CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 8, 2016
From	Virginia Ellen Maher, M.D.
Subject	Atezolizumab
BLA #/Supplement#	761034/0
Applicant	Genentech, Inc.
Date of Submission	January 12, 2016
PDUFA Goal Date	July 11, 2016
Proprietary Name / Established (USAN) names	Tencentriq (atezolizumab)
Dosage forms / Strength	1200 mg/20 mL for intravenous administration
Proposed Indication(s)	Tecentriq is a humanized programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with: • locally advanced or metastatic urothelial carcinoma (b) (4) [redacted]
Recommended:	Approval

1. Introduction

On January 12, 2016, the Applicant submitted a biologics licensing application for a new molecular entity, atezolizumab, for the following indication.

Tecentriq is a humanized programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- locally advanced or metastatic urothelial carcinoma (b) (4) [redacted]

The application is supported by a Phase 2 study that included a cohort of patients who had received prior platinum-based therapy (N = 310) and a Phase 1 extension study (N = 94) in patients with urothelial cancer. The Applicant also provided safety data from patients with other cancer types who were enrolled in their large Phase 1 study, patients with treatment-naïve urothelial cancer (N = 119), and patients from their non-small cell lung cancer studies.

2. Background

Atezolizumab is a monoclonal antibody directed against programmed death-ligand 1. The Fc portion of the molecule is mutated to prevent receptor binding. Atezolizumab blocks the interaction of PD-L1 with PD-1 and B7.1 (CD80).

- PD-L1 is found on activated T cells, natural killer cells, macrophages, myeloid dendritic cells, B cells, vascular endothelial cells and tumor cells.
- PD-1 is found on activated T cells.
- B7.1 is found on antigen presenting cells and T cells.

Normally, PD-1 binds to PD-L1 or B7.1 to stop an immune response and prevent autoimmunity/promote self-tolerance. Cancer cells are able to express PD-L1 and can use this to evade the body's immune response. An anti-PD-L1 antibody such as, atezolizumab could prevent PD-1/PD-L1 binding and reactivate the anti-tumor immune response.

Urothelial cancer is known to express PD-L1. The Applicant's discussion of the prognostic value of PD-L1 cites the examination of 65 urothelial cancers for PD-L1 expression. Here, an increase in grade and T stage and a decrease in overall survival were associated with increased PD-L1 staining (Cancer Immunol Immunother 2007 56:1173). Review of the literature found that PD-L1 expression is increased in urothelial cancers with diffuse lymphocytic infiltration (Cancer 2007 109:1499). Bellmunt et al found positive PD-L1 tumor cell staining in 32/160 (20%) and positive PD-L1 infiltrating mononuclear cell staining in 59/143 (40%) bladder cancer specimens. Positive PD-L1 staining of infiltrating mononuclear cells was associated with improved survival (Ann Oncol 2015 26:812).

Importantly, the Applicant's complementary diagnostic stains tumor-infiltrating cells for PD-L1 rather than tumor cells. Thus, we would have to postulate that the immune response is inhibited by tumor-infiltrating mononuclear cells that express PD-L1 and inactivate T cells expressing PD-1. Atezolizumab would then prevent this interaction, allowing the T cells to attack the tumor. In this scenario, tumor-infiltrating cells are potentially harmful to the host and beneficial to the tumor. However, tumor-infiltrating lymphocytes (lymphocytes rather than mononuclear cells) are typically thought to lead to a better prognosis (Exp Biol Med 2011 236:567). Further, Bellmunt et al found that PD-L1 stained tumor-infiltrating mononuclear cells were associated with an improvement in survival. From the single-arm studies included in this submission, it cannot be determined whether PD-L1 is a prognostic factor in urothelial cancer and the role of PD-L1 stained tumor-infiltrating cells is unclear.

This submission seeks an indication for the use of atezolizumab, an anti-PD-L1 antibody, in the 2nd-line treatment of urothelial cancer. Platinum-based therapy is typically used in the 1st-line treatment of metastatic disease or in the neoadjuvant/adjuvant setting. No drugs/biologics have been approved in the US for use in the 2nd-line setting. However, a wide variety of medications are used off-label. In the EU, vinflunine was approved as a 2nd-line treatment in patients with metastatic urothelial cancer on the basis of a study comparing vinflunine + best supportive care to best supportive care (hazard ratio 0.88 (95% CI; 0.69, 1.12)).

Products commonly used in the US in patients with metastatic urothelial cancer who have received prior platinum-based therapy are shown in the table below. Single-agents have included taxanes and gemcitabine. The response rates of docetaxel and paclitaxel are approximately 10%. One study of nab-paclitaxel reported a response rate of 28%. Since gemcitabine has become part of the standard first-line regimen for the treatment of bladder cancer, it is often avoided in the 2nd line setting. The use of combination therapy in the 2nd-

line setting is controversial. Combination therapy results in a higher response rate, but it is unclear if there is a benefit in terms of overall survival. Some of the more promising combinations are shown in the table below.

Table 1: Agents Used in the 2nd-line Treatment of Metastatic Bladder Cancer				
Single-agent Taxanes				
Lancet Oncol 2013 14:769	N = 47	Nab-paclitaxel	28% RR	Median OS 10.8 mos
JCO 2011 30:507	N = 70	Docetaxel	11% RR	Median OS 7 mos
Clin Genitourin Cancer 2009 7:E28	N = 45	Paclitaxel	9% RR	Median OS 6.8 mos
JCO 2002 20:937	N = 31	Paclitaxel	10% RR	Median OS 7.2 mos
Single-agent Gemcitabine				
JCO 2007 37:201	N = 44	Gemcitabine	25% RR	Median OS 12.6 mos
Combination Therapy				
Annals of Oncol 2011 22:288	N = 40	Gemcitabine Paclitaxel	38% RR	Median OS 7.8 mos
Eur Urol 2007 52:1115	N = 35	Paclitaxel Carboplatin	32% RR	Median OS 7.9 mos
JCO 2015 GU Symp 33s: Abstract 294	N = 32	Pazopanib Paclitaxel	58% RR	
JCO 2015 GU Symp 33s: Abstract 295	N = 46	Ramucirumab Docetaxel	19.6% RR	

Regulatory History

IND 111,271 for atezolizumab was submitted to the Division of Oncology Products 2 in 2012. A Phase 1 study with multiple extension cohorts was conducted under this IND. After activity was noted in bladder cancer, IND 120,827 was submitted to the Division of Oncology Products 1 in January 2014. Breakthrough therapy status was granted for atezolizumab in the 2nd-line treatment of urothelial cancer on May 22, 2014 based on confirmed responses in 9/19 patients (response duration 2.9+ to 7.5+ months) with metastatic bladder cancer who had received prior platinum-based therapy. All patients had strong staining, using a prototype assay, for PD-L1 in their tumor infiltrating cells. Following Breakthrough Designation, the Applicant met with the Agency on several occasions to discuss a single-arm Phase 2 trial and two randomized Phase 3 trials. Meetings have included a multidisciplinary post-Breakthrough Designation meeting, 2 pre-BLA meetings, 2 meetings to discuss CMC issues, and a Type A meeting.

3. CMC/Device

Atezolizumab Manufacture

Atezolizumab is an IgG1 monoclonal antibody produced in Chinese hamster ovary cells. (b) (4)

(b) (4) Excipients include L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injection. The product is (b) (4) including sterile filtration, and filled into a glass vial with a rubber stopper. Stability data is available up to 24 months with storage at 2-8^{0}C.

Inspection of the drug substance facility was conducted in (b) (4) There was one finding (b) (4) The inspection recommendation was Voluntary Action Indicated. A waiver has been issued for inspection of the drug product facility.

Complementary Diagnostic

An assay for the assessment of PD-L1 staining of cells within the tumor area was submitted to CDRH by Ventana. This assay uses a rabbit anti-PD-L1 antibody clone, SP142, and is for use with formalin-fixed, paraffin-embedded tissue. (b) (4) The assay was analytically validated to use a cutoff of 5%. That is, if ≥ 5% of tumor-infiltrating cells stain for PD-L1, the specimen is considered PD-L1 positive. Likewise, is staining is < 5%, the specimen is considered PD-L1 negative. Both positive and negative controls are used during staining. In developing the assay, differences between readers and between laboratories were assessed and found to be acceptable.

The table below provides the percentage of tumor infiltrating cells at each level of immunohistochemical (IHC) positivity. This approach was used by the Applicant and is used in this review, but is not a component of the approved test. The test will be approved to distinguish between ≥ 5% (immune cell IHC 2/3) and < 5% (immune cell IHC 0/1).

Table 2: IHC Positivity and Percentage Immune Cell Staining	
Immune Cell Immunohistochemistry Status	Percentage of Cells with PD-L1 Staining in the Tumor Area
0	< 1%
1	1 to < 5%
2	5 to < 10%
3	≥ 10%

4. Nonclinical Pharmacology/Toxicology

Nonclinical toxicology studies were conducted in Cynomolgus monkeys at doses of atezolizumab up to 50 mg/kg. At lower doses (5 mg/kg), anti-therapeutic antibodies interfered with the pharmacokinetics of atezolizumab. A periarteritis was seen in monkeys along with irregular menses. The effect on menses was reversible. In mice, vacuolization was seen in the sciatic nerve.

PD-1 is important in fetal tolerance and it is thought that an anti-PD-L1 antibody would lead to fetal loss. Embryo-fetal toxicology studies were not conducted.

PD-1 knockout mice are susceptible to mycobacterium. This is relevant to the current application since 1 patient who had receive a BCG vaccine for bladder cancer developed a retroperitoneal abscess containing mycobacterium tuberculosis complex. Of concern, many patients with bladder cancer would have received BCG.

5. Clinical Pharmacology/Biopharmaceutics

The Phase 1 study of atezolizumab administered 0.01 to 20 mg/kg with no dose limiting toxicity. In pre-clinical studies, a target trough concentration of 6 μg/mL was active.

In the Phase 1 study, the concentration of atezolizumab was affected by anti-therapeutic antibodies at doses of 0.3-3 mg/kg, but not at higher doses. The incidence of anti-therapeutic antibodies was 42% in Cohort 2 of GO29293. Cohort 2 received 1200 mg of atezolizumab intravenously every 3 weeks. In a 70 kg patient, the 1200 mg corresponds to ~ 17 mg/kg. At this dose level, anti-therapeutic antibodies do not appear to affect the pharmacokinetics of atezolizumab.

The terminal half-life of atezolizumab is 27 days. A steady state level is obtained after 6-9 weeks of dosing with 1200 mg every 3 weeks. The trough concentration at Cycle 1 is 95 μg/mL and 142-143 μg/mL at steady state. There was no relationship between response and trough concentration. Weight, gender, albumin, and tumor burden affect atezolizumab pharmacokinetics, but these differences are not thought to be clinically relevant.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

This application is supported by:

1. GO29293: A Phase II, Multicenter, Single-arm Study of MPDL3280A in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer
2. PCD4989g: A Phase 1, Open-label, Dose Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies

GO29293

This BLA is focused on the efficacy results from patients in Cohort 2 of GO29293. Safety findings from both Cohorts 1 and 2 are discussed.

Eligibility Criteria

1. Metastatic or locally advanced (T4bNany, TanyN2-3) urothelial cancer
    a. Cohort 1: Included treatment-naïve pts with locally advanced/metastatic urothelial cancer who were ineligible for cisplatin.

   b. Cohort 2: Included pts with locally advanced/metastatic urothelial cancer with disease progression during or following at least 1 platinum-containing regimen in the metastatic setting. It also included pts with disease progression within 12 months of their last dose of a neoadjuvant/adjuvant platinum-containing regimen. Performance status of 0-1

3. A prior platinum-containing regimen was defined as ≥ 2 cycles or discontinuation after 1 cycle due to toxicity
4. Measurable disease was required in both cohorts.
5. Tumor samples were required (archival or fresh samples). However, patients could enter regardless of the degree of PD-L1 staining in their tumor samples.
6. Patients with a history of autoimmune disease, except pts with hypothyroidism on thyroid replacement or type 1 diabetes on insulin, were excluded.
7. No systemic immunosuppressive medications within 2 weeks of entry; However, inhaled steroids, physiologic replacement doses of steroids, or acute, low dose steroids were allowed.

Treatment
Atezolizumab 1200 mg IV every 3 weeks

- The 1st dose was given over 1 hr. Subsequent doses could be given over 30 minutes.
- Pts with progression by RECIST could continue atezolizumab if they had no signs/symptoms of unequivocal progression, no decrease in performance status, no tumor growth at critical sites, and evidence of clinical benefit per investigator.
- Investigators and the Applicant were blinded to PD-L1 status.

Dose Modification: The dose was not reduced, but could be held. If atezolizumab was held for > 42 days, pts were to discontinue study drug. An exception was made for pts on a prolonged steroid taper.

- Atezolizumab was permanently discontinued for a grade 4 immune-mediated event.
- Atezolizumab was held for grade 2-3 colitis, grade 3 AST/ALT, concurrent AST/ALT and bilirubin elevation, grade 3 rash, symptomatic thyroid disease, grade 2-3 pneumonitis, grade 4 amylase, symptomatic pancreatitis, and symptomatic eye toxicity.
- Steroids were given for grade 3-4 and recurrent grade 2 toxicity.

Monitoring

- Routine laboratories at baseline and each cycle; Urinalysis at baseline and every other cycle
- TSH and free T4 at baseline and end of study; Auto-immunity panel at baseline and each cycle; T, B, and NK cells at baseline and throughout the study
- Pulse oximetry at baseline and each cycle; ECGs at baseline
- Anti-atezolizumab antibodies at baseline, Cycles 2-4, Cycle 8, discontinuation, and 120 d post-discontinuation.
- Tumor biopsies were to be obtained at progression.
- Adverse events were collected up to 30 days after the last dose of study drug.

Tumor assessments were done every 9 weeks x 54 weeks then every 12 weeks.

Statistical Plan

Primary Analysis:

1. The Applicant defined two primary endpoints: response rate, by RECIST v1.1, as assessed by independent review (IRC) and response rate, by Modified RECIST, as assessed by the Investigator (INV).
2. Response rate was assessed in response-evaluable pts which was defined as all patients with measurable disease who had received atezolizumab. Several IHC defined population were tested in a hierarchical order.
3. In each IHC defined population, RECIST response rate by IRC was tested followed by response rate by INV using Modified RECIST. Each of these was tested against a "control" response rate of 10% using an exact binomial test.

Modified RECIST:

- New lesions were not considered progression and were added to the sum of the longest diameters.
- Changes in the non-target lesions were not considered in the assessment of progression.
- Radiographic progression was defined as a $\geq$ 20% increase in the sum of the longest diameters, but had to be confirmed.

Sample Size: The sample size was based on a projected response rate of 40% in patients who were IHC 2/3. The Applicant's interim analysis for futility was such that the study was unlikely to be stopped for futility.

Secondary Analyses: These included duration of response, PFS and OS. Duration of response was defined as the time from initial response to progression or death. The median duration of response was estimated using the Kaplan-Meier method and 95% confidence intervals (CIs) were obtained using the Brookmeyer and Crowley method. Time to response was considered an exploratory endpoint.

PCD4989g

Patients with urothelial cancer were included in an expansion cohort.

Eligibility Criteria

1. Locally advanced or metastatic urothelial cancer that had progressed since the last therapy and for which no standard curative therapy exists.
2. Archival or fresh tumor specimen available. The study initially required IHC 2/3 tumor-infiltrating cell staining for PD-L1. The criteria then changed to include pts regardless of PD-L1 status and later changed back to IHC 2/3 staining for PD-L1.
3. Performance status 0-1
4. Measurable disease
5. No history of autoimmune disease except hypothyroidism on replacement therapy, type 1 diabetes on insulin, or skin disease that was controlled with steroid creams.
6. No systemic immunosuppressive medications except acute, low dose steroids, inhaled steroids, or physiologic steroid replacement.

Treatment
Atezolizumab 15 mg/kg, 20 mg/kg, or 1200 mg IV every 3 weeks

- The 1st dose was given over 1 hr with subsequent doses over 30 mins if tolerated.
- Both the Phase 1 and Phase 3 formulations of atezolizumab were used. There was a difference (b) (4) in these 2 formulations.
- Patients with RECIST progression could continue atezolizumab if they had evidence of clinical benefit, no signs/symptoms of unequivocal progression, no decline in performance status, and no tumor progression at critical sites. Patients with underlying tumors in which additional treatment options were available had to provide written consent to continue dosing.

Dose Modification: Atezolizumab could be held, but not dose reduced. Treatment could be held up to 84 days (longer for steroid taper) prior to discontinuation.

Monitoring:
- CBC and chemistries at baseline, each cycle, and end of study; Urinalysis at baseline, every other cycle, and end of study
- TSH and free T4 at baseline and end of study; Autoimmunity panel at baseline and each cycle; T, B, and NK cells at baseline and throughout the study
- Anti-therapeutic antibodies at baseline, Cycles 2-5, 7, Cycle 8, Cycle 16, discontinuation, and up to 120 d post-discontinuation.
- ECGs at baseline, Cycle 4, and treatment discontinuation

Tumor assessments were done every 6 weeks x 24 weeks then every 12 weeks.

Statistical Plan
The protocol was amended to enter patients with urothelial cancer in August 2012. A statistical analysis plan for the urothelial cancer pts entered on this study was finalized in June 2015. This plan assessed the confirmed response rate as determined by an IRC using RECIST v1.1. Response was to be assessed in all pts with measurable disease who had at least 12 weeks of follow up. Best overall response, objective response rate, duration of response, and time to initial response were also evaluated in all patients and by PD-L1 status. Objective response rate and duration of response by IRC using RECIST v1.1 were additional endpoints.

Disposition

G029293 was conducted at 70 centers beginning in May 2014. It entered its last patient in March 2015. The table below provides information on the patient disposition in Cohort 2. Note that in the disposition dataset 13 pts discontinued due to an adverse event while in the adverse event dataset, 11 pts discontinued due to an adverse event. Among the patients who discontinued due to an adverse event in the 2 datasets, 5 do not overlap.

PCD4989g was conducted at 20 centers beginning in June 2011. The protocol was amended to enter patients with urothelial cancer in August 2012. Enrollment is ongoing. In this study,

only 1 pt discontinued due to an adverse event in the disposition dataset while in the adverse event dataset, 11 pts discontinued due to an adverse event.

Table 3: Patient Disposition		
	GO29293	PCD4989g
Enrolled and Treated	310	94
Remain On Study	59 (19%)	26 (28%)
Discontinued Study Drug	251 (81%)	68 (72%)
Disease Progression	216	60
Death	2	1
Adverse Reaction	13	1
Withdrawal	9	2
Other[1]	20	6
[1]Includes patient or investigator decision, non-compliance, and lost to follow up	Data Cutoff: 11-2015	Data Cutoff: 8-2015

Demographics and Baseline Characteristics

In the Cohort 2 of the Phase 2 study G029293, the median age was 66 years (range; 32-91), 78% were male, and 91% of patients were White. Sixty-one (61%) percent of patients had a treatment free interval > 3 months prior to study entry. This suggests, by the pace of their disease, that these were good prognosis patients despite their Bellmunt scores. Bellmunt risk scores were derived from an analysis of the Phase 3 vinflunine study. Risk factors include performance status ≥ 1, the presence of liver metastases, and hemoglobin < 10 g/dL. One point is assigned for each and scores are 0 to 3 with a worsening prognosis with an increasing score.

In the urothelial cancer patients in the Phase 1 study, the median age was 66 years (range; 36-89), 76% were male, and 79% of patients were White. Treatment free interval was not recorded. Based on their Bellmunt scores, this study appears to have enrolled a good prognostic group. The primary differences between the patients enrolled on the Phase 1 and the Phase 2 study are in the number of prior regimens for metastatic disease, prior nephrectomy/cystectomy, prior neoadjuvant or adjuvant therapy, and in their Bellmunt scores.

Table 4: Baseline Disease Characteristics		
	G029293 N = 310	PCD4989g N = 94
Performance Status		
0	117 (38%)	37 (39%)
1	193 (62%)	57 (61%)
Bellmunt Risk Score		
0	83 (27%)	33 (35%)
1	117 (38%)	44 (47%)
2	89 (29%)	16 (17%)
3	21 (7%)	1 (1%)
PD-L1 Immune Cells		
IHC 0	103 (33%)	18 (19%)
IHC 1	107 (35%)	30 (32%)
IHC 2	100 (32%)	17 (18%)
IHC 3	0	4 (4%)
Unknown	0	25 (27%)
Primary Site		
Bladder	230 (74%)	75 (80%)
Non-bladder	80 (26%)	19 (20%)
Extent of Disease		
Metastatic	290 (94%)	94 (100%)
Locally Advanced	20 (6%)	0
Median Sum of the Longest Diameter (range)	6.4 cm (2.0-36.4)	5.3 cm (1.2-22.3)
Sites of Disease		
Liver	96 (31%)	31 (33%)
Lung	135 (44%)	46 (49%)
Prior Neoadjuvant/Adjuvant Therapy	59 (19%)	44 (47%)
Number of Prior Regimens for Metastatic Disease		
0	0	18 (19%)
1	182 (59%)	6 (6%)
> 1	128 (41%)	70 (74%)
Prior Therapy		
Cis-platinum	227 (73%)	72 (77%)
Carboplatin	80 (26%)	36 (38%)
Other	3 (1%)	2 (2%)
Prior Cystectomy/Nephrectomy	116 (37%)	65 (69%)

[1]Using the to-be-marketed assay

In the urothelial cancer cohort of the Phase 1 study, PD-L1 status was initially determined using a prototype assay. Patients with sufficient specimen remaining were retrospectively tested with the to-be-marketing device. The table below provides information on the correlation between the 2 assays. The to-be-marketed assay appears to be more likely to label specimens 0/1 than the prototype assay.

Table 5: Comparison of To-Be-Marketed and Prototype PD-L1 Assays			
	To-Be-Marketed Assay		
Prototype Assay	IHC 0/1	IHC 2/3	Unknown
IHC 0/1	31	2	11
IHC 2/3	17	19	14

Primary Endpoint

The independent review (IRC)-assessed confirmed response rates by RECIST and their 95% confidence intervals are shown in the table below. These analyses were conducted in all treated patients, in patients whose tumor-infiltrating cells had ≥ 5% staining for PD-L1 and in patients who tumor-infiltrating cells had < 5% staining for PD-L1. PD-L1 staining is based on the to-be-marketed assay. The overall response rate was 14.8%. The median duration of response had not been reached at the time of data cutoff. Thirty-seven (37) pts had an ongoing response of at least 6 months and 6 had an ongoing response of at least 12 months.

Response was more common in the PD-L1 positive (≥ 5% staining) subgroup, but was also seen in the patients whose tumor-infiltrating cells were PD-L1 negative (< 5% staining). It is unclear whether PD-L1 status is a prognostic factor for response. The table below uses the to-be-marketing assay. A number of pts on the Phase 1 study did not have tumor specimens available for staining with this assay. The response rate among these pts was 28% and the median duration of response 17.5 months. Finally, response rate, by tumor staining for PD-L1 (rather than infiltrating cell staining), was examined as an exploratory endpoint. The assay for tumor cell staining has not been validated for urothelial cancer. Here, the response rate did not change with the degree of tumor staining. Response rate was 14.5% if the tumor cells were IHC 0, 13.6% if IHC 1+, 17.9% if 2+, and 16.7% if 3+ by IHC.

The median time to response was 2.1 months in Cohort 2 of GO29293 and 1.4 months in the Phase 1 study PCD4989g. This represents the time to first assessment, 9 weeks for Cohort 2 and 6 weeks for the Phase 1 study. As in most studies, the disease burden in the responders was lower than that of the population as a whole. In Cohort 2, the median SLD was 6.4 cm in all pts and 4.3 cm in responders. Likewise in the urothelial cell cohort of PCD4989g, the median SLD in all pts was 5.3 cm and 4.1 cm in responders. Further, among 45 of the 46 responders in Cohort 2, 13/45 had lymph node only disease (includes target and non-target). In the Phase 1 study, 9/24 responders had lymph node only disease.

Table 6: Primary Analysis		
	G029293	PCD4989g
All Patients	N = 310	N = 94
Response Rate (95% CI)	14.8% (11.1, 19.3)	25.5% (17.1, 35.6)
Complete Response	17	9
Partial Response	29	15
Median Duration of Response	NE (2.1+, 13.8+ mos)	NE (2.9, 24+ mos)
Immune Cell PD-L1 < 5%	N = 210	N = 48
Response Rate (95% CI)	9.5% (5.9, 14.3)	20.8% (10.5, 35.0)
Median Duration of Response	12.7 mos (2.1+, 12.7)	NE (2.9, 21.4+)
Immune Cell PD-L1 ≥ 5%	N = 100	N = 21
Response Rate (95% CI)	26% (17.7, 35.7)	33.3% (14.6, 57.0)
Median Duration of Response	NE (4.2, 13.8+ mos)	NE (9.2, 24+mos)
	Data Cutoff: 11-2015	Data Cutoff: 8-2015

In Cohort 2 of GO29293, the secondary endpoint Investigator (INV)-determined confirmed response rate using RECIST was 16.1% in all pts, 11.9% in the PD-L1 < 5% subgroup, and 25.0% in the PD-L1 ≥ subgroup. Examination of the discordance between IRC and INV-determined response using RECIST is shown in the table below. The INV and IRC disagreed on the response status in 18 of 310 patients.

Table 7: Cohort 2 of GO29293: INV and IRC-determined Response by RECIST			
	IRC RECIST		
INV RECIST	Responder	Non-responder	Total
Responder	39	11	50
Non-responder	7	253	260
Total	46	264	310

The Applicant's primary endpoint, INV-determined confirmed response rate using modified RECIST, was 19.4% in all patients, 14.8% in the PD-L1 < 5% subgroup, and 29.0% in the PD-L1 ≥ 5% subgroup. Differences between INV-determined RECIST and INV-determined Modified RECIST response are shown in the table below. Here, 10 pts who were responders by Modified RECIST were considered non-responders by RECIST.

Table 8: Cohort 2 GO29293: INV-determined Response by RECIST and Modified RECIST		
	INV RECIST	
INV Modified RECIST	Responder	Non-responder
Responder	50	10
Non-responder	0	200

Subgroup Analyses

Subgroup analyses of Cohort 2 of GO29293 found that the response rate in patients who had received prior neoadjuvant/adjuvant therapy and relapsed within 12 months was 22%. This response rate is surprising because this is, in general, thought to be a poor prognostic group.

The response rate among patients whose urothelial cancer did not arise in the bladder was 7.5%. Finally, in US patients the response rate was 13.3% in Cohort 2 of GO29293 and 32.7% in the urothelial cancer patients enrolled in the Phase 1 study.

Secondary Endpoints

In Cohort 2 of GO29293, median progression-free survival was 2.1 months, regardless of PD-L1 IHC score in tumor-infiltrating cells. In Cohort 2, median overall survival was 7.9 months in all patients. Overall survival was 6.5 months in patients whose tumor-infiltrating cells were IHC 0, 6.7 months in IHC 1+, and 11.9 months in patients with IHC 2+ staining. Progression-free and overall survival are uninterpretable in this single arm study, but it is of concern that overall survival is similar to that seen in patients treated with chemotherapy in this disease setting.

In the urothelial cancer patients on PCD4989g, median progression-free survival was 1.8 months in all patients, 1.6 months in patients whose tumor-infiltrating cells were IHC 0/1, and 2.7 months with IHC 2/3 staining. Median overall survival was 10.6 months in all patients, 9.9 months with IHC 0/1 and 11.2 months with IHC 2/3 staining. Again, PFS and OS are uninterpretable in this single arm study, but it is of concern that survival is similar to that seen in patients treated with chemotherapy in this disease setting.

8. Safety

Safety Database

The safety review primarily focuses on the 310 patients in Cohort 2 of GO29293, but also includes analyses of adverse events that are thought to be immune-mediated from:

1. Patients with treatment-naïve urothelial cancer on Cohort 1 of GO29293, N = 119
2. Patients with urothelial cancer from PCD4989g, N = 94
3. Patients with non-urothelial cancers from PCD4989g, N = 517
4. Patients with non-small cell lung cancer in FIR, N = 137
5. Patients with non-small cell lung cancer in POPLAR, N =142.

The data cutoff for Cohort 2 of GO29293 is May 2015. The Applicant did not provide data with a later cutoff in the Safety Update. In Cohort 2, adverse events were collected up to 30 days after the last dose of atezolizumab.

Exposure

The median duration of dosing was 12.3 weeks with 20% of patients required dose delay or interruption. While the exposure dataset contains 62 pts with dose delay or interruption, the adverse event dataset list 83 pts as experiencing an adverse event leading to dose interruption. In the adverse event dataset, the most common reasons for dose interruption (>1%) were increase in liver-related laboratories, urinary tract infection, diarrhea, fatigue, confusional state, urinary tract obstruction, pyrexia, dyspnea, and pneumonitis.

Table 9: Atezolizumab Exposure in Cohort 2 GO29293	
	GO29293 Cohort 2 N = 310
Median Treatment Duration (range)	12.3 weeks (0.1-46)
Median Number of Doses (range)	5 (1-6)
Dose Omitted or Delayed	62 (20%)

Data Cutoff: May 2015

In the Safety Update, no adverse event information is available for patients in Cohort 2 who received atezolizumab > 1 year. In the safety database, 21 pts with bladder cancer and 138 pts in total received atezolizumab > 1 year.

Overview of Adverse Events

The table below differs in several ways from the primary review. This table includes only deaths due to adverse events that occurred within 30 days of the last dose of study drug. It also includes only grade 1-4 adverse events leading to discontinuation. This table also provides the incidence of immune-mediated adverse events. These are adverse events that were thought to be immune-mediated and that were treated with steroids.

Table 10: Overview of Adverse Events	
	Cohort 2 GO29293 N = 310
Deaths due to AE within 30 Days[1]	3 (1%)
Discontinuations	10 (3%)
Serious Adverse Events	141 (45%)
Grade 3-4 Adverse Events	154 (50%)
Immune-mediated AEs	20 (6%)

Data Cutoff: May 2015

- Deaths due to adverse events within 30 days of atezolizumab included sepsis, pneumonitis, and intestinal obstruction.
- Grade 1-4 adverse events leading to permanent discontinuations included acute/chronic renal insufficiency, fatigue, foot infection, opiate toxicity, PRES, pruritus, pulmonary sepsis, retroperitoneal hemorrhage, and sepsis.
- Serious adverse events in > 3% of patients included urinary tract infection, hematuria, acute kidney injury, and intestinal obstruction.
- Grade 3-4 adverse events in > 2% of patients included urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.
- Grade 1-4 adverse events in > 20% of patients included fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation.

Significant Adverse Events

Pneumonitis: The incidence of pneumonitis in Cohort 2 of GO29293 was 2%, 0.6% grade 3-4. There was 1 death and 1 patient permanently discontinued atezolizumab. The median day of onset was Day 81. Among the 6 pts in Cohort 2, 5 received corticosteroids and 3 of these recovered. In the safety database, the incidence of pneumonitis was 2.6%, 0.8% grade 3-4.

Hepatitis**:** The incidence of grouped terms for hepatic adverse events in Cohort 2 was 13%, 3% grade 3-4. Ten of these 27 pts had liver metastases at baseline. No pt died and none permanently discontinued due to immune-mediated hepatitis. The median day of onset was Day 26. Three pts received corticosteroids for immune-mediated hepatitis. All were able to continue atezolizumab during the event (1 pt) or resume atezolizumab (2 pts). The incidence of grade 3-4 laboratory abnormalities in Cohort 2 was ALT 2%, AST 2.4%, and bilirubin 1.3%. The table below provides adverse events, including laboratories reported as AEs.

In the safety database, the incidence of grouped terms for hepatic adverse events was 10%, 4% grade 3-4. There was 1 pt with increasing liver enzymes 42 d after the last dose of atezolizumab who was treated with prednisone.

Table 11: Grade 1-4 Hepatic Adverse Events

	Cohort 2 N = 310		Safety Database N = 1978	
Adverse Events	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any	27 (13%)	10 (3%)	200 (10%)	70 (4%)
Increased ALT	12	3	97	27
Increased AST	13	2	105	28
Increased Bilirubin/Hyperbilirubinemia	7	2	36	16
Increased AKP	10	4	57	14
Increased GGT	1	0	22	11
Transaminases/Hepatic Enzymes Increased	3	1	13	3
Hepatitis	1	1	2	1
Autoimmune Hepatitis	1	1	4	4
Drug-Induced Liver Injury	0	0	1	0
Hepatic Function Abnormal	0	0	3	0
Hepatocellular Injury	0	0	4	1
Jaundice[1]	0	0	6	0
Liver Disorder			1	1
Liver Function Test Abnormal			7	3

[1]Only includes jaundice in pts who did not report gall stones

Diarrhea: The incidence of diarrhea in Cohort 2 was 19%, 2% grade 3-4. There were no deaths or permanent discontinuations due to diarrhea and no pts received corticosteroids. In the safety database, the incidence of diarrhea was 20%, 2% grade 3-4. Also in the safety database, there was 1 death due to diarrhea and associated renal failure. Four pts received corticosteroids and among these 4, 1 patient died and 3 had resolution of their diarrhea.

Endocrine Disorders

Hypophysitis: Hypophysitis was not reported in Cohort 2. In the safety database, there was 1 report of an inflammatory lesion in the hypothalamus that was treated with dexamethasone. The pt was said to have pituitary deficiency, but detailed information was not provided.

Thyroid Disease: The incidence of hypothyroidism is Cohort 2 was 2%, 0.3% grade 3. There were no deaths or permanent discontinuations. In Cohorts 1 and 2 of GO29293, 3% of pts had a laboratory TSH > 3x ULN and 2% had a TSH > 10xULN. Hyperthyroidism was not reported in Cohort 2. In the safety database, the incidence of hypothyroidism was 4%, 0.2% grade 3. Hyperthyroidism was reported in 0.5% of patients in the safety database, all grade 1-2.

Adrenal Insufficiency: Adrenal insufficiency was not reported in Cohort 2. In the safety database, adrenal insufficiency occurred in 0.4% of patients, 0.1% grade 3.

Diabetes: New onset diabetes without an alternative etiology was not seen in Cohort 2. In the safety database, 0.4% of pts developed immune-mediated diabetes. Two of these pts had anti-GAD65 antibodies.

Pancreatitis: Acute pancreatitis was not reported in Cohort 2. In the safety database, the incidence of acute pancreatitis was 0.1%, both grade 3. Both patients received steroids and permanently discontinued atezolizumab. The event resolved in 1 pt and was ongoing at data cutoff in the 2nd pt.

Neurological Disorders

Meningitis/Encephalitis: Meningitis or encephalitis was not reported in Cohort 2. In the safety database, 1 case of meningitis, possibly immune-mediated, was reported. This pt developed mental status changes and fever after 1 dose of atezolizumab. Elevated protein and lymphocytes were found in the CSF, but cultures were negative. He did not receive steroids. Antibiotics were given for concurrent pneumonia. He resumed atezolizumab without recurrence.

Guillain-Barre Syndrome: No pts in Cohort 2 developed this syndrome. In the safety database, 1 pt with non-small cell lung cancer developed Guillain-Barre Syndrome. This began as peripheral motor neuropathy followed by incontinence and peripheral sensory neuropathy. Lumbar puncture found an elevated protein and IgG. She had concurrent elevation in liver enzymes and hyperthyroidism. Atezolizumab was permanently discontinued and the event resolved after treatment with intravenous immunoglobulin.

Posterior Reversible Encephalopathy Syndrome (PRES): PRES was reported in 1 pt in Cohort 2. This pt experienced fainting seizures, and loss of consciousness. MRI diagnosed PRES and found a small brain metastasis. Atezolizumab was permanently discontinued.

Myasthenia Gravis: No patients in Cohort 2 developed a myasthenic syndrome. In the safety database, 1 pt with renal cell cancer developed myasthenia gravis after 2 doses of

atezolizumab. This began as blurred vision that was found to be gaze palsy. Laboratories were positive for acetylcholine receptor binding and modulating antibodies. He was treated with prednisone and atezolizumab was permanently discontinued. The symptoms improved, but did not resolve with an increase in prednisone.

Neuropathy: Neuropathy was seen in pre-clinical studies of atezolizumab and has been reported with PD-1 inhibitors. In Cohort 2, the incidence of grouped terms for neuropathy (hypoesthemia, peripheral neuropathy, paresthesia, peripheral sensory neuropathy) was 5%. All were grade 1-2. Among these 15 pts, 14 had received prior cisplatin.

In the safety database, 9% of pts reported adverse events included in a groupted term, neuropathy. Grade 3 events occurred in 0.4% of pts. One pt with RLE monoparesis after 1 dose of atezolizumab had a negative MRI of the spine and brain and responded to steroids.

Eye Disorders: No pts in Cohort 2 developed an eye disorder of concern. In the safety database, 6 pts developed the following: optic neuritis (1), uveitis (1), episcleritis (1), and keratitis (3). Details are unclear for the pt with optic neuritis, uveitis, and 2 of the pts with keratitis. Episcleritis also occurred after 1 dose of atezolizumab and was treated with steroid eyedrops with resolution. One pt with ulcerative keratitis was treated with steroid and antibiotic eye drops.

Musculoskeletal Disorders: In Cohort 2, one pt reported grade 3 arthralgia of the wrists, elbows, and shoulders. He was treated with steroids and atezolizumab was discontinued. In the safety database, one pt developed polymyalgia rheumatic which responded to steroids. This pt remained on atezolizumab. A 2nd pt received steroids for autoimmune arthritis and discontinued atezolizumab.

Rash: In Cohort 2, rash (combined terms) was reported in 15% of patients, 0.3% grade 3 (1 pt). Grade 3 rash was treated with oral steroids. This pt had underlying diabetes and developed cellulitis of the foot with ulceration and necrosis. Atezolizumab was permanently discontinued due to this infection. Rash remained unresolved at the time of death due to disease progression. In the safety database, the incidence of rash (combined terms) was 15%, 0.7 % grade 3.

Infection: A high incidence of infection, particularly urinary tract infections was noted in Cohort 2. Overall, infections occurred in 37% of pts in Cohort 2, 15% grade 3-4. Of concern, 1 pt in Cohort 2 had encephalopathy and non-encapsulated yeast in the CSF. A 2nd pt had an abscess which grew mycobacterium and possible osteomyelitis. In the safety database, the incidence of infection was 38%, 10% grade 3-4. Importantly, in a randomized trial in pts with lung cancer, infections occurred in 42% of pts on atezolizumab and in 33% of pts on docetaxel. Infections of concern in the safety database include herpetic meningoencephalitis (1 pt), actinomycosis (1 pt), coccidioidomycosis (1), and disseminated zoster (1). There are several other reports in which insufficient information is available.

Infusion Reactions: In Cohort 2, the incidence of infusion-related reactions was 3%. All events were grade 1-2. In the safety database, infusion-related reactions occurred in 1% of pts,

0.02% grade 3. Both of these analyses are limited to the preferred term infusion-related reaction. In the safety database, events which occurred during or within 24 hours of infusion and were suggestive of an infusion-related event were examined. These included cytokine release syndrome (1 pt), facial edema (1), flushing (8), hypersensitivity (12), urticaria (4), and wheezing (2). Adverse events such as, dyspnea and fever were only examined if they occurred during the infusion. Since adverse events such as dyspnea may be related to other processes, it was thought that limiting the analysis to events that occurred during infusion may help to isolate adverse events which were infusion-related. During the infusion, dyspnea occurred in 3 pts, chills in 5 pts, hypotension in 2 pts, pyrexia in 7 pts, and tachycardia in 1 pt. When all these events are considered, the incidence is 2.8%, 0.2% grade 3.

Laboratories
Grade 3-4 laboratory abnormalities in Cohort 2 of GO29293 are shown in the table below. The only grade 3-4 hematological toxicities that occurred in ≥ 2% of pts were lymphopenia and anemia. Grade 3-4 hyponatremia occurred in 10% of pts. Hyponatremia was examined for concurrent hyperkalemia (and possible adrenal insufficiency). No association could be found. Hyperglycemia and hyperglycemia are discussed under the significant adverse events.

Table 12: Grade 3-4 Laboratory Abnormalities in ≥ 2% of Patients

	Cohort 2 GO29293 N = 310
Lymphopenia	11%
Hyponatremia	10%
Anemia	6%
Increase Alkaline Phosphatase	5%
Hyperglycemia	5%
Increased Alanine Aminotransferase	2%
Increased Aspartate Aminotransferase	2%
Hypoalbuminemia	2%

Data Cutoff: May 2015

QT Prolongation: QTc prolongation was not detected with increasing doses of atezolizumab on the Phase 1 study.

Immunogenicity
The incidence of anti-therapeutic antibodies was 41% in pts on Cohort 2. This assay can detect 500 ng/mL of anti-therapeutic antibody in the presence of 200 μg/mL atezolizumab. An increased incidence of anti-therapeutic antibodies may be expected in a biologic that is thought to "activate" the immune system (although admittedly the T cell system). It is unknown whether neutralizing antibodies occurred. The Applicant will be asked to develop a sensitive assay for neutralizing antibodies as a postmarketing requirement. Anti-therapeutic antibodies did not affect atezolizumab exposure.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held.

10. Pediatrics

A pediatric waiver has been granted.

11. Other Relevant Regulatory Issues

Inspections of the clinical sites were all considered No Action Indicated or Voluntary Action Indicated. However, the Office of Scientific Investigations notified the review team that they found during their inspection of Memorial Sloan Kettering Cancer Center, adverse events (AEs) in the source documents and electronic case report forms that had occurred long before the cutoff date but were not included in their list of AEs for that site. The Applicant was informed and asked to investigate the extent to which AEs had been omitted from the datasets. The Applicant compared their original data sweep with a September 2015 data sweep for AEs. Both data sweeps used the May 2015 cutoff. The Applicant found 242 AEs that occurred prior to May 2015 and were put into the datasets between their initial and their September 2015 data sweep. The Applicant stated that these AES were entered into the electronic case report forms between these two data sweeps. The Applicant stated that this was the reason the inspectors found these AEs in the electronic case report forms, but not in the datasets. These 242 AEs involved 46 pts. Most sites had only a few AEs that were entered late (1-15 AEs). There were 172 AEs that were entered late at Memorial. That is, the problem appeared primarily at a single site that had been inspected. Note that the Applicant's method of assessment does not account for AEs that were not entered into the datasets by the September 2015 data sweep. The Applicant stated that they were aware of problems at Memorial earlier in the study and that this site had been audited. It is unclear why this remained a problem. The Applicant also provided a list of grade 3-4 AEs that had been omitted from the dataset. The omitted AEs were carefully examined by the review team and it was decided that these would not impact the conclusions concerning the safety profile of atezolizumab.

12. Labeling

Please see final package insert.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: **Approval**

- Risk Benefit Assessment

Benefit

  - Atezolizumab demonstrated a response rate of 14.8% in all patients with metastatic/locally advanced bladder cancer who had received prior platinum-based therapy. The median duration of response was not reached, but was 2.1+ to 13.8+ months.
  - In patients whose tumor-infiltrating cells stain IHC 2/3 for PD-L1, the response rate was 26%. The response rate in patients whose tumor-infiltrating cells stain IHC 0/1 for PD-L1 was 9.5%. At present, testing for PD-L1 in tumor-infiltrating cells is not able to distinguish responders from non-responders and atezolizumab will be approved along with a complementary diagnostic (optional use) for PD-L1 testing. Whether PD-L1 staining is a prognostic

factor in patients with metastatic urothelial cancer cannot be determined in this single-arm study.
- No therapies are approved for use in this patient population in the US. While several agents are available, their response rates are low and they are associated with considerable toxicity.

Risk

- The adverse event profile of atezolizumab is acceptable. Deaths due to an adverse event within 30 days of atezolizumab occurred in 1% of patients while 3% discontinued atezolizumab due to an adverse event. Grade 3-4 adverse events were reported in 50% of patients. This is consistent with, or lower than the incidence of grade 3-4 adverse events that have been seen with other oncology drugs/biologics.
- Adverse events that were likely to be immune-mediated and were treated with corticosteroids occurred in 6% of patients.
- Grade 1-4 adverse events in > 20% of patients included fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation.

Conclusion

- While the number of responders is small, the responses are durable and the adverse event profile appears to be improved when compared, across studies, to available agents used off-label in this patient population.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Requirements

The following have been agreed to with the Applicant.

Postmarketing Requirements

- Conduct "GO29294: A Phase III, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared with Chemotherapy in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer After Failure with Platinum-containing Chemotherapy" and provide a study report, datasets, and, if appropriate, revised labeling.

  Final Protocol Submission Date: September 12, 2014
  Study/Clinical Trial Completion Date: September 30, 2017
  Final Study Report Submission Date: December 31, 2017

- Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clinical thyroid disease. Submit the completed report, datasets, and revised labeling.

  Final protocol Submission Date: May 31, 2016
  Study/Clinical Trial Completion Date: August 31, 2020
  Final Report Submission Date: February 28, 2021

- Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that

are expected to be present in samples at the time of patient sampling.

Final protocol Submission Date: N/A
Study/Clinical Trial Completion Date: N/A
Final Report Submission Date: June 30, 2018

Postmarketing Commitments

- Submit the median duration of response for all patients, IHC 2/3, and IHC 0/1 patients who responded to atezolizumab on GO29293. Submit datasets and revised labeling concerning the median duration of response.

  Final protocol Submission Date: N/A
  Study/Clinical Trial Completion Date: September 30, 2016
  Final Report Submission Date: December 31, 2016

- Perform supplemental characterization of the Master Cell Bank to provide additional assurance that the cell bank was [redacted] (b) (4) These data should include the evaluation [redacted] (b) (4) analysis with respect to growth characteristics and product quality.

  Final protocol Submission Date: N/A
  Study/Clinical Trial Completion Date: N/A
  Final Report Submission Date: June 30, 2017

- Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g., KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate time-points.

  Final protocol Submission Date: November 30, 2016
  Study/Clinical Trial Completion Date: July 31, 2017
  Final Report Submission Date: January 31, 2018

- Recommended Comments to Applicant

Please see approval letter.

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

/s/

VIRGINIA E MAHER
05/03/2016