CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761041Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA	761041
Submission Date	February 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	117296
Applicant	Genentech, Inc.
OCP Reviewer	Wentao Fu, Ph.D.
Pharmacometrics Reviewer	Chao Liu, Ph.D.
Genomics Reviewer	Sarah Dorff, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
Pharmacometrics Team Leader	Jingyu (Jerry)Yu, Ph.D.
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	Non-small cell lung cancer

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1. EXECUTIVE SUMMARY

Atezolizumab (Tecentriq®) is a humanized, IgG1 monoclonal antibody targeting the programmed death-ligand 1 (PD-L1). The locally advanced or metastatic urothelial carcinoma indication was approved under accelerated approval on May 18, 2016 based on confirmed overall objective response rates (ORRs). The applicant seeks the approval of atezolizumab for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. The clinical data in support of this proposed indication is from a Phase 2 open-label, randomized (1:1) trial GO28753 (POPLAR) and a Phase 3 open label, randomized (1:1) trial GO28915 (OAK) primary efficacy analysis in patients with locally advanced or metastatic NSCLC.

OAK demonstrated a median overall survival (OS) 13.8 (95% CI: 11.8, 15.7) months for atezolizumab arm comparing to a median OS of 9.6 (95% CI: 8.6, 11.2) months for docetaxel arm for the first 850 patients. OS hazard ratio (HR) in the all comer population was 0.74 (95% CI: 0.63, 0.87); P = 0.0004. POPLAR demonstrated a median OS of 12.6 (95% CI: 9.7, 16.4) months for atezolizumab arm comparing to a median OS of 9.7 (95% CI: 8.6, 12.0) months for docetaxel arm for all patients. OS hazard ratio (HR) in the all comer population was 0.69 (95% CI: 0.52, 0.92); P < 0.011. The most common adverse reactions in the Phase 2 trial were fatigue, decreased appetite, dyspnea, cough, nausea, and constipation.

The submission contains updated information for the incidence of anti-drug antibody (ATA). The presence of ATAs did not have a clinically significant impact on pharmacokinetics, safety or efficacy. The applicant's final population pharmacokinetic (PK) model is not considered appropriate by the Pharmacometric review team as atezolizumab showed time-dependent PK. The PK labeling (Section 12.3) is updated based on the results of the improved population PK model.

Data regarding outcomes based on PD-L1 expression status in OAK were received on 22 September 2016. The results of POPLAR and OAK show a trend toward increased OS in patients with higher PD-L1 IHC scores, suggesting that a complementary diagnostic based on PD-L1 expression may be appropriate. However, OAK PD-L1 subgroup assignments were inconsistent between re-reads of the same assay, potentially leading to unreliable results. As such, whether these data are robust enough to support a complementary diagnostic claim and how such findings would be communicated in labeling is being evaluated by the review team.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology recommends approval of the BLA761041 from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

1.2 POST-MARKETING REQUIREMENTS

None.

Wentao Fu, Ph.D. Clinical Pharmacology Reviewer	Qi Liu, Ph.D. Clinical Pharmacology Team Leader
Chao Liu, Ph.D. Pharmacometrics Reviewer	Jingyu (Jerry) Yu, Ph.D. Pharmacometrics Team Leader

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DCP-5: DDD - Brian Booth; DD – Nam Atiqur Rahman

APPEARS THIS WAY ON ORIGINAL

2 CLINICAL PHARMACOLOGY REVIEW

(Reviewer's Note: this section includes updates on results of immunogenicity,exposure-response, and biomarker analyses. Please refer to the original review for other information.)

2.1 INTRODUCTION

Atezolizumab (Tecentriq®) is a human programmed death ligand 1 (PD-L1) blocking antibody. The locally advanced or metastatic urothelial carcinoma indication was approved under accelerated approval on May 18, 2016 based on confirmed overall objective response rates (ORRs).

In the current submission, the applicant is seeking the accelerated approval of atezolizumab for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. The proposed dose of atezolizumab is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks. Clinical data in support of this request is based on a Phase 3 study OAK (GO28915), a Phase 2 study POPLAR (GO28753), two supporting Phase 2 studies (BIRCH (GO28754) and FIR (GO28625)), and two supporting Phase 1 studies (PCD4989g and JO28944). In addition to the PK data from these 5 studies, PK data from Phase 2 study IMVigor 210 (GO29293) for patients with locally advanced or metastatic urothelial carcinoma is included in Pharmacometric review team's popPK model.

In study OAK, patients were randomized (1:1) to receive either atezolizumab or docetaxel. Only a primary efficacy analysis of the first 850 patients out of total 1225 patients in OAK is included in this submission. OAK demonstrated a median overall survival (OS) 13.8 (95% CI: 11.8, 15.7) months for atezolizumab arm comparing to a median OS of 9.6 (95% CI: 8.6, 11.2) months for docetaxel arm for the first 850 patients. OS hazard ratio (HR) in the all comer population was 0.74 (95% CI: 0.63, 0.87); P = 0.0004.

In study POPLAR, patients were randomized (1:1) to receive either atezolizumab or docetaxel. POPLAR demonstrated a median OS of 12.6 (95% CI: 9.7, 16.4) months for atezolizumab arm comparing to a median OS of 9.7 (95% CI: 8.6, 12.0) months for docetaxel arm for all patients. OS hazard ratio HR in the all comer population was 0.69 (95% CI: 0.52, 0.92); P < 0.011.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What is clinical pharmacology study design?

Four new studies (OAK, POPLAR, BIRCH and FIR) with patients with locally advanced or metastatic NSCLC administered atezolizumab intravenously at 1200 mg once every 3 weeks were included in this submission. In addition, this submission also included two Phase 1 studies (PCD4989g and JO28944), which were in the submission for urothelial carcinoma indication.

Tumor specimens in OAK and POPLAR could have been collected from any previous biopsy and were centrally tested for PD-L1 expression using the VENTANA PD-L1 (SP142) IHC assay. Four categories of expression on tumor-infiltrating immune cells (IC) were determined during screening and used to stratify patients at randomization (IC0, IC1, IC2, IC3) in both studies. Outcomes were evaluated in the overall population and by PD-L1 expression in PD-L1 selected subgroups.

2.2.1.1 POPLAR

POPLAR is a Phase 2, multicenter, randomized, open-label, controlled study in patients (N=287) with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. Patients were stratified by PD-L1 expression status, by the number of prior chemotherapy

regimens, and by histology (non-squamous versus squamous), and then randomized (1:1) to receive either atezolizumab administered intravenously at 1200 mg once every 3 weeks (atezolizumab arm, N = 144) or docetaxel administered intravenously at 75 mg/m^2 once every 3 weeks (docetaxel arm, N=143). The primary endpoint is overall survival (OS). Pharmacokinetics (PK) and Immunogenicity Assessment: Sparse PK blood samples and anti-drug antibody (ADA) samples were collected as shown in Table 1.

Table 1. PK and ADA Sampling Schedules in POPLAR

Study Visit	Time	Sample	
		Patients Randomized to Docetaxel	Patients Randomized to MPDL3280A
Screening	At visit	TBNK	TBNK
Cycle 1, Day 1	Predose	TBNK Pharmacodynamics [a]	ATA MPDL3280A pharmacokinetics TBNK Pharmacodynamics [a]
	30 min (±10 min) after end of MPDL3280A infusion		MPDL3280A pharmacokinetics
Cycles 2, 3, and 4, Day 1	Predose	TBNK Pharmacodynamics [a]	ATA MPDL3280A pharmacokinetics TBNK Pharmacodynamics [a]
Cycles 8,16, and every eight cycles thereafter, Day 1	Predose		ATA MPDL3280A pharmacokinetics
At time of fresh biopsy (pre- and on-treatment or at progression)		TBNK Pharmacodynamics [a]	TBNK Pharmacodynamics [a]
Treatment discontinuation visit	At visit	TBNK Pharmacodynamics [a]	ATA MPDL3280A pharmacokinetics TBNK Pharmacodynamics [a]
120 days (±30 days) after last dose of MPDL3280A	At visit		ATA MPDL3280A pharmacokinetics

ATA = anti-therapeutic antibody; TBNK = T, B, and NK cells.
[a] Plasma, serum, and whole blood for pharmacodynamic biomarkers.

Source: Appendix 2 of Protocol GO28753 (Report Number 1065672)

In POPLAR, four PD-L1 TC expression categories (TC0, TC1, TC2, TC3) were derived from the raw percentage staining scores determined at enrollment and subsequently used in the applicant's subgroup analyses along with the IC scores determined at screening.

2.2.1.2 BIRCH

BIRCH is a Phase 2, multicenter, single arm study with primary endpoint of IRF-assessed ORR (per RECISTv1.1) for PD-L1 selected patients (N=659) with locally advanced or metastatic NSCLC who had progressed on prior therapy.

PK serum sampling time points:

First 40 patients enrolled: Cycle 1 Day 1, Predose; Cycle 1 Day 1 30 min after end of infusion; Cycle 1 Day2, Day4, Day8 and Day15; Day 1 on Cycles 2, 3, 4, 8 and 16, Predose; Every 8th Cycle after Cycle 16, Predose; Treatment discontinuation visit; 120 days (± 30 days) after last

dose.

All other patients except first 40: Cycle 1 Day 1, Predose; Cycle 1 Day 1 30 min after end of infusion; Day 1 on Cycles 2, 3, 4, 8 and 16, Predose; Day 1 Every 8th Cycle after Cycle 16, Predose; Treatment discontinuation visit; 120 days (± 30 days) after last dose.

ADA serum sampling time points:

All patients: Cycle 1 Day 1, Predose; Day 1 on Cycles 2, 3, 4, 8 and 16, Predose; Day 1 Every 8th Cycle after Cycle 16, Predose; Treatment discontinuation visit; 120 days (± 30 days) after last dose.

2.2.1.3 FIR

FIR is a Phase 2, multicenter, single-arm trial designed to evaluate the efficacy and safety of atezolizumab in PD-L1− selected patients (N=137) with locally advanced or metastatic NSCLC. The primary efficacy endpoint was investigator-assessed ORR (per RECISTv1.1).

PK serum sampling time points: Cycle 1 Day 1, Predose; Cycle 1 Day 1 30 min after end of infusion; Day 1 on Cycles 2, 3, 4 and 8, Predose; Treatment discontinuation visit; Post treatment discontinuation visit (> 90 days after last dose of treatment).

ADA serum sampling time points: Cycle 1 Day 1, Predose; Day 1 on Cycles 2, 3, 4 and 8, Predose; Day 1 every 8 Cycles after 8, Predose; Treatment discontinuation visit; Post treatment discontinuation visit (> 90 days after last dose of treatment).

2.2.1.4 OAK

OAK (Study GO28915) is a phase 3 study in 1225 patients randomized 1:1 to receive either atezolizumab or docetaxel, with the primary analysis population consisting of the first 850 patients (425 patients per arm).

In OAK, tumor cell (TC) raw percentages of PD-L1 expression were determined at enrollment, but combined scores for TC and IC subgroup assignment were determined based on re-reads of the TC and IC expression levels by a second central laboratory.

2.2.2 What are the update on clinical pharmacology study results

Immunogenicity: The percentages of evaluable patients tested positive ATA were 54.1% (73/135), 38.5% (240/624), 51.2% (66/129) in studies POPLAR (Atezolizumab arm), BIRCH, FIR, respectively. In comparison, 41.9% (161/384) of evaluable patients tested positive ATA from Phase 2 registration trail (IMvigor 210) for urothelial carcinoma indication. No apparently altering or clinically meaningful difference in PK, safety and efficacy profiles were observed with the ATA presence.

PK: Based on a population analysis that included 1821 patients (from studies PCD4989g, JO28944, POPLAR, BIRCH, FIR and IMVigor 210) in the dose range, atezolizumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 17.1% (40.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 0.20 L/day (39.6%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 5.6 L (20.7%), and geometric mean of the terminal half-life (t1/2) at steady state was 23 days (22.8%). Please see details in the Pharmacometrics review in Section 4.

Genetics: The results of POPLAR and OAK show a trend toward increased OS in patients with higher PD-L1 IHC scores, suggesting that a complementary diagnostic based on PD-L1 expression may be appropriate. There was poor agreement between TC and IC expression levels. For example, a tumor sample categorized as IC3 could also be categorized as TC0, reflecting potential biological differences and/or methodological differences in the way these scores were determined. Also, based on the Applicant's response to FDA's information request dated 20 Sept 2016, PD-L1 expression in OAK was determined at screening by (b) (4) for stratification of randomization by IC score, and then PD-L1 subgroups used in the analyses were determined based on multiple re-reads of PD-L1 expression and scoring of IC and TC by a second laboratory, (b) (4). OAK PD-L1 subgroup assignments were inconsistent between re-reads, potentially leading to unreliable results. As such, whether these data are robust enough to support a complementary diagnostic claim and how such findings would be communicated in labeling is being evaluated by the review team. Please refer to the CDRH review (by Dr. Shyam Kalavar) and section 2.2.4 for additional details.

2.2.3 Does the exposure-response analysis for efficacy and safety support the proposed dose?

Population PK analysis by FDA reviewer demonstrated a time-varying PK profile which appeared to be associated with the post-treatment tumor response/progression. The results from exposure-response analysis for efficacy (OS) were not conclusive. Incidence of AESI increases mildly with greater atezolizumab exposure.

Please see details in the Pharmacometrics review in Section 4.

2.2.4 Does PD-L1 expression status influence atezolizumab treatment outcomes?

The majority of patients in OAK were white (70%), male (61%), had non-squamous histology (74%), and were current or previous smokers (82%). Tumor EGFR status (if unknown) was assessed by a central laboratory prior to enrollment in OAK, and known KRAS and ALK status was collected at screening if available. Approximately 10%, 7%, and 0.2 % were positive for EGFR, KRAS, and ALK alterations, respectively, although many patients had unknown status (defined as patients whose test results were not done, not evaluable, invalid or missing; 16%, 69%, and 50% for EGFR, KRAS, and ALK, respectively). The majority of patients in POPLAR were white (79%), male (59%), had non-squamous histology (66%), and were current or previous smokers (81%). Tumor EGFR, KRAS, and ALK status was not assessed as part of POPLAR, but known status was collected at screening if available. Approximately 7%, 9%, and 1% were positive for EGFR, KRAS, and ALK alterations, respectively, although most patients had unknown status (43%, 75%, and 59% for EGFR, KRAS, and ALK, respectively).

The distribution of TC and IC scores for both studies are shown in Table 2. For the combined "IC or TC" subgroups, patients were categorized according to their highest IC or TC score, regardless of the value of the other score. Overall, the percentage of patients whose tumors expressed the highest levels of PD-L1 expression (having either a IC3 or TC3) was similar in both OAK and POPLAR (16% in both studies), although OAK had a higher percentage of patients with tumors expressing the lowest levels of PD-L1 (having both TC0 and IC0) compared to POPLAR (45% and 32% for OAK and POPLAR, respectively).

Table 2. Baseline PD-L1 Expression Status in ITT Populations from (A) OAK and (B) POPLAR

(A) OAK

PD-L1 Status		Docetaxel n = 425	Atezolizumab n = 425	All Patients n = 850
IC Level (Screening)	0	157 (36.9%)	156 (36.7%)	313 (36.8%)
	1	171 (40.2%)	171 (40.2%)	342 (40.2%)
	2	51 (12.0%)	51 (12.0%)	102 (12.0%)
	3	46 (10.8%)	47 (11.1%)	93 (10.9%)
IC3 or TC3 (Re-read #3*)	TC3 or IC3	65 (15 3%)	72 (16.9%)	137 (16.1%)
	TC0/1/2 and IC0/1/2	356 (83.8%)	348 (81.9%)	704 (82.8%)
	Unknown	4 (0.9%)	5 (1.2%)	9 (1.1%)
IC2/3 or TC2/3 (Re-read #2*)	TC2/3 or IC2/3	136 (32.0%)	129 (30.4%)	265 (31.2%)
	TC0/1 and IC0/1	284 (66.8%)	290 (68.2%)	574 (67.5%)
	Unknown	5 (1.2%)	6 (1.4%)	11 (1.3%)
IC1/2/3 or TC1/2/3 (Re-read #1*)	TC1/2/3 or IC1/2/3	222 (52.2%)	241 (56.7%)	463 (54.5%)
	TC0 and IC0	199 (46.8%)	180 (42.4%)	379 (44.6%)
	Unknown	4 (0.9%)	4 (0.9%)	8 (0.9%)
IC/TC Level- Mutually Exclusive Subgroups	TC3 or IC3	65 (15.3%)	72 (16.9%)	137 (16.1%)
	TC2/3 or IC2/3 exclude TC3 or IC3	70 (16 5%)	59 (13.9%)	128 (15.2%)
	TC-IC1/2/3 exclude TC2/3 or IC2/3	87 (20 5%)	111 (26.1%)	198 (23.3%)
	TC0 and IC0	199 (46.8%)	180 (42.4%)	379 (44.6%)
	Unknown	4 (0.9%)	3 (0.7%)	8 (0.8%)

(B) POPLAR

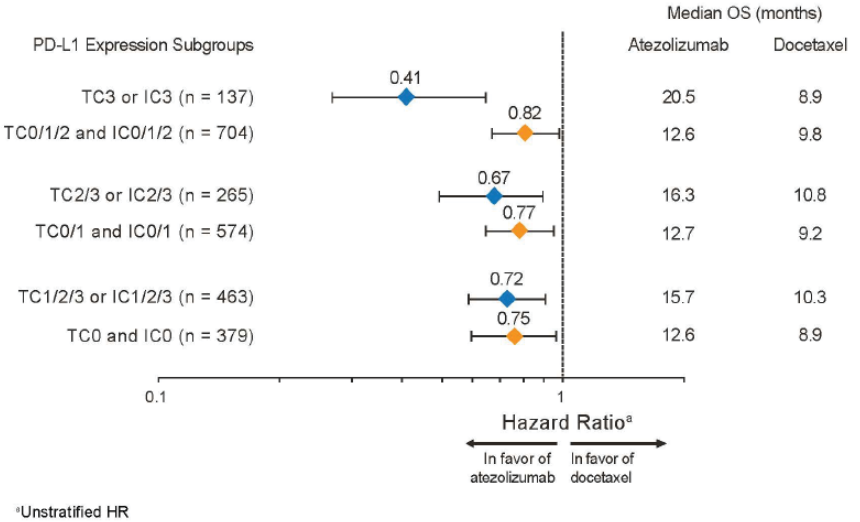
PD-L1 Status	Docetaxel	Atezolizumab	All patients
All Patients	**n=143**	**n=144**	**n=287**
IC Levels			
0	63 (44.1%)	62 (43.1%)	125 (43.6%)
1	54 (37.8%)	53 (36.8%)	107 (37.3%)
2	18 (12.6%)	19 (13.2%)	37 (12.9%)
3	8 (5.6%)	10 (6.9%)	18 (6.3%)
TC Levels			
0	82 (57.3%)	96 (66.7%)	178 (62.0%)
1	21 (14.7%)	19 (13.2%)	40 (13.9%)
2	25 (17.5%)	14 (9.7%)	39 (13.6%)
3	15 (10.5%)	15 (10.4%)	30 (10.5%)
IC3 or TC3			
TC3 or IC3	23 (16.1%)	24 (16.7%)	47 (16.4%)
TC0/1/2 and IC0/1/2	120 (83.9%)	120 (83.3%)	240 (83.6%)
IC2/3 or TC2/3			
TC2/3 or IC2/3	55 (38.5%)	50 (34.7%)	105 (36.6%)
TC0/1 and IC0/1	88 (61.5%)	94 (65.3%)	182 (63.4%)
IC1/2/3 or TC1/2/3			
TC1/2/3 or IC1/2/3	102 (71.3%)	93 (64.6%)	195 (67.9%)
TC0 and IC0	41 (28.7%)	51 (35.4%)	92 (32.1%)
IC/TC Level Mutually Exclusive Subgroups			
TC3 or IC3	23 (16.1%)	24 (16.7%)	47 (16.4%)
TC2/3 or IC2/3 exclude TC3 or IC3	32 (22.4%)	26 (18.1%)	58 (20.2%)
TC-IC1/2/3 exclude TC2/3 or IC2/3	47 (32.9%)	43 (29.9%)	90 (31.4%)
TC0 and IC0	41 (28.7%)	51 (35.4%)	92 (32.1%)

Sources: OAK: Data from Applicant's Appendix 1, Supplemental Results Report for Study GO28915; POPLAR: Applicant's table 20, CSR for Study GO28753. IC: Tumor–Infiltrating Immune Cells, defined as PD-L1 staining of any intensity in ICs covering the indicated percentage of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma; TC: Tumor Cells, defined as PD-L1 staining of any intensity in the indicated percentage of tumor cells; IHC scoring criteria: IC3 = IC ≥10% , IC2 = IC ≥5% and <10%, IC1 = IC ≥1% and <5%, IC0 = IC <1%, TC3 = TC ≥50%, TC2 = TC ≥5% and <50%, TC1 = TC ≥1% and <5%, TC0 = TC<1%.
*In OAK, three sets of re-reads for PD-L1 subgroups of interest (Re-read #1, Re-read #2, and Re-read #3) were performed at separate timepoints by (b) (4), and mutually exclusive TC/IC subgroups were determined per Re-read #1, Re-read #2, and Re-read #3.

Improved OS with atezolizumab treatment was observed across most PD-L1 expression subgroups. In OAK, all PD-L1 subgroups showed an increase in OS in patients receiving atezolizumab (Figure 1A). In POPLAR, subgroups including patients with at least one score at or above the TC1 or IC1 PD-L1 expression level showed OS benefit (Figure 1B). Data from POPLAR's primary analysis (data cutoff of 30 January 2015) suggested that OS in the IC0 and TC0 subgroup was similar to that observed in the docetaxel arm (Figure 1B), and while updated exploratory analyses in POPLAR (data cutoff of 1 December 2015) showed a numerical improvement in OS in this subgroup (HR 0.88 [95% CI: 0.55, 1.42]), median OS remained similar to that observed in patients receiving docetaxel (9.7 months in both arms). Exploratory analyses of mutually exclusive PD-L1 subgroups generally supported a contribution of higher IHC scores to OS improvement with atezolizumab (Figure **2**)

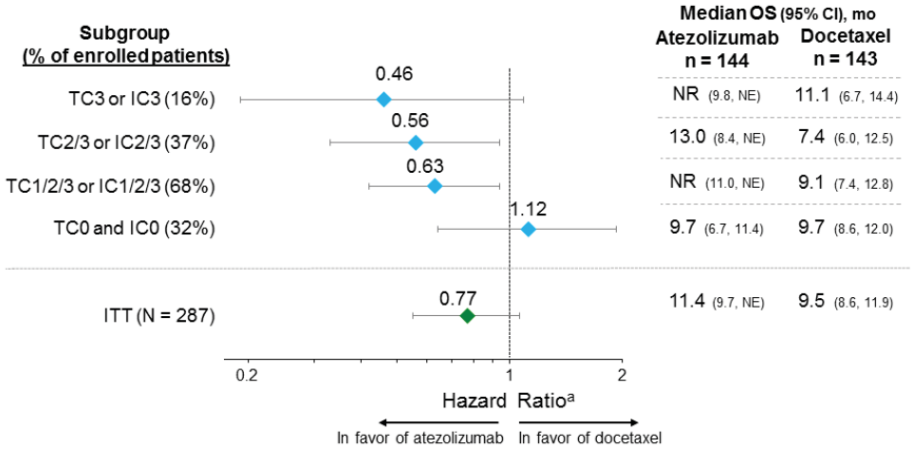
Figure 1. OS by PD‑L1 Mutually Exclusive Subgroups in (A) OAK and (B) POPLAR

(A) OAK



[a]Unstratified HR

(B) POPLAR

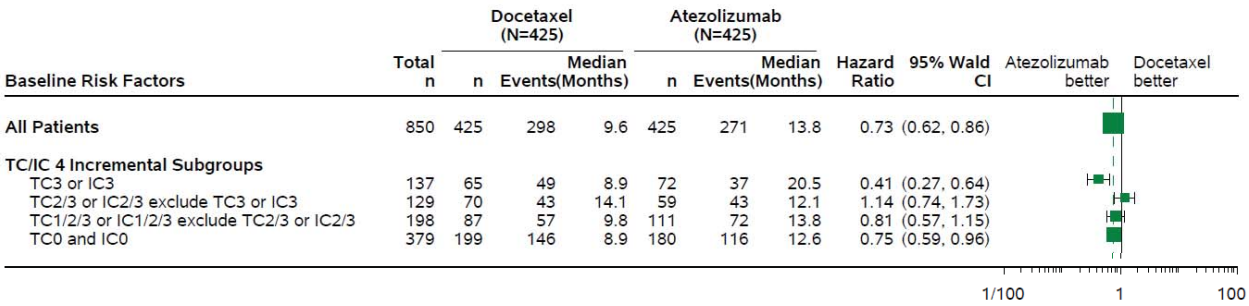


[a]Unstratified HR for subgroups and stratified HR for ITT.

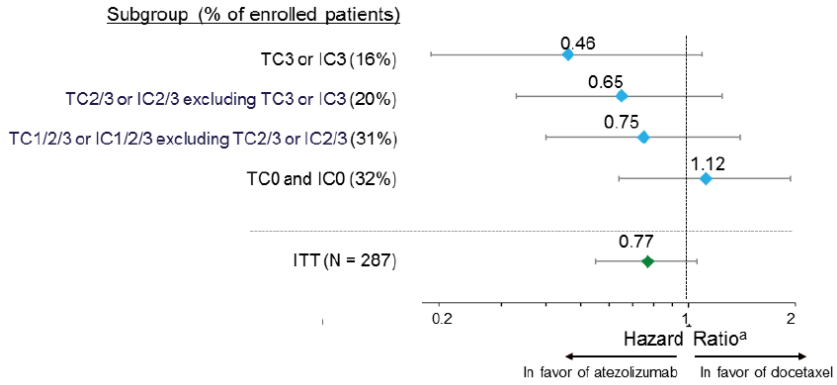
Sources: OAK Figure 3 of Supplemental Results Report for Study GO28915; POPLAR Figure 19 of CSR for Study GO28753 (primary analysis, cutoff date 30 January 2015). IC = tumor-infiltrating immune cell; ITT = intent to treat; NE = not estimable; OS = overall survival; PD-L1 = programmed death−ligand 1; TC = tumor cell.

Figure 2. OS by PD‑L1 Mutually Exclusive Subgroups in (A) OAK and (B) POPLAR

(A) OAK



(B) POPLAR



[a]Unstratified HR for subgroups and stratified HR for ITT.

Sources: OAK Forest Plot modified from Applicant's Appendix 1, Supplemental Results Report for Study GO28915; POPLAR Figure 24 of CSR for Study GO28753 (cutoff date 30 January 2015). IC = tumor-infiltrating immune cell; ITT = intent to treat; NE = not estimable; OS = overall survival; PD-L1 = programmed death−ligand 1; TC = tumor cell.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections with updates in black by the applicant 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 immunogenicity. Among 275 patients in 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. Among 135 patients in Study 3, 73 patients (54.1%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In Study 1 and Study 3, the presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.	As with all therapeutic proteins, there is a potential for immunogenicity. Among 275 patients in 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. Among 135 patients in Study 3, 73 patients (54.1%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. In Study 1 and Study 3, the presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.
8.5 GERIATRIC USE	
Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. Of the 142 patients with NSCLC	Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. Of the 142 patients with NSCLC

treated with TECENTRIQ in Study 3, 39% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.	treated with TECENTRIQ in Study 3, 39% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.
12.3 PHARMACOKINETICS	
Patients' exposures 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 population analysis that included 472 patients in the dose range, the typical population clearance was 0.20 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:* 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* The drug interaction potential of atezolizumab is unknown.	Patients' exposures 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 population analysis that included 472 patients in the dose range, the typical population clearance was 0.20 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. <u>In a posthoc analysis, atezolizumab clearance was found to decrease over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 17.1% (40.6%). However, the decrease in CL was not considered clinically relevant.</u> Specific Populations: 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 m2), 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* The drug interaction potential of atezolizumab is unknown.

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

BLA Number	761041
Drug Name	TECENTRIQ® (atezolizumab)
Dose Regimen	Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks
Indication	Locally advanced or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy
Pharmacometrics Reviewer	Chao Liu, Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
Applicant	Genentech, Inc.

Table of Contents

1. SUMMARY OF FINDINGS

The proposed dose of 1200 mg Q3W for atezolizumab is acceptable for the proposed indication. The apparent exposure-response relationship for efficacy could be confounded by the post-treatment effects. Meanwhile, there appears to be a positive exposure-safety relationship for AESI following 1200 mg Q3W dosing regimen based on the clinical safety data for NSCLC patients.

1.1.KEY REVIEW QUESTIONS

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

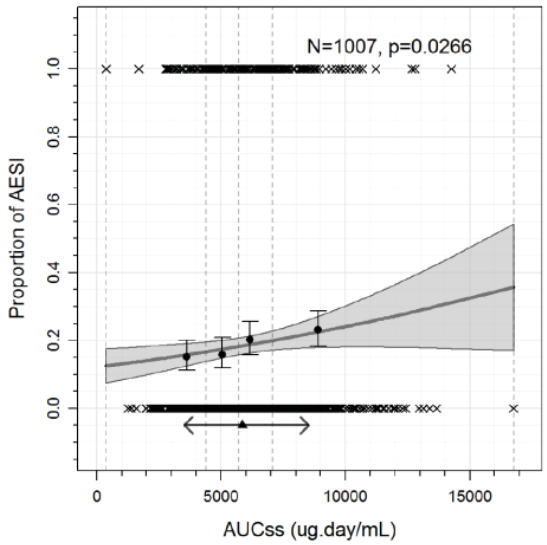
1.1.1. What are the characteristics of exposure-efficacy relationship following 1200 mg Q3W treatment for the proposed indication?

The exposure-efficacy relationship for overall survival is unknown at 1200 mg for NSCLC patients. According to FDA reviewer's analysis, atezolizumab PK appears to be associated with the post-treatment disease status: atezolizumab clearance decreases with the improvement of the disease status. Thus, the atezolizumab exposure carries the efficacy information after treatment, which leads to a biased estimation of exposure-efficacy relationship.

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

In NSCLC patients, a positive exposure-safety relationship was identified for AESI following the atezolizumab 1200 mg Q3W dosing regimen. **Figure 2** shows there is a trend of greater incidence of AESIs with increasing atezolimumab exposure. The parameter estimates of the logistic regression model for AUCss-AESI relationship are shown in **Table 3**.

Figure 3: Incidence of AESIs vs. Atezolizumab AUCss in Patients with NSCLC



Source: Applicant's Exposure-Response Analysis Report 1067243, Figure 4-3

Table 3: Logistic Regression Model Parameter Estimates for Incidence of AESI vs. AUCss

Parameter	Estimate	SE	z	p
(Intercept)	-1.976	0.2426	-8.144	3.821e-16
θ_{AUCss} (1/(µg.day/mL))	8.28e-05	3.734e-05	2.218	0.02659

SE=standard error, z=Wald test statistics, p Wald test (χ^2); θ_{AUCss}= regression parameter for AUCss effect

Source: Applicant's Exposure-Response Analysis Report 1067243, Table 4-10

1.1.3. What are the new findings based on population PK analysis?

Population PK analysis suggested atezolizumab clearance (CL) decreased over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 17.1% (40.6%). Population PK model with sigmoid Emax function on time-varying atezolizumab clearance (CL) was established with patients with solid tumors from 5 clinical studies (Section 4). In NSCLC patients, time-varying clearance appears associated with post-treatment disease response and survival experience. Patients who had better disease response and survival experience appeared to have greater reduction of clearance over time. The decrease in CL over time is not considered clinically relevant.

2. RECOMMENDATIONS

This application is acceptable from pharmacometrics perspective.

2.1.LABELIG RECOMMENDATIONS

12.3 Pharmacokinetics

Patients' exposures 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 population analysis that included 472 patients in the dose range, the typical population clearance was 0.20 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. In a posthoc analysis, atezolizumab clearance was found to decrease over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 17.1% (40.6%). However, the decrease in CL was not considered clinically relevant.

3. RESULTS OF APPLICANT'S ANALYSIS

3.1.Population PK Analysis

Applicant's PPK analysis is composed of two parts. The major goal of the part one 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 NSCLC in studies GO28754, GO28625 and GO28753 were included. This review will be focusing on the part two. The part one has been reviewed under the submission BLA761034.

The objectives of applicant's population PK analysis were:

- Assess the PK of atezolizumab in patients with NSCLC in the Phase 2 clinical Studies BIRCH, POPLAR, and FIR through external validation of the population PK Model using the Phase 1 popPK Model,
- Derive atezolizumab exposure metrics for a subsequent exploratory exposure-response analysis of atezolizumab in NSCLC patients.

3.2.Data

The population PK analysis included data obtained from three clinical studies of Atezolizumab (**Table 4**):

Table 4: Clinical Studies for Population PK Analysis

Study	Phase	N Treated Patients	N Eval PK	Population	Atezolizumab Dose and Schedule
BIRCH[1] (GO28754)	2	659[a] Cohort 1: 139 Cohort 2: 267 Cohort 3: 253	652 Cohort 1: 138 Cohort 2: 263 Cohort 3: 251	A Phase 2, Multicenter, Single-Arm Study of atezolizumab in PD-L1 Selected Patients With Locally Advanced Or Metastatic NSCLC	1200 mg q3w
FIR[2] (GO28625)	2	137[b] Cohort 1: 31 Cohort 2: 93 Cohort 3: 13	128 Cohort 1: 31 Cohort 2: 84 Cohort 3: 13	A Phase 2, Multicenter, Single-Arm Study of atezolizumab in PD-L1 Selected Patients With Locally Advanced Or Metastatic NSCLC	1200 mg q3w
POPLAR[3] (GO28753)	2	277 Atezolizumab: 142[c] Docetaxel: 135[d]	140 Atezo: 140	A Phase 2, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared With Docetaxel in Patients With NSCLC After Platinum Failure	1200 mg q3w or Docetaxel 75 mg/m^2 q3w

N=Number of patients, Eval=evaluable; [a] 652 patients had at least one evaluable PK sample; [b] 128 patients had at least one evaluable PK sample; [c] 140 patients in Atezolizumab arm had at least one evaluable PK, [d] Patients did not receive atezolizumab (atezo) but docetaxel, data not used in this analysis; q3w=every 3 weeks

Source: Applicant's Population PK Analysis Report 1067735, Table 2-1

The summary of demographics is presented in **Table 3** and **Table 4**.

Table 5: Descriptive Statistics of Continuous Covariates at Baseline Overall and By Study in the PK Population

Covariate (unit)	Study	Number of patients	Median	Min	Max
Age (year)	Overall	920	64	29	88
	BIRCH	652	64	29	88
	FIR	128	66	42	85
	POPLAR	140	62	42	82
Albumin [a] (g/L)	Overall	886	39	18	51
	BIRCH	623	39	22	51
	FIR	127	40	23	49
	POPLAR	136	40	18	48
ALT (U/L)	Overall	903	18	4	131
	BIRCH	638	18	4	110
	FIR	127	16	4	68
	POPLAR	138	19	4	131
AST[b] (U/L)	Overall	149	14	10	121
	BIRCH	102	13	10	121
	FIR	22	14	10	15
	POPLAR	25	14	10	15
Bilirubin (µmol/L)	Overall	901	6.8	1.4	61.6
	BIRCH	636	7.0	1.4	30.8
	FIR	127	6.8	3.0	61.6
	POPLAR	138	6.8	1.7	23.9
Body weight (kg)	Overall	895	71.1	34.9	175.8
	BIRCH	629	71.0	34.9	132.4
	FIR	127	71.0	39.1	175.8
	POPLAR	139	72.0	41.2	122.3
Creatinine Clearance [c] (mL/min)	Overall	868	81.4	8.9	331.3
	BIRCH	604	81.0	31.3	331.3
	FIR	126	76.7	29.3	185.6
	POPLAR	138	87.1	8.9	199.5
eGFR [c] (mL/min/1.73m^2)	Overall	887	82.0	6.2	305.0
	BIRCH	621	81.1	6.2	305.0
	FIR	127	83.7	37.5	167.5
	POPLAR	139	84.2	6.7	164.5
Tumor burden (mm)	Overall	907	64	10	277
	BIRCH	639	62	10	243
	FIR	128	68	11	277
	POPLAR	140	71	11	241

N=number of patients; ALT=alanine aminotransferase (U/L); AST=aspartate aminotransferase (U/L); eGFR=estimated Glomerular Filtration Rate); [a] exclusion of 9 aberrant values for the summary statistic (i.e. <1g/L) [b] exclusion of 8 aberrant values for the summary statistic (i.e. >15000 U/L); [c] exclusion of 16 aberrant values for the summary statistic (i.e. <1 mL/min or mL/min/1.73m^2)

Source: Synopsis of applicant's Pop PK Report 1067735, Table 4-2

Table 6: Descriptive Statistics of Categorical Covariates at Baseline Overall and By Study in the PK Population

		Number of patients (%*)			
Covariate	**Category**	**Overall N=920**	**BIRCH N=652**	**FIR N=128**	**POPLAR N=140**
Gender	Male	549 (59.7%)	384 (58.9%)	74 (57.8%)	91 (65%)
	Female	371 (40.3%)	268 (41.1%)	54 (42.2%)	49 (35%)
ECOG	0	315 (34.2%)	229 (35.1%)	41 (32.0%)	45 (32.1%)
	1	594 (64.6%)	415 (63.7%)	86 (67.2%)	93 (66.4%)
	2	8 (0.9%)	8 (1.2%)	0 (0%)	0 (0%)
	missing	3 (0.3%)	0 (0%)	1 (0.8%)	2 (1.4%)
Race	White	762 (82.8%)	542 (83.1%)	114 (89.1%)	106 (75.7%)
	Asian	106 (11.5%)	78 (12.0%)	5 (3.9%)	23 (16.4%)
	Black	21 (2.3%)	10 (1.5%)	8 (6.2%)	3 (2.1%)
	Native Hawaiian	3 (0.3%)	1 (0.2%)	0 (0%)	2 (1.4%)
	American Indian	1 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)
	Other	9 (1.0%)	4 (0.6%)	1 (0.8%)	4 (2.9%)
	Multiple	5 (0.5%)	5 (0.8%)	0 (0%)	0 (0%)
	Unknown	13 (1.4%)	11 (1.7%)	0 (0%)	2 (1.4%)
Region	USA	381 (41.4%)	214 (32.8%)	101 (78.9%)	66 (47.1%)
	Spain	58 (6.3%)	48 (7.4%)	0 (0%)	10 (7.1%)
	France	74 (8.0%)	63 (9.7%)	3 (2.3%)	8 (5.7%)
	Great Britain	26 (2.8%)	11 (1.7%)	12 (9.4%)	3 (2.1%)
	Japan	27 (2.9%)	27 (4.1%)	0 (0%)	0 (0%)
	Belgium	32 (3.5%)	20 (3.1%)	6 (4.7%)	6 (4.3%)
	Netherlands	6 (0.7%)	0 (0%)	6 (4.7%)	0 (0%)
	Germany	36 (3.9%)	25 (3.8%)	0 (0%)	11 (7.9%)
	Canada	51 (5.5%)	47 (7.2%)	0 (0%)	4 (2.9%)
	Italy	26 (2.8%)	24 (3.7%)	0 (0%)	2 (1.4%)
	Korea	9 (1.0%)	0 (0%)	0 (0%)	9 (6.4%)
	Poland	11 (1.2%)	0 (0%)	0 (0%)	11 (7.9%)
	Thailand	9 (1%)	0 (0%)	0 (0%)	9 (6.4%)
	Turkey	19 (2.1%)	18 (2.8%)	0 (0%)	1 (0.7%)
	Australia	21 (2.3%)	21 (3.2%)	0 (0%)	0 (0%)
	Bulgaria	4 (0.4%)	4 (0.6%)	0 (0%)	0 (0%)
	Bosnia	8 (0.9%)	8 (1.2%)	0 (0%)	0 (0%)
	Switzerland	41 (4.5%)	41 (6.3%)	0 (0%)	0 (0%)
	Georgia	20 (2.2%)	20 (3.1%)	0 (0%)	0 (0%)
	Hong Kong	6 (0.7%)	6 (0.9%)	0 (0%)	0 (0%)
	Niger[a]	28 (3.0%)	28 (4.3%)	0 (0%)	0 (0%)
	Singapore	18 (2.0%)	18 (2.8%)	0 (0%)	0 (0%)
	Slovenia	8 (0.9%)	8 (1.2%)	0 (0%)	0 (0%)
	Missing[b]	1 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)
IC3 Flag	Yes	209 (22.7%)	170 (26.1%)	30 (23.4%)	9 (6.4%)
	Unknown	2 (0.2%)	1 (0.2%)	1 (0.8%)	0 (0.0%)
	No	709 (77.1%)	481 (73.8%)	97 (75.8%)	131 (93.6%)
TC3 Flag	Yes	210 (22.8%)	171 (26.2%)	25 (19.5%)	14 (10.0%)
	Unknown	1 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)
	No	709 (77.1%)	480 (73.6%)	103 (80.5%)	126 (90.0%)
Formulation	F01	268 (29.1%)	0 (0%)	128 (100%)	140 (100%)
	F03	652 (70.9%)	652 (100%)	0 (0%)	0 (0%)
Brain metastasis	No	901 (97.9%)	650 (99.7%)	118 (92.2%)	133 (95.0%)
	Yes	19 (2.1%)	2 (0.3%)	10 (7.8%)	7 (5.0%)
Liver metastasis	No	752 (81.7%)	543 (83.3%)	102 (79.7%)	107 (76.4%)
	Yes	168 (18.3%)	109 (16.7%)	26 (20.3%)	33 (23.6%)
Number of metastatic sites	0	34 (3.7%)	32 (4.9%)	2 (1.6%)	0 (0%)
	1	205 (22.3%)	161 (24.7%)	25 (19.5%)	19 (13.6%)
	2	284 (30.9%)	211 (32.4%)	39 (30.5%)	34 (24.3%)
	3	225 (24.5%)	151 (23.2%)	28 (21.9%)	46 (32.9%)
	4 or more	172 (18.7%)	97 (14.9%)	34 (26.6%)	41 (29.3%)
ATAG	Negative	505 (54.9%)	381 (58.4%)	63 (49.2%)	61 (43.6%)
	Positive	376 (40.9%)	238 (36.5%)	65 (50.8%)	73 (52.1%)
	missing	39 (4.2%)	33 (5.1%)	0 (0%)	6 (4.3%)
Smoking status	Never	155 (16.8%)	110 (16.9%)	18 (14.1%)	27 (19.3%)
	Current	112 (12.2%)	70 (10.7%)	17 (13.3%)	25 (17.9%)
	Previous	653 (71%)	472 (72.4%)	93 (72.7%)	88 (62.9%)

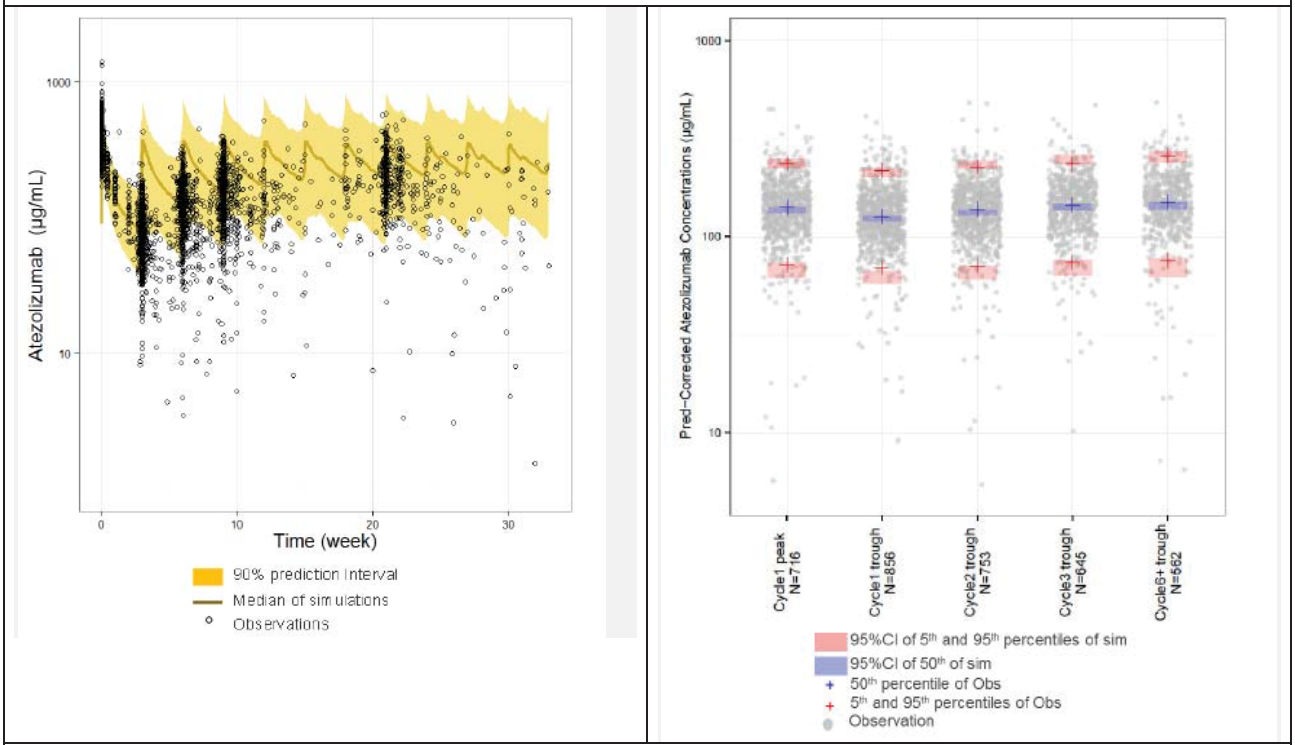
*IC =Tumor-infiltrating immune cells; TC =Tumor cell; F01=Phase 1 formulation; F03=Phase 3 formulation ATAG=Post-baseline anti-therapeutic antibody; * % of the total*

Source: Synopsis of applicant's Pop PK Report 1067735, Table 4-3, 4-4

3.2.1. Results

The ability of the Phase 1 popPK Model to describe atezolizumab PK in NSCLC patients was evaluated by external pcVPC based on atezolizumab concentration from a total of 920 patients out of 938 treated (98.1%). The pcVPC was performed using Cmax and Cmin atezolizumab data obtained as shown in **Figure 3** in semi-logarithm scale for all patients. The 90% PIs of the PK profiles using the Phase 1 popPK Model with observed concentrations are presented as well.

Figure 4 : 90% Prediction Interval of the PK profile Using the Phase 1 PopPK Model with BIRCH, FIR and POPLAR Observed Concentrations (Left Panel) and Prediction-Corrected VPC of Peaks and Troughs of Atezolizumab with all patients (Right Panel)



Source: Synopsis of applicant's Pop PK Report 1067735, Figure 4-2 and Appendix 8-17

Model diagnostics (external pcVPC, goodness-of-fit plots) indicated that the Phase 1 popPK Model was adequate to predict PK in BIRCH, FIR and POPLAR and estimate individual exposure parameters for BIRCH, FIR and POPLAR patients in subsequent exposure-safety and exposure-efficacy analyses.

Estimated patient-level CL, V1 and V2 random effects (ETAs) were explored by study and cohort; this exploratory graphical evaluation suggested no bias in random effects for both BIRCH and FIR while there was a trend to faster CL and larger V1 in POPLAR, consistent with the over-prediction of observed concentrations in the pcVPC for POPLAR. Exploratory graphical analyses of random-effects that are adjusted to Phase 1 popPK Model covariate effects indicate that BIRCH, FIR and POPLAR covariate effects are generally consistent with those estimated in Phase 1. The

relationship between random effect of CL and body weight is characterized with a negative correlation coefficient suggesting that the relationship in NSCLC patients may be not as steep as the one estimated in the Phase 1 popPK model.

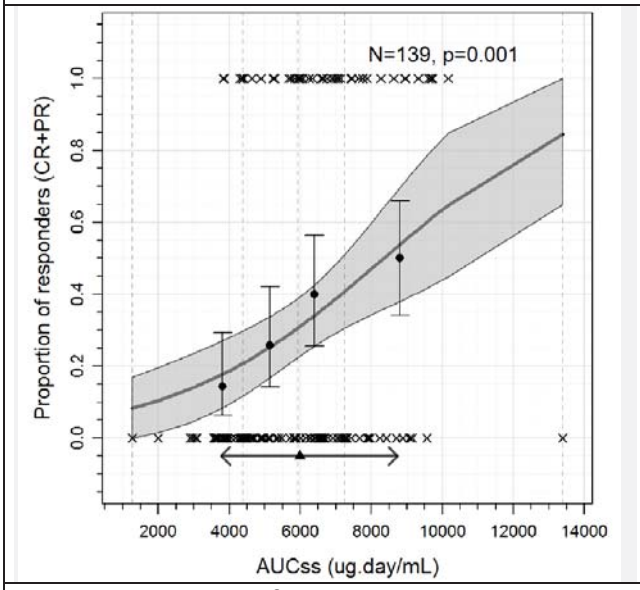
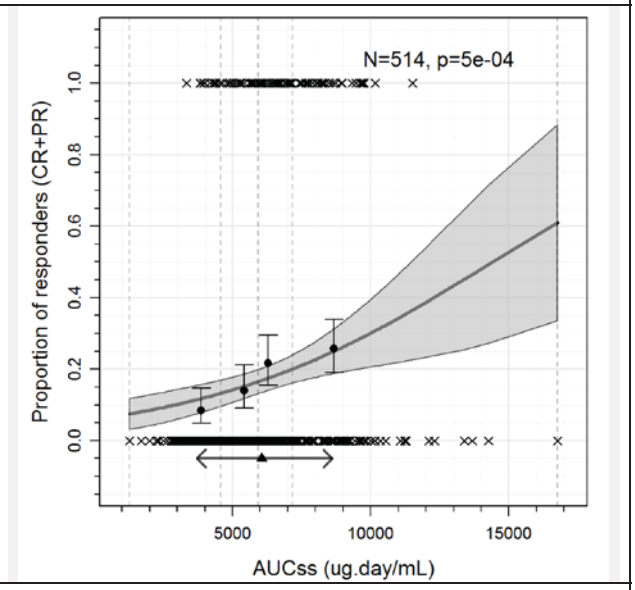
Reviewer's comment: Applicant's population PK analysis failed to describe a time-varying feature of PK parameters (eg. clearance). See reviewer's analysis in section 4 for more details.

3.3.Exposure-ORR Analysis:

ORR from BIRCH was considered in the exposure-efficacy assessment in two populations. The first population comprised 2L+ TC3 NSCLC patients; the second population included 2L+ TC2/3 or IC2/3 NSCLC patients who represented the intent-to-treat population in Cohorts 2 and 3 in BIRCH.

The exposure-response for atezolizumab in the 2L+ TC3 NSCLC population is shown in **Figure 4.** The ORR in the analysis population was 32.4% (45 responders over 139 patients with exposure data). The probability of response increased with atezolizumab exposure as illustrated in **Figure 4** for AUCss. For 2L+ TC2/3 or IC2/3 NSCLC patients treated with atezolizumab 1200 mg q3w, the probability of response likewise increased with atezolizumab AUCss.

Figure 5 : Objective Response Rate vs. Atezolizumab AUCss (BIRCH)

2L+ TC3 NSCLC Patients	2L+ TC2/3 or IC2/3 NSCLC Patients
	

Source: Synopsis of applicant's ER Report 1067243, Figure 4-1 and Appendix 8.1.5

Reviewer's comment: Applicant's exposure-ORR analysis is biased because the atezolizumab exposure could be affected by the disease progression post treatment. See reviewer's analysis in section 4 for more details.

3.4.Exposure-Safety Analysis:

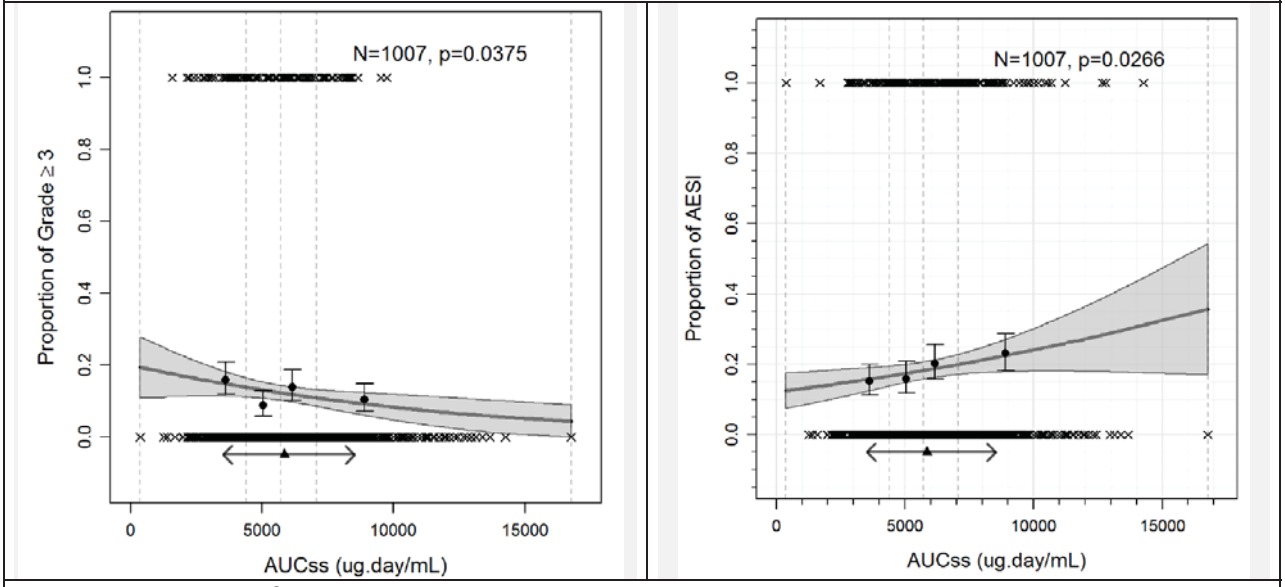
The atezolizumab exposure-safety analysis was performed on all atezolizumab-treated NSCLC patients in the Phase 1a Study PCD4989g and in the Phase 2 Studies BIRCH, FIR and POPLAR.

The data set was comprised of a total of 1007 patients with exposure data (out of 1026 treated patients included in the four studies, 98.1%).

The analysis of the incidence of AEG35 did not show any statistically significant exposure-response relationship with AUCss (left panel **Figure 5**) or any other exposure metrics investigated.

The incidence of AESI tended to increase with exposure (Cmin, AUC) as shown for AUCss (right panel **Figure 5**). Simulation of the logistic regression model for AUCss suggests a slight increase in the probability of AESI from 0.18 (0.16, 0.21) to 0.22 (0.18, 0.26) for patients with the median and 90th percentile of AUCss, respectively. This increase in AESI is not anticipated to be clinically meaningful or to require dose adjustment.

Figure 6 : Incidence of AEs vs. Atezolizumab AUCss in Patients with NSCLC: Left Panel: AEG35; Right Panel: AESI



Source: Synopsis of applicant's ER Report 1067243, Figure C

Reviewer's comment: Applicant's exposure-safety analysis for AESI seems reasonable.

3.5.Conclusion

3.5.1.PPK Analysis

- Post-hoc estimation using the Phase 1 popPK Model was performed to obtain individual random effects and PK parameters in BIRCH, FIR and POPLAR patients.
    - Covariate effects in BIRCH, FIR and POPLAR data were generally consistent with those identified in the Phase 1 popPK Model.
    - No new unexpected covariate effect was identified in BIRCH, FIR and POPLAR.

- Combined atezolizumab PK data obtained in BIRCH, FIR and POPLAR in NSCLC patients are consistent with Phase 1 popPK Model estimates.

3.5.2.Exposure-ORR Analysis

- A statistically significant E-R relationship was identified with ORR for atezolizumab 1200 mg q3w in BIRCH 2L+ TC3 NSCLC patients and 2L+ TC2/3 or IC2/3 NSCLC patients.
- The statistically significant increasing trend with ORR does not support a dose lower than 1200 mg q3w, and the statistically significant increasing trend with AESI suggests a dose higher than 1200 mg q3w would not be supported

3.5.3.Exposure-Safety Analysis

- AESI and AEG35 following atezolizumab 1 to 20 mg/kg, including the 1200 mg flat dose q3w in patients with NSCLC in Studies PCD4989g (NSCLC cohort), BIRCH, POPLAR, and FIR were evaluated in the exposure-safety analysis. A statistically significant exposure-safety relationship was identified for AESI. No statistically significant increasing exposure-safety relationship was identified with AEG35.
- The statistically significant increasing trend with AESI suggests a dose higher than 1200 mg q3w would not be supported, and the statistically significant increasing trend with ORR does not support a dose lower than 1200 mg q3w.

4. REVIEWER'S ANALYSIS

4.1.OBJECTIVE

The analysis objectives are

- To assess the adequacy of applicant's PPK model to describe the PK data
- To explore the association between disease progression and PK in NSCLC patients

4.2.METHODS

4.2.1. Data Sets

Data sets used are summarized in **Table 7**.

Table 7: Analysis Datasets for FDA Reviewer's Analysis

Study Number	Name	Link to EDR
PCD4989g	ars.xpt	\\cdsesub1\evsprod\bla761041\0001\m5\datasets\go27831-pcd4989g\analysis\adam\datasets\ars.xpt
GO28625	ars.xpt	\\cdsesub1\evsprod\bla761041\0001\m5\datasets\go28625-fir\analysis\adam\datasets\ars.xpt
GO28754	ars.xpt	\\cdsesub1\evsprod\bla761041\0001\m5\datasets\go28754-birch-octcut\analysis\adam\datasets\ars.xpt
GO28753	ars.xpt	\\cdsesub1\evsprod\bla761041\0012\m5\datasets\go28753-poplar-deccut\analysis\adam\datasets\ars.xpt
GO28753	ate.xpt	\\cdsesub1\evsprod\bla761041\0012\m5\datasets\go28753-poplar-deccut\analysis\adam\datasets\ate.xpt
GO28753	adsl.xpt	\\cdsesub1\evsprod\bla761041\0012\m5\datasets\go28753-poplar-deccut\analysis\adam\datasets\adsl.xpt
PPK	poppk1.xpt	\\cdsesub1\evsprod\bla761041\0001\m5\datasets\poppk\analysis\legacy\datasets\poppk1.xpt
	poppk2.xpt	\\cdsesub1\evsprod\bla761034\0002\m5\datasets\poppk\analysis\legacy\datasets\poppk2.xpt
	Poppk3.xpt	\\cdsesub1\evsprod\bla761041\0001\m5\datasets\poppk\analysis\legacy\datasets\poppk3.xpt

4.2.2. Software

NONMEM 7 and R were used for the reviewer's analysis.

4.2.3. Method

- The FDA reviewer explored the applicant's final PPK model by evaluating the diagnostic plot and examined the PK parameters at different time periods. Applicant's PPK model was modified for further improvement to describe the time-varying characteristics of CL.

4.3.RESULTS

4.3.1. Evaluation of Applicant's PPK model

Applicant's PPK model was re-fitted using data from study study 4989g, GO28625, GO28753, and GO28754. FDA reviewer explored diagnostic plot of applicant's PPK model for NSCLC patients (Mod1, **Figure 6)**. An underestimation of the observed atezolizumab concentrations was observed at the later time points, suggesting a potential time-varying PK property might not be captured by the applicant's PPK model. The extent of the deviation along with time seems to be more pronounced in responders (CR+PR) than in non-responders. The structure of Mod1 was described as follows:

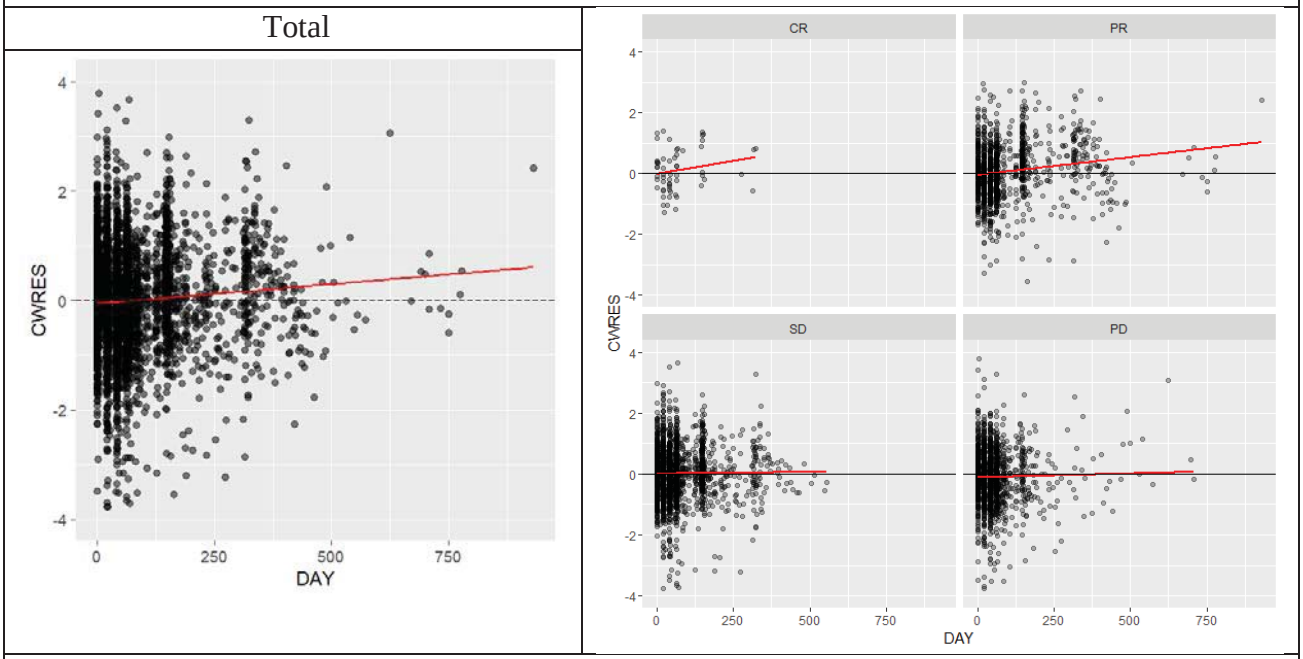
$$CL_i = \left(TVCL \cdot \left(\frac{ALBU_i}{40}\right)^{\theta_{ALBU\_CL}} \cdot \left(\frac{BWT_i}{77}\right)^{\theta_{BWT\_CL}} \cdot \left(\frac{Baseline\ tumor\ burden_i}{63}\right)^{\theta_{tum\_CL}}\right) \cdot \left(\theta_{BWT\_CL}\right)^{ATAG}$$

$$V1_i = \left(TVV1 \cdot \left(\frac{ALBU_i}{40}\right)^{\theta_{ALBU\_V1}} \cdot \left(\frac{BWT_i}{77}\right)^{\theta_{BWT\_V1}} \cdot\right) \cdot \left(\theta_{gender\_V1}\right)^{gender}$$

$$V2_i = TVV2 \cdot \left(\theta_{gender\_V1}\right)^{gender}$$

BWT = body weight (kg); ALBU = Albumin (g/L); ATAG = Post-baseline status of anti-therapeutic antibodies. Reference is made to applicant's Pop PK Report 1067735.

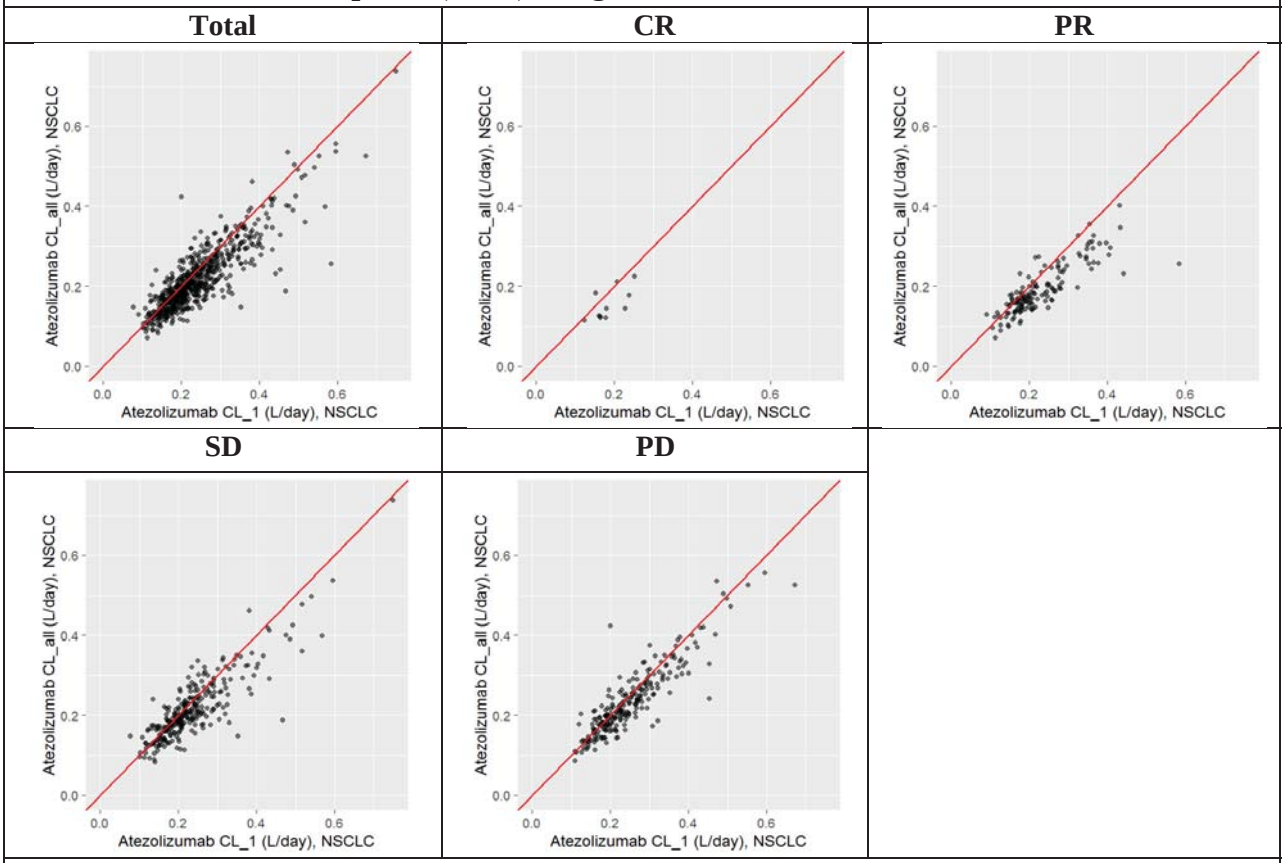
Figure 7: CWRES Versus Time After First Dose from the applicant's PPK model. Each panel showed data from patients with different best response categories.



Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated
Source: FDA reviewer's analysis based on applicant's PPK model. Data from trial 4989g, GO28625, GO28753, and GO28754

Because a constant clearance was assumed under the two compartment linear PK model, the applicant's PPK model would estimate an "average" clearance over different time intervals (CL_all) if data from all doses were used, and that estimate would be valid only if clearance does not change with time. To further explore the potential time-varying PK characteristics, applicant's PPK model was re-fitted using data only from the first dose. Clearance estimated from data after the first dose (CL_1) describes the PK at the beginning of the trial. The ratio of these two types of individual *post-hoc* clearance is expected to be distributed around one when clearance is time-independent. The comparison of CL_1 and CL_all was shown in **Figure 7.** The results showed that the CL_all tended to be smaller than CL_1.

Figure 8: Estimation of CL_1 Versus CL_all based on Applicant's Final PPK Model structure. Only NSCLC patients were shown. Each panel showed data from patients with different best overall response (BOR) categories.

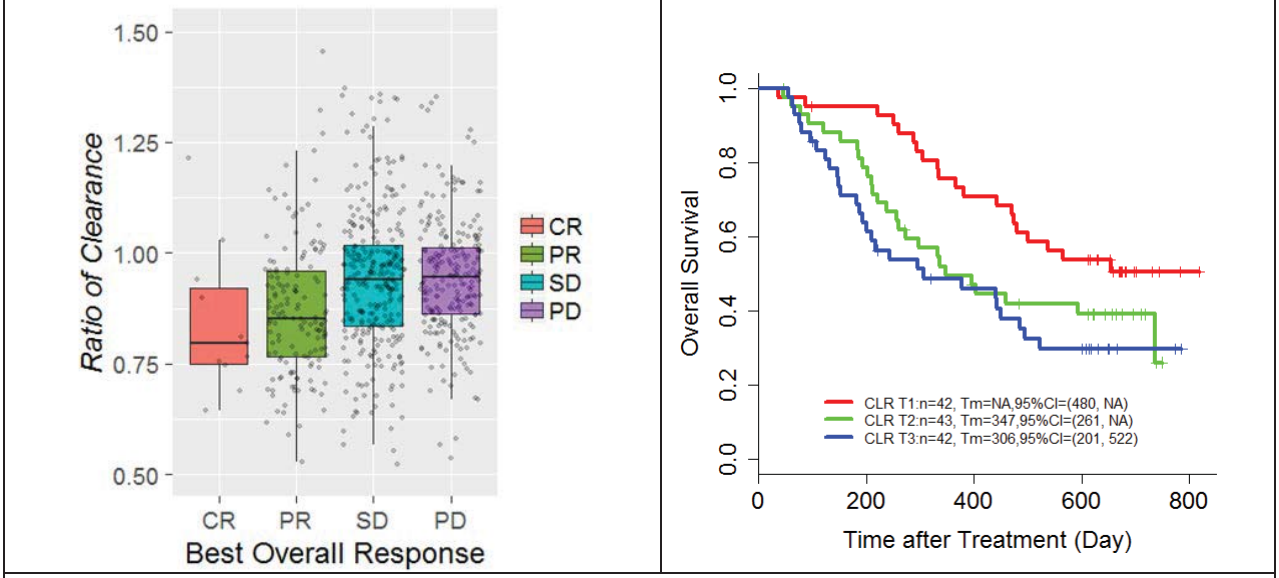


Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated
Source: FDA reviewer's analysis based on applicant's final model structure. Data from trial 4989g, GO28625, GO28753, and GO28754.

This association between post-treatment effects and change of clearance was then explored by the FDA reviewer. The ratio of *post-hoc* individual CL_all and CL_1 (CLR=CL_all/CL_1) was employed as the indicator of the clearance change with time. Smaller CLR corresponds to greater clearance reduction. NSCLC patients were stratified according to their best disease responses (BOR) to atezolizumab and the distributions of individual CLR values were shown in **Figure 8**. There was a trend that better BOR was associated with smaller CLR, suggesting greater time effects on clearance in treatment responders.

In addition, patients were divided into three tertiles based on CLR and the overall survival was compared among these three sub-populations. There was an evident relationship between CLR and OS based on the data from study GO28753: subjects with greater clearance reduction (smaller CLR) showed better OS than those with milder or no clearance reduction (**Figure 8**).

Figure 9: Ratio of iCL_all and iCL_1 (CLR) versus best disease response in NSCLC patients. Applicant's final PPK model was re-fitted to estimate individual CL_1 based on the data from the first dose in the studies used in applicant's PPK study.



Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated
Source: FDA reviewer's analysis. Left panel: data from trial 4989g, GO28625, GO28753, and GO28754; right panel: Data from trial GO28753..

The FDA reviewer then explored the time-varying PK by adding a time effect term to clearance based on applicant's final PPK model structure. The time effect term was added in the following format:

$$CL_i(Time) = e^{\frac{(Tmax+\eta_i)\times Time^{\gamma}}{T50^{\gamma}+Time^{\gamma}}} \times CL_{mod1}$$

Here e^{Tmax} is the maximum change of CL, T50 is time for half of the maximum change of CL and η_i is the inter-subject variability term. Due to limited time and data (availability of tumor response data for all studies included in the PPK dataset), no further analysis was conducted to include tumor response as a covariate for T_{max}. A negative Tmax suggests a decreasing clearance over time, while a positive Tmax supports an increasing clearance over time. If clearance is time independent, Tmax estimation should be around 0. The a head to head comparison between applicant's PPK model and time-varying PPK model (Mod 2) was shown in **Table 8**. Data from trial 4989g, GO29293, GO28625, GO28753, and GO28754 were employed in the PPK analysis.

Table 8. PPK Model Parameter Estimates

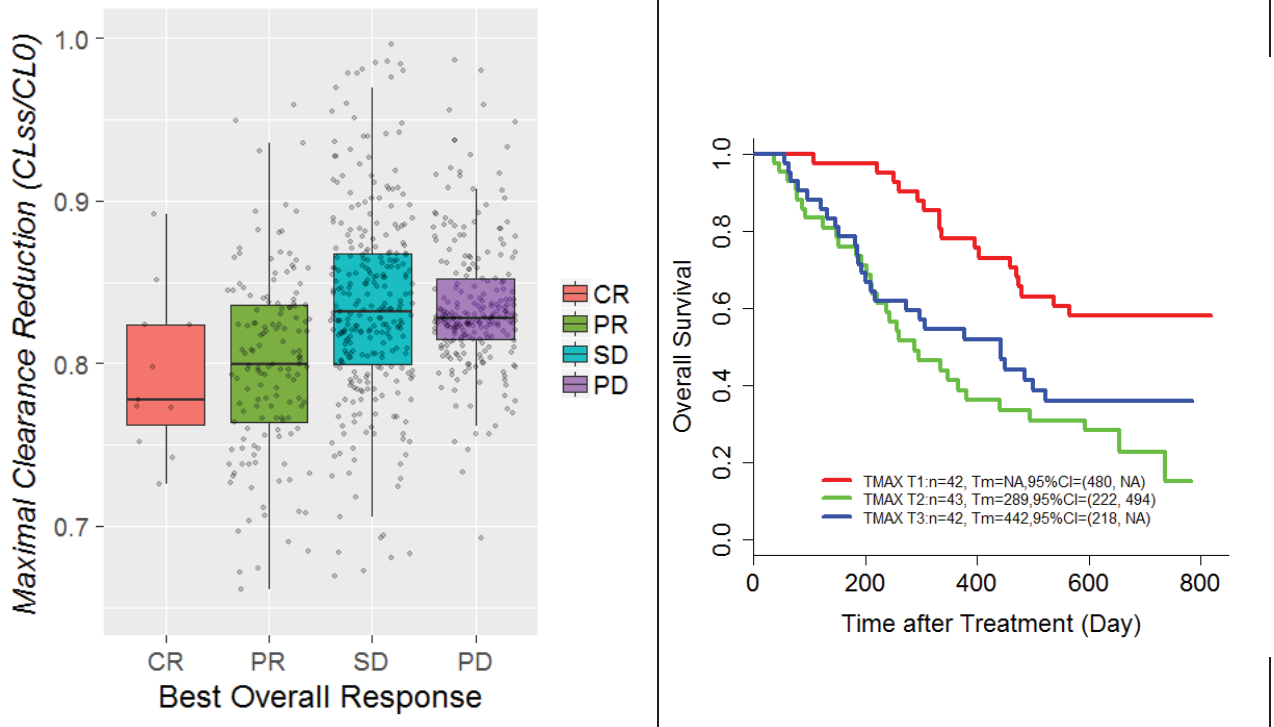
	Estimate (RSE%)	
	Mod1	**Mod2**
Objective Function Value	83694.8	83444.2
CL (L/day)	0.201 (1%)	0.23 (2%)
V1 (L)	3.3 (1%)	3.25 (1%)
V2 (L)	3.72 (3%)	2.88 (5%)
Q (L/day)	0.5 (7%)	0.603 (8%)
Albumin on CL	-0.958 (7%)	-0.901 (7%)
ATAG on CL	0.172 (10%)	0.158 (11%)
Tumor burden on CL	0.124 (9%)	0.116 (9%)
Body weight on CL	0.666 (5%)	0.668 (5%)
Albumin on V1	-0.332 (14%)	-0.345 (13%)
Body weight on V1	0.518 (5%)	0.533 (5%)
Gender (female) on V1	-0.117 (10%)	-0.104 (12%)
Gender (female) on V2	-0.296 (9%)	-0.293 (11%)
Tmax: Maximum fold change of log(CL)	N/A	-0.193 (13%)
T50: time for 0.5 fold increase of CL (day)	N/A	62.8 (11%)
Hill	N/A	2.67 (16%)
IIV on CL	29.40%	26.3%
IIVon V1	18.4%	17.2%
IIV on V2	37.3%	35.2%
IIV on Tmax	N/A	89.7%
Residual Error		
Proportional	0.035	0.034
Additive	26.2	18.1

Source: FDA reviewer's analysis based on applicant's PPK model. Data from trial 4989g, GO29293, GO28625, GO28753, and GO28754

In the time-varying PPK model, Tmax was estimated to be -0.19. This suggests that the clearance could maximally on average decrease to about 81% of its original level. Mod2 was employed as FDA reviewer's final model.

According to the *post-hoc* estimates of T_{max} in NSCLC patients, there was an apparent relationship between T_{max} and BOR: responders showed lower T_{max}, suggesting that the maximal clearance reduction is more significant in disease responders. Also, similar to the analysis of CLR, when patients were grouped into three tertiles based on *post hoc* e^{Tmax} estimates, subjects with smaller T_{max} showed better OS experience (**Figure 9).**

Figure 10: Post-hoc individual T_{max} versus best disease response in NSCLC patients



Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease
Source: FDA reviewer's analysis. Left panel was based on data from trial 4989g, GO28625, GO28753, and GO28754. Right panel was based on data from trial GO28753.

5. LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
001.lst	Applicant's Final PPK model with data from poppk1.xpt and poppk3.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\001.lst
sdtab001	Model output for 001.lst	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\ sdtab001
003.lst	Applicant's Final PPK model with data from poppk1 and poppk2. Only 1st dose data were used.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\003.lst
sdtab003	Model output for 003.lst	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\ sdtab003
004.lst	Sigmoidal Tmax model for time-varying PK, with data from poppk1.xpt, poppk2.xpt and poppk3.xpt. This model was used to provide information for labeling.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\004.lst
sdtab004	Model output for 004.lst	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\ sdtab004
005.lst	Applicant's Final PPK model, with data from poppk1.xpt, poppk2.xpt and poppk3.xpt.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\005.lst
sdtab005	Model output for 005.lst	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\sdtab005
761041 PPK.R	Graph generation	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atezolizumab BLA761041_CLiu\PPK Analysis\sdtab005

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/s/

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09/28/2016

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09/28/2016

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ROSANE CHARLAB ORBACH
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QI LIU
09/28/2016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	**761041**	**Brand Name**	**Tecentriq**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Atezolizumab**
Medical Division	**DOP1**	**Drug Class**	**humanized programmed death-ligand 1 (PD-L1) blocking antibody**
OCP Reviewer	**Wentao Fu**	**Indication(s)**	**TECENTRIQ is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:** • **Have received a prior platinum-containing chemotherapy regimen in the metastatic setting** • **Had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen**
OCP Team Leader	**Qi Liu**	**Dosage Form**	**Infusion: 60 mg/mL solution in a single use 20 mL vial**
Pharmacometrics Reviewer	**Chao Liu**	**Dosing Regimen**	**1200 mg, IV infusion over 60 minutes, Q3W**
Pharmacometrics Team Leader	**Jingyu (Jerry) Yu**	**Date of Submission**	**February 19, 2016**
Genomics Reviewer	**Sarah Dorff**	**Estimated OCP Due Date**	**June 10, 2016**
Genomics Team Leader	**Rosane Charlab Orbach**	**Medical Division Due Date**	**June 17, 2016**
Sponsor	**Genentech, Inc.**	**PDUFA Due Date**	**October 19, 2016**
Priority Classification	**Expedited**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				Not applicable. Atezolizumab is a biological product. Mass balance studies were not conducted.
Isozyme characterization:				Not applicable. Atezolizumab is a biological product. Isozyme characterization studies were not conducted.
Blood/plasma ratio:				Not applicable. Atezolizumab is a biological product. Blood/plasma ratio studies were not conducted.
Plasma protein binding:				Not applicable. Atezolizumab is a biological product. Plasma protein binding studies were not conducted.
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				**All of the submitted PK data were collected in patients with cancer**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**5**		• PCD4989g (GO27831): Phase 1a trial in patients (multiple dose cohorts: 0.3, 1, 3, 10 and 20 mg/kg q3w as well as 1200 mg q3w) with locally advanced or metastatic solide malignancies or hematologics malignancies. • JO28944: Phase 1 trial in Japanese patients at 10 and 20 mg/kg q3w with locally advanced or metastatic solid malignancies. • BIRCH (GO28754): Phase 2 trial at 1200 mg q3w in patients with locally advanced or metastatic NSCLC. Patients were PD-L1 selected (TC2/3 or IC2/3) • POPLAR (GO28753): Phase 2 trial at 1200 mg q3w in patients with locally advanced, metastatic or recurrent NSCLC. Patients were unselected for PD-L1. • FIR (GO28625): Phase 2 trial at 1200 mg q3w in patients with locally advanced or metastatic NSCLC. Patients were PD-L1 selected (TC2/3 or IC2/3)
Dose proportionality -	**X**	**1**		• PCD4989g (GO27831): exposure increase dose proportional over a dose range of 1 to 20 mg/kg including a fixed 1200 mg dose.
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				No drug-drug interaction studies have been conducted
In-vivo effects on primary drug:				
In-vivo effects on other drugs:				
In-vitro:				
Subpopulation studies -				No formal studies conducted. Based on the population pharmacokinetic analysis, weight, age, race, and gender do not have a significant effect on atezolizumab exposure.
ethnicity:				
gender:				
pediatrics:				The safety and effectiveness of atezolizumab in pediatric patients have not been studied.
geriatrics:				No dose adjustment is required for patients age 65 and older based on population pharmacokinetic analyses
renal impairment:				Dose adjustment is not recommended for patients with mild or moderate renal impairment based on population PK analysis. An appropriate dose has not been established for patients with severe renal impairment
hepatic impairment:				Dose adjustment is not recommended for patients with mild hepatic impairment based on a population PK analysis. An appropriate dose has not been established for patients with moderate to severe hepatic impairment
PD -				
Phase 2:				
Phase 3:				
PK/PD -				1) E-R analyses based on study BIRCH, FIR, POPLAR and PCD4989g (Report 1067243): • ORR (BIRCH) • Adverse Events (All above four studies) 2) C-QTC assessments based on study PCD4989g (Report 1066934)
Phase 1 and/or 2, proof of concept:	**X**	**4**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 3 clinical trial:				
Population Analyses -				Population pharmacokinetic analysis (Report 1066935) using 4563 PK samples from 472 patients in Study PCD4989g and JO28944. The popPK model was externally validated using 3891 PK samples from 920 patients in Studies BIRCH (N=652), FIR (N=128) and POPLAR (N=140). (Report 1067735)
Data rich:	**X**	**2**		PCD4989g and JO28944
Data sparse:	**X**	**5**		PCD4989g , JO28944, BIRCH, FIR and POPLAR
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment	**x**	**5**		PCD4989g , JO28944 , BIRCH, FIR and POPLAR
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		PCD4989g , JO28944 , BIRCH, FIR and POPLAR

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			To be marketed formulation used in the pivotal trial.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	It is a biological product
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	It is an NME.
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing	X			

	interval and dose adjustment?				
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		The safety and efficacy of atezolizumab in children and adolescents below 18 years of age has not been established

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		The safety and efficacy of atezolizumab in children and adolescents below 18 years of age has not been established
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wentao Fu, Ph.D. 03/18/2016
Reviewing Clinical Pharmacologist Date

Qi Liu, Ph. D 03/18/2016
Team Leader/Supervisor Date

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

/s/

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