is the 95% CI.
Source: The two panels are from FDA reviewer's analysis based on dataset er.xpt for Study IMvigor 210.

In addition, exposure-PFS relationship was also explored (**Figure 3)**. The analysis showed no clear differences in PFS among the atezolizumab exposure quartiles.

Figure 3: Exposure-Response for the Cmin1 versus PFS for Study IMvigor 210



Kaplan-Meier Plots of the PFS for Different Exposure Quartiles of the First Dose (Cmin1). Data for analysis were from IMvigor 210.

Source: FDA reviewer's analysis based on dataset er.xpt for Study IMvigor 210.

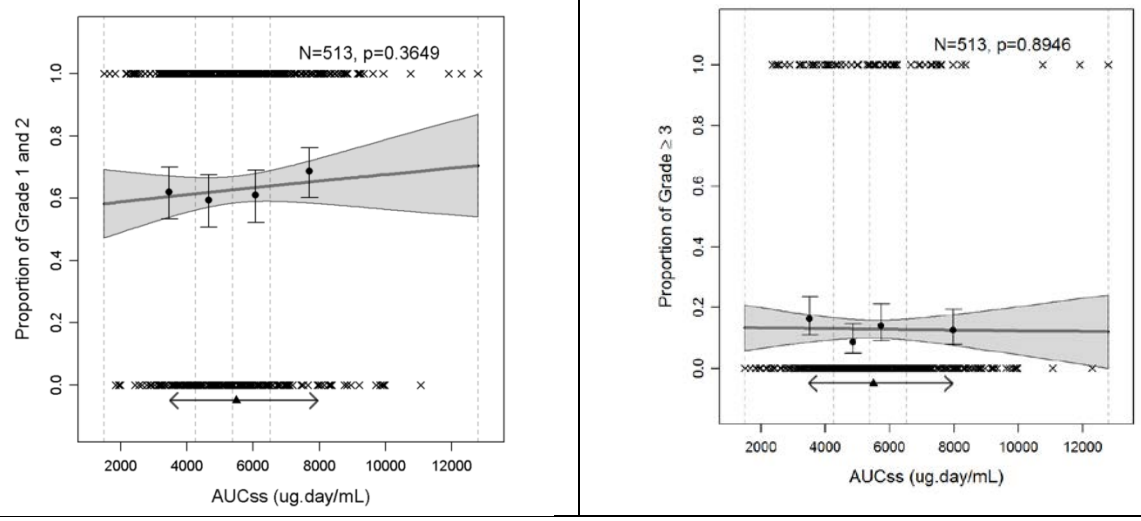
Overall, the exposure-ORR/PFS relationship for atezolizumab appeared to be flat at the 1200 mg Q3W dose.

4.1.1.2 What are the characteristics of exposure-safety relationships for atezolizumab?

Overall, there appeared to be no clear exposure-safety relationships following the atezolizumab 15 mg/kg and 1200 mg Q3W dosing regimen for the proposed indication based on the Study IMvigor 210 and PCD4989g. However, there is a slight numerical increase in AESIs (Adverse Event of Special Interest) with increasing exposure.

- **Figure 4** shows the relationship between the steady-state AUC and incidence of AEs appears to be flat.
- **Figure 5** shows the analysis results of exposure-safety relationship for all grade AESIs. It appears that there is a numerical trend (not statistical significant) of increased incidence of AESIs with increasing atezolimumab exposure. The parameter estimates of the logistic regression model for AUCss-AESI relationship are shown in **Table 11**.

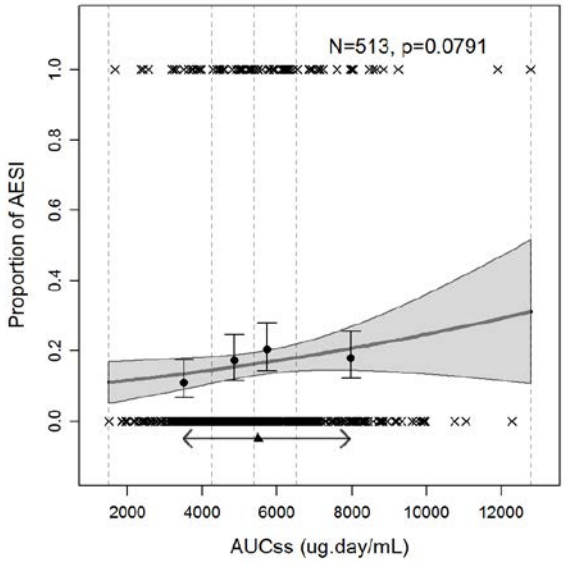
Figure 4: : Incidence of AEs vs. Atezolizumab AUCss in Patients with mUC:



N=number of patients; p=p value of Wald test in logistic regression of incidence vs. exposure. The thick solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the incidence in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The crosses are the events (0: no, 1: yes).

Source: Left panel: Sponsor's Response to IR dated 16 February 2016, Figure 1
Right panel: Sponsor's Exposure-Response Analysis Report, Figure 4-2

Figure 5: Incidence of AESIs vs. Atezolizumab AUCss in Patients with mUC



Source: Sponsor's Exposure-Response Analysis Report, Figure 4-3

4.1.1.3 Is the relevant labeling regarding intrinsic factors adequately supported by population PK analysis?

Yes. Although in the population PK analysis, age, serum albumin, body weight, tumor burden, and gender were identified as statistically significant covariates, no dose adjustments based these factors are recommended. Only mild impacts were identified upon atezolizumab exposure from

these factors. No covariate induced more than 27% change from typical for extreme values (**Table 1**). Additionally, since no ER relationships for ORR and AEs are identified, dose adjustment would have no clinically significant impact. Renal and hepatic function was not identified as statistically significant factors in the population PK model.

Table 1: Effect of Baseline Covariates and ATAG on Atezolizumab PK Parameters

PK Parameters and Baseline Covariates		Covariate Value	Estimate	Percent Change from Typical (%)
CL (L/day) for a typical patient			**0.200**	
Albumin (g/L)	10th percentile	33	0.248	+24%
	90th percentile	45	0.175	-12%
ATAG		positive	0.232	16%
Body weight (kg)	10th percentile	54	0.150	-25%
	90th percentile	104	0.255	+27%
Tumor burden (mm)	10th percentile	25	0.178	-11
	90th percentile	157	0.224	+12%
V1 (L) for a typical patient			**3.28**	
Albumin (g/L)	10th percentile	33	3.51	+7%
	90th percentile	45	3.15	-4%
Body weight (kg)	10th percentile	54	2.69	-18%
	90th percentile	104	3.88	+18%
Gender		female	2.86	-13%
V2 (L) for a typical patient			**3.63**	
Gender		female	2.64	-27%

For a typical patient defined as a male patient with negative ATAG, a body weight of 77 kg, an albumin level of 40 g/L, and a tumor burden of 63 mm; CL=clearance; V1=volume of distribution of central compartment; V2=volume of distribution of peripheral compartment; ATAG=Post-baseline status of anti-therapeutic antibodies

Source: Sponsor's Population PK Analysis Report 1066935, Table 4-10

4.1.2 Recommendations

This application is acceptable from pharmacometrics perspective. The proposed dosing regimen (1200 mg Q3W) is acceptable for the proposed indication.

4.2 RESULTS OF SPONSOR'S ANALYSIS

4.2.1 Population PK Analysis

Sponsor's PPK analysis is composed of two parts. The major goal of the first part is model development where subjects from study PCD4989g and JO28944 were included. Part two is to evaluate the PK and derive exposure metrics for ER analysis where subjects with mUC in the Phase 2 clinical Study IMvigor 210 were included.

The objectives of sponsor's population PK analysis were:

Part 1:

- Describe the PK profiles of atezolizumab in cancer patients and estimate typical values and interpatient variability of PK parameters.
- Evaluate the effects of patient demographics, pathophysiologic factors, renal function, and hepatic function in order to better understand clinical factors that might affect atezolizumab exposure in individual patients.
- Compare PK parameters in patients with mUC and patients with other tumor types.
- Derive atezolizumab exposure metrics for a subsequent exploratory exposure-response analysis of atezolizumab

Part 2:

- Assess the PK of atezolizumab in patients with mUC in the Phase 2 clinical Study GO29293 through external validation of the population PK Model using Phase 1 data (Phase 1 popPK Model).
- Derive atezolizumab exposure metrics for a subsequent exploratory exposure-response analysis of atezolizumab in mUC. Post-hoc estimation using the part 1 popPK model was performed to obtain individual random effects and PK parameters in Study GO29293 patients.

4.2.2 Data

For the model development, two studies were included:

- PCD4989g (GO27831) (N=481): Phase 1a, multicenter, first-inhuman, nonrandomized, open-label, safety and PK dose escalation study (3+3 design) to evaluate the safety, tolerability, and pharmacokinetics of atezolizumab administered as a single agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- JO28944 (N=6): Open-label, multicenter, dose-escalation study to investigate the safety, tolerability, and pharmacokinetics of atezolizumab in Japanese patients with advanced solid tumors.

The summary of demographics is presented in **Table 2** and **Table 3**.

Table 2: Descriptive Statistics of Continuous Covariates at Baseline in PK Evaluable Patients

Covariate (unit)	Number of patients	Min	Median	Max
Age (year)	472	21	62	89
Body weight (kg)	472	36.5	76.9	168
Albumin (g/L)	472	16	40	53
Bilirubin * (µmol/L)	467	1.7	6.8	23.9
AST (U/L)	472	0.8	22	183
ALT** (U/L)	471	4.0	19	138
eGFR (mL/min/1.73m^2)	472	5.8	76.1	218
Creatinine Clearance (mL/min)	472	5.7	86.3	294
Tumor burden (mm)	460	11	63	323

*N=number of patients; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated Glomerular Filtration Rate based on Modification of diet in renal disease (MDRD) equation; Creatinine Clearance calculated using Cockcroft & Gault equation; * exclusion of 2 aberrant values for the summary statistic (i.e. 0 µmol/L); ** exclusion of 1 aberrant values for the summary statistic (i.e. 0 U/L).*
Before imputation of missing data

Source: Synopsis of sponsor's Pop PK Report 1066935, Table 4-4

Table 3: Descriptive Statistics of Categorical Covariates at Baseline in PK Evaluable Patients

Covariate	Category	Number of patients (%)
Gender	Female	196 (41.5%)
	Male	276 (58.5%)
ECOG	0	211 (44.7%)
	1	258 (54.7%)
	2	2 (0.4%)
	missing	1 (0.2%)
Race	Asian	17 (3.6%)
	Black	15 (3.2%)
	White	375 (79.4%)
	missing	65 (13.8%)
Region	ESP	27 (5.7%)
	FRA	66 (14%)
	GRB	32 (6.8%)
	JPN	6 (1.3%)
	USA	341 (72.2%)
Ethnicity	Hispanic	16 (3.4%)
	Not Hispanic	364 (77.1%)
	Unknown	92 (19.5%)
ATAG	Negative	304 (64.4%)
	Positive	136 (28.8%)
	missing	32 (6.8%)
IC Score	IC0	108 (22.9%)
	IC1	80 (16.9%)
	IC2	117 (24.8%)
	IC3	100 (21.2%)
	Unknown	67 (14.2%)
TC Score	TC0	286 (60.6%)
	TC1	51 (10.8%)
	TC2	50 (10.6%)
	TC3	19 (4%)
	Unknown	66 (14%)

ATAG=Post-baseline status of anti-therapeutic antibodies;ECOG=Eastern cooperative oncology group performance status; ESP: SPAIN, FRA=FRANCE; GRB=Great Britain; JPN=JAPAN; IC=Tumor-infiltrating immune cells; TC=Tumor cell Before imputation of missing data

Source: Synopsis of sponsor's Pop PK Report 1066935, Table 4-5

4.2.2.1 Results

Serum PK of atezolizumab across the 2 studies (doses ranged from 1 to 20 mg/kg q3w, or the fixed-dose equivalent to 15 mg/kg of 1200 mg dose of atezolizumab q3w) was described by a linear two-compartment disposition model with first-order elimination.

The estimated typical population clearance (CL) was 0.200 L/day and typical central volume of distribution (V1) was 3.28 L for a male patient with 40 g/L of albumin. The typical volume of distribution at steady-state (Vss) and terminal half-life estimates were 6.91 L and 27 days. Based on simulations in the current population, 90% of steady-state was attained after the following median [range] number of cycles: 3 cycles [1-6], 2 cycles [1-4] and 3 cycles [1-5] for Cmin, Cmax and AUC, respectively. Inter-individual variability (IIV) was estimated to be 29%, 18% and 34%,

for CL, V1 and V2, respectively. The following statistically significant parameter-covariate relationships were identified (i denotes a specific patient):

$$CL_i = \left(0.200 \cdot \left(\frac{ALBU_i}{40}\right)^{-1.12} \cdot \left(\frac{BWT_i}{77}\right)^{0.808} \cdot \left(\frac{Tumor\ burden_i}{63}\right)^{0.125}\right) \cdot (1.159\ if\ ATAG\ is\ positive)$$

$$V1_i = \left(3.28 \cdot \left(\frac{BWT_i}{77}\right)^{0.559} \cdot \left(\frac{ALBU_i}{40}\right)^{-0.350}\right) \cdot (0.871\ if\ female)$$

$$V2_i = 3.63 \cdot (0.728\ if\ female)$$

BWT=body weight (kg); ALBU=Albumin (g/L); Tumor burden (mm); ATAG= Post-baseline status of anti-therapeutic antibodies

In patients who were positive for ATAG, CL was estimated to be 16% higher than in patients with negative ATAG. In females, V1 and V2 would be 13% and 27% lower than in males, respectively. No covariate induced more than 27% change from typical for extreme values.

The final population PK parameter estimates are presented in **Table 4**.

Table 4 PK parameter estimates in the final model

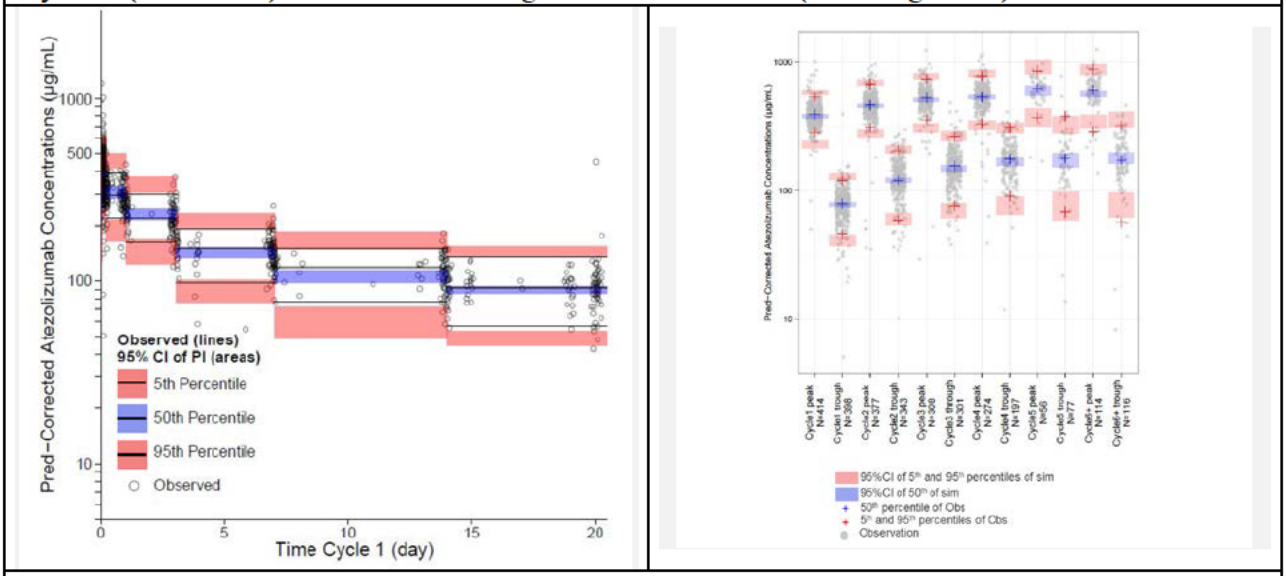
Parameters	Estimate	RSE (%)	Shrinkage (%)	Residual Error or IIV
CL (L/day)	0.200	2		
V1 (L)	3.28	2		
V2 (L)	3.63	4		
Q (L/day)	0.546	8		
Albumin on CL	-1.12	10		
Positive ATAG on CL	0.159	25		
Tumor burden on CL	0.125	17		
Body weight on CL	0.808	8		
Albumin on V1	-0.350	21		
Body weight on V1	0.559	8		
Gender (female) on V1	-0.129	16		
Gender (female) on V2	-0.272	16		
σ^2 Proportional residual error	0.0433	7	9	21%
σ^2 Additive residual error	16.6	39	9	4 µg/mL
ω^2 CL	0.0867	9	9	29%
ω^2 V1	0.0328	18	17	18%
ω^2 V2	0.114	25	33	34%
Correlation CL.V1	0.341			
Correlation CL.V2	-0.236			
Correlation V1.V2	0.434			
Objective function	40748			

CL=clearance; IIV=inter-individual variability; Q=inter-compartmental clearance; RSE=relative standard error; V1=volume of distribution of central compartment; V2=volume of distribution of peripheral compartment; ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight normalized to 77kg; Albumin normalized to 40 g/L; Tumor burden normalized to 63 mm; ω^2=variance of omega; σ^2=variance of sigma

Source: Synopsis of sponsor's Pop PK Report 1066935, Table 4-7

The results of the visual predictive check revealed that the model adequately described the observed data (**Figure 6**).

Figure 6 : Prediction-Corrected VPC of Atezolizumab Concentration (Semi-log Scale) versus on Cycle 1 (Left Panel) or Peaks and Troughs of Atezolizumab (Semi-log Scale)



Source: Synopsis of sponsor's Pop PK Report 1066935, Figure 4-6 and 4-7

The impact of the degree of renal impairment on atezolizumab CL was assessed by categorizing patients with varying degrees of renal impairment into 4 categories based on their estimated eGFR (Normal: eGFR ≥ 90 mL/min/1.73 m2, Mild: eGFR ≥ 60 and < 90 mL/min/1.73 m2, Moderate: eGFR ≥ 30 and <60 mL/min/1.73 m2, and Severe: eGFR <30 mL/min/1.73 m2). **Table 5** shows that no clinically important differences in the CL of atezolizumab were found between patients with renal impairment and patients with normal renal function.

Table 5 Comparison of Bayesian Post-hoc Atezolizumab Covariate-Normalized CL for Renal Function Categories (Mean, 90% CI of the Mean)

	RENAL FUNCTION			
Characteristics	**Normal N=140**	**Mild N=208**	**Moderate N=116**	**Severe N=8**
eGFR (mL/min/1.73 m^2)	112 (109; 115)	75.1 (74.1; 76.1)	48.8 (47.7; 50.0)	25.7 (20.4; 31.1)
Normalized CL (L/day)	0.212 (0.204; 0.220)	0.210 (0.203; 0.217)	0.202 (0.194; 0.210)	0.202 (0.169; 0.235)

Source: Synopsis of sponsor's Pop PK Report 1066935, Table 4-12

In the current population, only 2 categories were represented: 401 patients (85%) had normal hepatic function, 71 patients (15%) mild hepatic impairment. No assessment in patients with moderate or severe hepatic impairment was possible. The comparison of atezolizumab CL normalized on other covariates significant in the model in the patients with different hepatic functions is given in **Table 6** and showed that no dose adjustment in patients with mild hepatic impairment is required.

Table 6 Comparison of Bayesian Post-hoc Atezolizumab Covariate-Normalized CL for Hepatic Function Categories (Mean, 90% CI of the Mean)

	HEPATIC FUNCTION	
Characteristics	**Normal N=401**	**Mild N=71**
Normalized CL (L/day)	0.208 (0.203; 0.213)	0.210 (0.200; 0.221)

Source: Synopsis of sponsor's Pop PK Report 1066935, Table 4-13

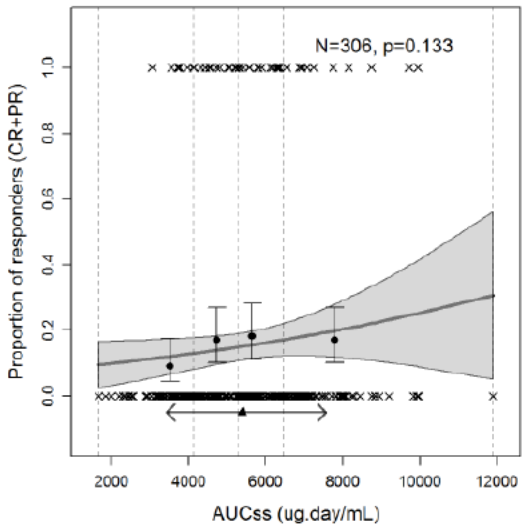
Reviewer's comments:

- *Sponsor population PK model seems reasonable.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on bodyweight, age, gender, hepatic function (mild_impairment) and renal function (mild/moderate impairment) is needed.*

4.2.3 Exposure-ORR Analysis:

Exposure-response relationships were assessed for efficacy endpoint, ORR, based on Study GO29293. Multiple exposure metrics were employed in this analysis (**Table 7**). Proportion of responders (ORR) was explored by logistic regression. The exposure-response for atezolizumab (proportion of responders by quartiles of AUCss) is shown in **Figure 7**. The proportion of responders (complete response (CR) + partial response (PR)) in the analysis population was 15.4% (47 responders over 306 patients with exposure data in Study GO29293, Cohort 2). In addition, the probability of response did not depend on atezolizumab exposure with any other exposure metrics considered (**Table 7)**.

Figure 7: Summary of Steady-State Average Concentrations ($C_{avg,ss}$) for Patients with and without Any Grade 3+ Adverse Events for 1200 mg Q3W in Phase III Study CA209037



AUCss=AUC at steady-state; CR=complete response; PR=partial response; N=number of patients; p=p value of Wald test in logistic regression of proportion of responders vs. exposure). The grey solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the proportion of responders in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The crosses are the patient response events (0: No, 1: Yes). The triangle and two-headed arrow represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 1200 mg atezolizumab, respectively.

Source: Sponsor's Exposure-Response Analysis Report, Figure A

Table 7: Summary of Logistic Regression Results for the Probability of Response vs. Exposure

Exposure Metrics (unit)	N	p	Sign
AUC cycle 1 (µg.day/mL)	306	0.5167	-
Cmax cycle 1 (µg/mL)	306	0.08112	-
Cmin cycle 1 (µg/mL)	306	0.6784	+
AUCss (µg.day/mL)	306	0.133	+

N=number of patients; p value of exposure metrics parameter estimate using Wald test; Sign=Sign of exposure metrics parameter estimate in logistic regression, negative sign: probability of response tends to decrease with exposure, positive sign=response probability of response tends to increase with exposure.

Source: Sponsor's Exposure-Response Report, Table 4-3

Reviewer's comment: Sponsor's ER analysis seems reasonable. This analysis is based on the univariate analysis, which may be confounded by factors associating with both atezolizumab exposure and ORR. Multi-variant analysis would address this issue (at least partially). Based on FDA reviewer conducted multivariate analysis, there is no significant ER relationship for ORR was identified. Refer to Section 4 for details.

4.2.4 Exposure-Safety Analysis:

The atezolizumab exposure-safety analysis was performed on all treated mUC patients in the Phase 1a Study PCD4989g and in the Phase 2 Study GO29293 (Cohort 1 and Cohort 2). Data set

comprised a total of 513 patients with exposure data (out of 521 included in the two studies, 98.5%), those patients received atezolizumab 15 mg/kg q3w (N = 85), or 1200 mg q3w (N = 428). Three main adverse events were investigated: Grade ½ AE, Grade 3+ AEs and AESI. The analysis of the incidence of Grade ½ or Grade 3+ AEs, as well as AESIs, did not show any statistically significant exposure-response relationship with any of the exposure metrics. A statistically insignificant trend of increase in incidence with AUCss was observed. (**Table 8**, **Table 9**, **Table 10**).

Table 8: Summary of Logistic Regression Results for the Incidence of Grade ½ AEs vs. Exposure

Exposure Metrics (unit)	N	p value	Sign
AUC cycle 1 (µg.day/mL)	513	0.6559	+
Cmax cycle 1 (µg/mL)	513	0.6966	-
Cmin cycle 1 (µg/mL)	513	0.6384	-
AUCss (µg.day/mL)	513	0.3649	+

N=number of patients; p value of exposure metrics parameter estimate, Wald test Sign=Sign of exposure metrics parameter estimate in logistic regression, negative sign=probability of response tends to decrease with exposure, positive sign=response probability of response tends to increase with exposure.

Source: Sponsor's Response to IR dated 16 February 2016, Table 1

Table 9: Summary of Logistic Regression Results for the Incidence of Grade 3+ AEs vs. Exposure

Exposure Metrics (unit)	N	p value	Sign
AUC cycle 1 (µg.day/mL)	513	0.8837	-
Cmax cycle 1 (µg/mL)	513	0.9528	+
Cmin cycle 1 (µg/mL)	513	0.8413	-
AUCss (µg.day/mL)	513	0.8946	-

N=number of patients; p value of exposure metrics parameter estimate, Wald test Sign=Sign of exposure metrics parameter estimate in logistic regression, negative sign=probability of response tends to decrease with exposure, positive sign=response probability of response tends to increase with exposure.

Source: Sponsor's Exposure-Response Report, Table 4-6

Table 10: Summary of Logistic Regression Results for the Incidence of AESIs vs. Exposure

Exposure Metrics (unit)	N	p value	Sign
AUC cycle 1 (µg.day/mL)	513	0.4639	+
Cmax cycle 1 (µg/mL)	513	0.7811	-
Cmin cycle 1 (µg/mL)	513	0.4958	+
AUCss (µg.day/mL)	513	0.07906	+

N=number of patients; p value of exposure metrics parameter estimate, Wald test; Sign=Sign of exposure metrics parameter estimate in logistic regression, negative sign=probability of response tends to decrease with exposure, positive sign=response probability of response tends to increase with exposure

Source: Sponsor's Exposure-Response Report, Table 4-7

Table 11: Logistic Regression Model Parameter Estimates for Incidence of Adverse Events of Special Interest vs. AUCss

Parameter	Estimate	SE	z	p
(Intercept)	-2.262	0.3936	-5.746	<0.0001
θ_{AUCss}	0.000115	0.00006551	1.756	0.0791

Source: Table 4-8 of Sponsor's Exposure-Response Analysis Report

Based on the exposure-safety analysis, the extreme values of AUCss (10^{th} to 90^{th} percentile) were simulated, and the results showed a mild impact of atezolizumab on incidence of AESI. But the 95% prediction interval of the odds ratio vs. expected incidence at median AUCss would always include 1 in this range (**Table 12)**.

Table 12: Simulation of Expected Incidence of AESI vs. AUCss							
	AUCss (µg.day/mL)	**Expected Incidence**	**95% PI**		**Odds Ratio vs. Median**	**95% PI**	
Median	5377	0.16	0.13	0.2			
10th percentile	3388	0.13	0.09	0.18	0.8	0.62	1.03
25th percentile	4262	0.15	0.11	0.19	0.88	0.76	1.02
75th percentile	6519	0.18	0.15	0.22	1.14	0.98	1.32
90th percentile	7947	0.21	0.15	0.27	1.34	0.96	1.86
Source: Table 4-9 of Sponsor's Exposure-Response Analysis Report							

Reviewer's comment: Sponsor's exposure-safety analysis seems reasonable. No evident exposure-safety relationship was identified for grade ½, grade 3+ AEs and AESIs.

4.2.5 Conclusion

4.2.5.1 PPK Analysis

- The PK of atezolizumab is linear.
- Statistically-significant covariates were identified for CL, V1, and V2; however none of these covariate effects resulted in more than 27% change from typical values of CL, V1, and V2 when evaluated at the extreme values (i.e. 10th and 90th percentiles) of their distributions.
- Body weight was identified as a statistically significant covariate on both CL and V1. For a typical patient (male), there would be up to a 32%, 28% and 40% change in AUC,ss, Cmax,ss or Cmin,ss, respectively when evaluated at extreme values of weight compared to the typical patient.
- Positive ATAG was identified as statistically significant covariate on CL, however positive ATAG did not result in more than a 19% change in AUC,ss, Cmax,ss or Cmin,ss from the typical patient.
- Age, race, albumin, tumor burden, mild renal/hepatic impairment, formulation and PD-L1 expression did not have clinically relevant effects on atezolizumab CL.
- Patients with mUC did not show any trend of having different PK parameters than patients with other tumor types.

4.2.5.2 Exposure-ORR Analysis

- No statistically significant ER relationships were identified with ORR following Atezolizumab 1200 mg q3w in Study GO29293, Cohort 2. None of the fold-changes in atezolizumab exposure associated with the statistically-significant covariates identified

with the popPK model would be expected to be clinically meaningful or require dose adjustment.

- The fold-reduction in atezolizumab exposure when evaluated at extreme values (i.e., 90th percentile) of weight compared to the typical patient following administration of the atezolizumab 1200 mg q3w flat dose would not be expected to be clinically meaningful or require dose adjustment by body size.
- These results suggest no improved efficacy would be expected with atezolizumab doses higher than 1200 mg q3w.

4.2.5.3 Exposure-Safety Analysis

- No statistically significant exposure-safety relationships were identified with AEG35 or AESI following atezolizumab 15 mg/kg and 1200 mg q3w in mUC patients in the Phase 1a Study PCD4989g and in the Phase 2 Study GO29293 (Cohort 1 and Cohort 2).
- None of the fold-changes in atezolizumab exposure associated with the statistically significant covariates identified with the Phase 1 model would be expected to be clinically meaningful or require dose adjustment.
- The fold-elevation in atezolizumab exposure when evaluated at extreme values (i.e., 10th percentile) of weight compared to the typical patient following administration of the atezolizumab 1200 mg q3w flat dose would not be expected to be clinically meaningful or require dose adjustment by body size.
- These results suggest no improved safety would be expected with atezolizumab doses lower than 1200 mg q3w.

4.3 REVIEWER'S ANALYSIS

4.3.1 Objective

The analysis objectives are

- To explore exposure-response relationship for confirmed ORR (IRR) and PFS for mUC patients in Study IMvigor 210 (Cohort 2).
- To explore exposure-response relationship for confirmed ORR (IRR) in subpopulations group by IC PDL1 score.

4.3.2 Methods and Results

4.3.2.1 Data Sets

Data sets used are summarized in **Table 13**.

Table 13: Analysis Datasets for FDA Reviewer's Analysis

Study Number	Name	Link to EDR
PCD4989g	expo1.xpt	\\cdsesub1\evsprod\bla761034\0002\m5\datasets\1067242\analysis\legacy\datasets\ expo1.xpt
GO29293	expo2.xpt	\\cdsesub1\evsprod\bla761034\0002\m5\datasets\1067242\analysis\legacy\datasets\ expo2.xpt
GO29293	er.xpt	\\cdsesub1\evsprod\bla761034\0002\m5\datasets\go29293-imvigor210\analysis\legacy\datasets\er.xpt

4.3.2.2 Software

R was used for the reviewer's analysis.

4.3.2.3 Exposure-Response Relationship for ORR and PFS

The mUC patients (n=306) from IMvigor 210 were included in the exposure-efficacy analysis. For ORR, univariate analysis was performed using logistic model and showed that there is no relationship between ORR and trough concentration of atezolizumab in the first cycle (C_{min1}) (**Figure** 8). Multivariate analysis was performed to adjust for other covariates. No correlation was identified between ORR and atezolizumab C_{min1} (**Table 14**). Progression-free survival (PFS) was stratified by Cmin1quantiles. There was no ER relationship identified between the C_{min1} and the PFS.

Table 14: Multivariate Logistic Regression Model Parameter Estimates for ORR vs. Cmin1

Parameter	Estimate	SE	P-value
(Intercept)	-1.568	0.8474	0.0642
θ_{Cmin1}	-0.002	0.0090	0.8305
θ_{ECOG}	-0.972	0.3363	0.0038
θ_{IC}	0.737	0.2189	0.0008
$\theta_{Met.sites}$	-0.315	0.1554	0.0424

Source: FDA reviewer's analysis

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