

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761034Orig1s000**

**MEDICAL REVIEW(S) / STATISTICAL  
REVIEW(S)**

### CLINICAL and STATISTICAL REVIEWS

<b>Application Type</b>	BLA 505 (b) (1)
<b>Application Number(s)</b>	761034
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<b>Division/Office</b>	DOP1/OHOP/OND/CDER
<b>Reviewer Name(s)</b>	Efficacy Review: Yang-Min (Max) Ning, MD, PhD Safety Review: Daniel Suzman, MD Statistical Review: Lijun Zhang, PhD
<b>Review Completion Date</b>	April 21, 2016
<b>Established Name</b>	Atezolizumab
<b>(Proposed) Trade Name</b>	TENCENTRIQ
<b>Applicant</b>	Genentech, Inc.
<b>Formulation(s)</b>	Injection for intravenous administration 1200 mg/20 mL (60 mg/mL), single-dose vials
<b>Dosing Regimen</b>	1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks
<b>Applicant Proposed Indication(s)/Population(s)</b>	<p><i>“Tecentriq is a humanized programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:</i></p> <ul style="list-style-type: none"> <li><i>locally advanced or metastatic urothelial carcinoma (b) (4)</i></li> </ul> <p>”</p>
<b>Recommendation on Regulatory Action</b>	Accelerated Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	<p>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 who:</p> <ul style="list-style-type: none"> <li>Have disease progression during or following platinum-containing chemotherapy</li> <li>Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy</li> </ul>

**Disclaimer Statement:** *This combined review contains assessments from individual reviewers based on their best knowledge, interpretation, and analyses of the clinical data submitted to this BLA for atezolizumab. The assessments are in the best interest of patients to their best understandings of study disease, study treatment and relevant sciences. Different views and writing styles may exist among individual reviewers. Finally, the reviewers’ recommendations do not necessarily reflect the final regulatory recommendation or action on this BLA from the Review Division and Review Office of FDA.*

## Table of Contents

Common Abbreviations Used in the Review .....	10
1 Executive Summary .....	12
1.1. Product Introduction.....	12
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	12
1.3. Benefit-Risk Assessment .....	13
2 Therapeutic Context.....	17
2.1. Analysis of Condition.....	17
2.2. Analysis of Current Treatment Options .....	17
3 Regulatory Background .....	19
3.1. U.S. Regulatory Actions and Marketing History.....	19
3.2. Summary of Presubmission/Submission Regulatory Activity .....	20
3.3. Foreign Regulatory Actions and Marketing History .....	21
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety .....	21
4.1. Office of Scientific Investigations (OSI) .....	21
4.2. Product Quality .....	23
4.3. Clinical Microbiology.....	23
4.4. Nonclinical Pharmacology/Toxicology .....	23
4.5. Clinical Pharmacology .....	23
4.5.1. Mechanism of Action.....	23
4.5.2. Pharmacodynamics.....	23
4.5.3. Pharmacokinetics.....	23
4.6. Devices and Companion Diagnostic Issues .....	23
4.7. Consumer Study Reviews.....	25
5 Sources of Clinical Data and Review Strategy .....	25
5.1. Table of Clinical Studies .....	25
5.2. Review Strategy .....	27
6 Review of Relevant Individual Trials Used to Support Efficacy .....	27

6.1.	Studies Supporting the BLA.....	27
6.1.1.	Study Design .....	27
6.1.2.	Study Results .....	36
7	Integrated Review of Effectiveness.....	59
7.1.	Assessment of Efficacy Across Trials .....	60
7.1.1.	Primary Endpoints .....	60
7.1.2.	Secondary and Other Endpoints.....	61
7.1.3.	Subpopulations .....	62
7.1.4.	Dose and Dose-Response .....	63
7.1.5.	Onset, Duration, and Durability of Efficacy Effects.....	63
7.2.	Additional Efficacy Considerations.....	64
7.2.1.	Considerations on Benefit in the Postmarket Setting.....	65
7.2.2.	Other Relevant Benefits.....	65
7.3.	Integrated Assessment of Effectiveness .....	65
8	Review of Safety.....	66
8.1.	Safety Review Approach .....	66
8.2.	Review of the Safety Database .....	66
8.2.1.	Overall Exposure.....	69
8.2.2.	Relevant characteristics of the safety population: .....	70
8.2.3.	Adequacy of the safety database: .....	72
8.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	73
8.3.1.	Issues Regarding Data Integrity and Submission Quality.....	73
8.3.2.	Categorization of Adverse Events.....	73
8.3.3.	Routine Clinical Tests.....	74
8.4.	Safety Results.....	75
8.4.1.	Deaths.....	75
8.4.2.	Serious Adverse Events.....	79
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects.....	79
8.4.4.	Significant Adverse Events.....	80
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions .....	81
8.4.6.	Laboratory Findings .....	83

8.4.7. Vital Signs.....	84
8.4.8. Electrocardiograms (ECGs) .....	84
8.4.9. QT .....	84
8.4.10. Immunogenicity.....	84
8.5. Analysis of Submission-Specific Safety Issues .....	85
8.5.1. Pneumonitis .....	86
8.5.2. Hepatitis.....	87
8.5.3. Diarrhea/Colitis.....	94
8.5.4. Thyroid Disease.....	97
8.5.5. Hyperglycemia/Diabetes Mellitus.....	98
8.5.6. Adrenal Insufficiency .....	100
8.5.7. Hypophysitis .....	101
8.5.8. Other Endocrinopathies.....	101
8.5.9. Neurological Disorders .....	102
8.5.10. Musculoskeletal Disorders .....	104
8.5.11. Skin Disorders .....	105
8.5.12. Increased Amylase and Lipase.....	107
8.5.13. Renal Abnormalities .....	107
8.5.14. Infusion Reactions .....	110
IMVigor Cohorts 1 and 2.....	110
8.5.15. Corticosteroid Use .....	111
8.6. Specific Safety Studies/Clinical Trials .....	112
8.7. Specific Safety Studies/Clinical Trials .....	114
8.8. Additional Safety Explorations .....	114
8.8.1. Human Carcinogenicity or Tumor Development .....	114
8.8.2. Human Reproduction and Pregnancy .....	114
8.8.3. Pediatrics and Assessment of Effects on Growth .....	114
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....	114
8.9. Safety in the Postmarket Setting .....	114
8.9.1. Safety Concerns Identified Through Postmarket Experience .....	114
8.9.2. Expectations on Safety in the Postmarket Setting.....	115
8.10. Additional Safety Issues From Other Disciplines .....	115

8.11.	Integrated Assessment of Safety.....	115
9	Advisory Committee Meeting and Other External Consultations .....	115
10	Labeling Recommendations .....	116
10.1.	Prescribing Information.....	116
10.2.	Patient Labeling.....	118
10.3.	Nonprescription Labeling .....	118
11	Risk Evaluation and Mitigation Strategies (REMS) .....	119
12	Postmarketing Requirements and Commitments.....	119
13	Appendices .....	121
13.1.	References.....	121
13.2.	Financial Disclosure .....	121

**Table of Tables**

Table 1: Benefit-Risk Assessments of Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma.....	15
Table 2: Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma.....	18
Table 3: Key Regulatory Activities during Clinical Development of Atezolizumab in Advanced Urothelial Carcinoma.....	20
Table 4: OSI Inspected Sites and Inspectional Classification .....	22
Table 5: Clinical Studies Supporting BLA 761034 for Second-Line Use of Atezolizumab in Advanced Urothelial Carcinoma .....	26
Table 6: Key Differences between RECIST v1.1 and Modified RECIST .....	29
Table 7: Hierarchical Tests of Cohort 2 of GO 29293.....	30
Table 8: Protocol Milestones and Amendments of Study GO 29293 .....	32
Table 9: Patient Disposition in Cohort 2 of Study GO29293.....	37
Table 10: Major Protocol Violations/Deviations in Cohort 2 of Study GO29293.....	38
Table 11: Baseline Demographics of Cohort 2 of Study GO29293 .....	39
Table 12: Disease Characteristics of Cohort 2 of Study GO29293 .....	39
Table 13: Confirmed ORR as Assessed by IRF in Cohort 2 of Study GO29293 .....	42
Table 14: Confirmed, IRF-Assessed ORR by Individual PD-L1 IC Score .....	42
Table 15: ORR as Assessed by Investigator per Modified RECIST in Cohort 2 of Study GO29293.....	43
Table 16: Discordance between IRF Assessment per RECIST 1.1 and Investigator Assessment per Modified RECIST .....	43
Table 17: Difference in Tumor Responses between IRF-Assessed per RECIST v1.1 and Investigator-Assessed per Modified RECIST .....	44
Table 18: Response Duration in Responders of Cohort 2 of GO 29293.....	45
Table 19: Investigator-Assessed ORR and DOR per RECIST v1.1 in Cohort 2 of GO 29293.....	46
Table 20: Discordance between IRF- and Investigator-Assessed Responses per RECIST v1.1.....	47
Table 21: Difference in Distribution of Investigator-Assessed Tumor Responses between RECIST v 1.1 and Modified RECIST .....	47
Table 22: ORR and DOR in Important Subgroups in Cohort 2 of Study GO29293 .....	48
Table 23: Estimated PFS and OS in Cohort 2 of Study GO 29293 .....	49
Table 24: Enrollment of Patients by Time Periods and Preliminary PD-L1 Scores in the UBC Cohort.....	50
Table 25: PD-L1 Expression Status in Reanalysis with PD-L1 IUO Assay.....	51
Table 26: Patient Disposition in the Phase 1 UBC Cohort.....	51
Table 27: Major Protocol Violations/Deviations in the Phase 1 UBC Cohort .....	52
Table 28: Demographic Characteristics in the UBC Cohort .....	53
Table 29: Disease Characteristics in the Phase 1 UBC Cohort .....	53
Table 30: Confirmed ORR and DOR as Assessed by IRF in the UBC Cohort .....	55
Table 31: ORR and DOR by Individual IC score per the IUO assay in the UBC Cohort .....	56
Table 32: PFS and OS in the Phase 1 UBC Cohort.....	57

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Table 33: Exploratory Evaluation of ORR by the Reported PD-L1 TC Scores in Cohort 2 of Study GO 29293.....	58
Table 34: Exploratory Evaluation of ORR per PD-L1 Expression Status as Reported with Prototype Assay in the Phase 1 UBC Cohort.....	59
Table 35: ORR as Assessed by IRF per RECIST v1.1 in the Two Study Cohorts and Pooled PD-L1 Subgroups.....	60
Table 36: Other Efficacy Measurements in the Two Studies and Relevant Subgroups.....	61
Table 37: Analysis of ORR in Key Subgroups in the Two Cohorts.....	62
Table 38: Time to Onset of Responses in Cohort 2 of Study GO 29293.....	64
Table 39: Time to Onset of Responses in the Phase 1 UBC Cohort.....	64
Table 40: Pooled terms.....	67
Table 41: Safety Population, Size and Denominators.....	69
Table 42: Safety Population Demographics.....	70
Table 43: Integrated Summary of Safety.....	75
Table 44: Cohort 2 Deaths on Study.....	76
Table 45: Brief Summaries of Related Deaths.....	76
Table 46: Serious Adverse Events (Cohort 2) [Database cut-off 5-5-15].....	79
Table 47: Adverse Events Resulting in Permanent Discontinuation.....	80
Table 48: Grade 1-4 Adverse Reactions in $\geq 10\%$ of Patients with Urothelial Carcinoma in Cohort 2.....	81
Table 49: Incidence of Grade 3-4 Laboratory Abnormalities (Data cut-off 5-7-15).....	84
Table 50: Adverse Effect Incidence by Presence of Anti-therapeutic Antibodies.....	85
Table 51: Immune-mediated Adverse Events in Patients with Urothelial Carcinoma (including IMVigor 210 Cohorts 1 and 2 and PCD4989g).....	86
Table 52: Liver Function Test Abnormalities in the Adverse Event Datasets.....	87
Table 53: Incidence of Hepatic Adverse Events in Cohort 2 (Data cut-off May 5, 2015).....	88
Table 54: Incidence of Hepatic Adverse Events in PCD4989g (Data cut-off August 7, 2015).....	93
Table 55: Hepatic Laboratory Abnormalities in PCD4989g.....	93
Table 56: Diarrhea/Colitis Adverse Events in Cohort 2.....	94
Table 57: Diarrhea/Colitis events in Cohort 1.....	95
Table 58: Diarrhea/colitis Events in PCD4989g.....	96
Table 59: Thyroid Stimulating Hormone (TSH) Changes in Cohorts 1 and 2.....	97
Table 60: Thyroid Events in PCD4989g.....	97
Table 61: Changes in TSH in PCD4989g.....	98
Table 62: Glycemic Events in Cohort 2.....	99
Table 63: Glycemic Events in PCD4989g.....	99
Table 64: Neurologic Events in PCD4989g and IMVigor Cohorts 1 and 2.....	103
Table 65: Dermatitis Events in PCD4989g and IMVigor Cohorts 1 and 2.....	106
Table 66: Renal Events in PCD4989g and IMVigor 210 Cohorts 1 and 2.....	109
Table 67: Creatinine Changes in PCD4989g.....	109
Table 68: Infusion Reactions in PCD4989g and IMVigor 210 Cohorts 1 and 2.....	110
Table 69: Grade 1-4 Adverse Events in $>15\%$ of Patients by Age (Cohort 2).....	113

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Table 70: Grade 1-4 Adverse Events in > 15% of Patients by Sex (Cohort 2).....113

**Table of Figures**

Figure 1: Design of Study PCD4989g.....	34
Figure 2: Safety Population Age .....	70
Figure 3: Safety Population Geography .....	71
Figure 4: Time to Grade 3-4 AE in Cohort 2 .....	83
Figure 5: Hy's Law Cases in Cohort 2 .....	90
Figure 6: Time Course of Hy's Law Cases in Cohort 2 .....	91

## Common Abbreviations Used in the Review

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AC	advisory committee
AE	adverse event
ATA	anti-therapeutic antibody
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
IC	immune cell
IDMC	data monitoring committee
IHC	immunohistochemistry
IND	investigational new drug
DOR	duration of response
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
imAE	immune-mediated adverse event
IND	Investigational New Drug
ISS	integrated summary of safety
IRF	Independent Review Facility
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PD-L1	Programmed death-ligand 1
PFS	progression-free survival

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
RECIST v1.1	Response Evaluation Criteria in Solid Tumors v1.1
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
UC	urothelial carcinoma

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## 1 Executive Summary

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### 1.1. Product Introduction

Atezolizumab (TECENTRIQ) is a new molecular entity that is an Fc-engineered, humanized, monoclonal antibody that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7.1 receptors. The product belongs to a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

The Applicant's proposed indication for this BLA was: "*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* <sup>(b) (4)</sup>

The recommended dose for atezolizumab is 1200 mg, administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical and statistical reviewers recommend accelerated approval of atezolizumab for the proposed indication under Subpart E of the Biological Licensing Regulations<sup>1</sup>.

Our review found that this BLA provides substantial evidence to support second-line use of atezolizumab in patients with advanced urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months after neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. In the United States, this represents the first approval of a second-line treatment in this disease setting.

As summarized in the following Benefit-Risk Assessment, evidence supporting this BLA came from two single-arm studies that showed consistent results in both efficacy and safety. Treatment with atezolizumab in the intended patient population elicited confirmed objective antitumor responses in approximately 15-25% of patients. The median response durations were not reached at the data cutoff for the response analyses. The majority of responding patients maintained their response for  $\geq 6$  months and some for  $\geq 12$  months. These observed response durations are substantial, and are considerably prolonged relative to the response durations associated with chemotherapeutic products used in the same disease (See Section 2.2).

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<sup>1</sup> 21 Code of Federal Regulations, Part 601.41

Overall, the improvement in the surrogates, objective response rate (ORR) and duration of response (DOR), is reasonably likely to predict clinical benefit for the use of atezolizumab in the intended patient population. Combined with the demonstrated safety profile, the evidence contained in this BLA is considered sufficient for accelerated approval of atezolizumab for the proposed indication. An ongoing randomized, active controlled trial of atezolizumab versus the Investigator's choice of a chemotherapeutic (NCT02302807) may provide confirmatory evidence to verify the clinical benefit in the same patient population.

Use of the PD-L1 (SP142) assay, (b) (4), may identify patients who may have a modestly higher chance to respond to atezolizumab. Nevertheless, the observed durable responses in patients with no PD-L1 (IC0) or a lower PD-L1 level (IC1) in their tumor-infiltrating immune cells argues against mandatory use of the PD-L1 assay for selection of patients. Given the limited treatment options available for such patients and based on the reviewers' best clinical judgments, it is important to make atezolizumab clinically available to all patients who may benefit from this second-line treatment. For most patients, a few cycles (e.g., 2-3 cycles per Tables 38 and 39) of treatment with atezolizumab may be adequate to distinguish responders from non-responders and to assess whether patients may benefit from continuation of the treatment provided that they tolerate it with manageable adverse reactions.

### **1.3. Benefit-Risk Assessment**

### Benefit-Risk Summary and Assessment

Atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, is recommended for approval as a second-line therapy for locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-containing chemotherapy.

In the USA, there is no FDA approved second-line therapy for this indication. Standard of care for patients with advanced urothelial carcinoma is platinum-containing chemotherapy. However, almost all patients experience disease progression during or after platinum-containing chemotherapy. There is no effective or standard second-line therapy. Patients with progressive disease may have a limited survival time of 5-10 months. Off-label use of a few chemotherapeutics in this disease setting is associated with low response rates and short response durations along with considerable toxicities.

The effectiveness of atezolizumab is demonstrated in 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression after prior platinum-containing chemotherapy. Atezolizumab was administered intravenously at a dose of 1200 mg every 3 weeks. Confirmed ORR, as assessed by IRF per RECIST v1.1, was 14.8% (95% CI: 11.1%, 19.3%). At the data cutoff time for the ORR analysis, median DOR in responders was not reached (range: 2.1+ to 13.8+ months). Of the 46 responders, 37 patients had ongoing responses of  $\geq 6$  months and 6 had ongoing responses of  $\geq 12$  months. ORR was also analyzed as pre-specified by PD-L1 expression status in tumor-infiltrating immune cells, which was prospectively assayed in tumor specimens at a central laboratory. The confirmed ORR was 9.5% (95% CI: 5.9%, 14.3%) in 210 patients with a PD-L1 IC score of 0/1 and 26.0% (95% CI: 17.7%, 35.7%) in 100 patients with a PD-L1 IC score of 2/3. Response durations in the PD-L1 subgroups were similar to those in the 310 patients.

Supportive evidence was available from additional 94 patients who were enrolled in another study cohort in a similar disease setting. The results of this small cohort are consistent with the findings from the 310 patients.

The most common adverse reactions of atezolizumab in at least 20% of patients were fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation. Grade 3-4 adverse events were seen in 50% of patients. Infection and immune-related adverse events such as pneumonitis, hepatitis, colitis, thyroid disease, adrenal insufficiency, and diabetes were also seen with atezolizumab.

Overall, the atezolizumab-induced objective and durable responses are clinically meaningful to patients with the study disease. This represents an important, new, and non-chemotherapeutic option that will address an unmet medical need in this patient population. The benefit-risk profile for the approved indication is favorable. A randomized trial to verify and/or establish the benefit-risk profile of atezolizumab is ongoing.

**Table 1: Benefit-Risk Assessments of Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#"><u>Analysis of Condition</u></a>	<ul style="list-style-type: none"> <li>Progressive advanced urothelial carcinoma following platinum-based first line therapy has a poor prognosis, with a median survival of 6-10 months.</li> <li>Approximately 15,000 deaths from advanced urothelial carcinoma each year.</li> </ul>	<p>This disease is serious and life-threatening. There is a significant unmet medical need for patients with the disease.</p>
<a href="#"><u>Current Treatment Options</u></a>	<ul style="list-style-type: none"> <li>There are no approved products in the USA for second-line therapy for the disease.</li> <li>Off-label use of a taxane (docetaxel, paclitaxel, nab-paclitaxel), or combination of paclitaxel with gemcitabine; vinflunine is available outside the USA</li> </ul>	<p>All the products are palliative and have significant adverse reactions and/or intolerance. Patients generally have low response rates and short response durations. Vinflunine is associated with a survival trend compared to best supportive care.</p>
<a href="#"><u>Benefit</u></a>	<ul style="list-style-type: none"> <li>Of the unenriched population of 310 patients, 14.8% had confirmed responses. The ORR was 26% in the PD-L1 IC 2/3 group and 9.5% in the PD-L1 IC 0/1 group.</li> <li>Median response duration was not reached (range 2.1+, 13.8+ months). Of the responders, 80% (37/46) had ongoing responses of ≥6 months and 13% (6/46) had ongoing responses of ≥12 months.</li> <li>In a PD-L1 enriched population of 94 patients, 25.5% of patients had confirmed responses. Median response duration was not reached (range 2.9, 26.3+ months), with responses of ≥6 months in 92% (22/24) of responders and of ≥12 months in 58% (14/24) of responders.</li> </ul>	<p>Substantial evidence of effectiveness for second-line use of atezolizumab monotherapy in advanced urothelial carcinoma, as supported by similar ORRs and durable responses, was found from the two single-arm studies. The results are consistent between the two studies. Patients positive for PD-L1 expression in their ICs appear to have a higher response rate relative to patients negative for PD-L1 expression. Durable responses are observed in both PD-L1 positive (IC2/3) and negative (IC0/1) responders.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<ul style="list-style-type: none"> <li>• Tolerated in most study patients</li> <li>• Important risks include hepatitis, pneumonitis, endocrine disorders, colitis, infection, and neurological disorders</li> </ul>	<p>The profile of adverse reactions associated with atezolizumab is similar to that observed in other PD-1 targeted products.</p>
<u>Risk Management</u>	<ul style="list-style-type: none"> <li>• Non-endocrine immune-mediated adverse events were largely reversible with the use of corticosteroids.</li> <li>• A medication guide for atezolizumab describing the risks of immune-mediated adverse events will be required to better allow early recognition and initiation of treatment of these events.</li> <li>• To better estimate the incidence of hypothyroidism, the Applicant will fulfill a PMR for more frequent routine TSH evaluation during therapy in one planned trial.</li> </ul>	<p>The safe use of atezolizumab can be managed through accurate labeling and routine pharmacovigilance. No REMS is indicated.</p>

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Urothelial carcinoma is the most common malignancy in the urinary tract system and accounts for approximately 16,000 deaths yearly in the USA<sup>2,3</sup>. Although most urothelial carcinomas are non-muscle invasive at diagnosis and can be managed effectively with surgical resection and/or intravesical therapies, approximately 10-15% of patients may develop invasive, locally advanced and metastatic urothelial carcinoma<sup>4</sup>. In addition, approximately 10% of patients have regionally advanced or metastatic disease at diagnosis<sup>2</sup>.

Standard of care for patients with advanced disease is platinum-containing chemotherapy, such as gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). However, almost all patients experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy. There is no efficacious or standard second-line therapy after disease progression (See Section 2.2). The reported median survival of patients after platinum-containing therapy ranges from 5 to 10 months (Table 2). Clearly, there is an unmet need for patients with this serious and life-threatening disease.

### 2.2. Analysis of Current Treatment Options

In the USA, there is no FDA approved second-line therapy for locally advanced or metastatic urothelial carcinoma.

Outside the USA, vinflunine is approved as a second-line treatment. Table 2 summarizes key efficacy and safety information about vinflunine and other second-line chemotherapies studied or used off-label in such patients after platinum-containing chemotherapy. As shown in the table, these chemotherapeutics, either used alone or in combination, are associated with a low response rate but considerable toxicities. Except for vinflunine, response durations remain unknown or unreported. Nab-paclitaxel monotherapy was associated with a response rate of 28% and a longer survival time relatively to other agents. However, the results may not be reliably interpreted given the small sample size of a single-arm study. In addition, the heterogeneity of study patient populations is an issue among these studies, which may contribute to the varying response rates and survival times.

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<sup>2</sup> Siegel RL et al. *Cancer Statistics 2016*. *CA Cancer J Clin* 2016; 66:7-30

<sup>3</sup> NCCN Guidelines v1 2016: *Bladder Cancer*

<sup>4</sup> Park JC et al. *Multimodal management of muscle invasive bladder cancer*. *Curr Probl Cancer* 2014; 38:80-108

In general, no standard of care exists in the second-line setting. Taxane monotherapy may be a preferred off-label treatment of advanced urothelial carcinoma after platinum-containing chemotherapy. Given the modest activity of a taxane or other optional chemotherapeutics in the disease setting, participation in clinical trials is recommended<sup>3</sup>.

**Table 2: Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma**

	<b>Vinflunine<sup>a</sup> +BSC</b>	<b>Gemcitabine + Paclitaxel<sup>b</sup></b>	<b>Docetaxel<sup>c</sup></b>	<b>Nab-paclitaxel<sup>d</sup></b>
Trial Phase	III	III	II	II
Patient Population Regarding Prior Platinum Use Requirement	After first-line platinum-containing chemotherapy; no time interval specified	During or after cisplatin-based first-line chemotherapy; no time interval specified	After platinum-containing chemotherapy; no time interval specified	Progression on or within 12 months of treatment with one prior platinum-containing regimen

	<b>Vinflunine<sup>a</sup> +BSC</b>	<b>Gemcitabine + Paclitaxel<sup>b</sup></b>	<b>Docetaxel<sup>c</sup></b>	<b>Nab-paclitaxel<sup>d</sup></b>
<b>Objective Response (#Evaluable Patients)</b>	<b>N = 185</b>	<b>N = 40</b>	<b>N = 70</b>	<b>N = 47</b>
Overall Response Rate	16 (9%)	15 (38%)	5 (11%)	13 (28%)
Response Duration (mos), median	7.4	NR	NR	NR
<b>Overall Survival*, median</b>	6.9 months (vs 4.6 mos with BSC, HR 0.88 p=0.287)	7.8 months	7.0 months	10.8 months
<b>Key Safety Issues (Grade 3 or 4 Toxicity)** (%)</b>	Neutropenia (50%);  Febrile neutropenia (6%);  Anemia (19%);  Fatigue (19%);  Constipation (16%)	Anemia (7%)	Neutropenia (14%);  Anemia (1%);  Fatigue (6%);  Infection (6%);  Electrolyte abnormalities (6%)	Fatigue (10%);  Weakness (8);  Neuropathy (6%);  Dyspnea (6%);  Hypertension (6%)
<p>NR: not reported;</p> <p>*In the relevant treatment arm or study of the enrolled patients.</p> <p>** As reported from each study, which may not represent the comprehensive safety profile of each treatment based on the approved product label.</p> <p>a) Bellmunt J. et al. (2009) <i>J Clin Oncol</i> 27:4454-4461. An improvement in OS (not statistically significant) was seen. This trial led to the EMA approval of vinflunine for its use as a second-line treatment.</p> <p>b) Albers P et al. (2011) <i>Annals of Oncology</i> 22: 288–294. Results from the short-treatment arm (6 cycles) are shown for its tolerability. The prolonged treatment arm was intolerable due to safety concerns and the results are not listed.</p> <p>c) Choueiri TK et al (2011) <i>J Clin Oncol</i> 30:507-512. The results as shown were from the docetaxel + placebo arm alone.</p> <p>d) Ko YJ et al (2013) <i>Lancet Oncol</i> 2013; 14: 769–76. The preliminary results from this trial were reported in an abstract in the 2010 GUASCO meeting. The ORR at that time was 33% in 40 study patients.</p>				

### 3 Regulatory Background

#### 3.1. U.S. Regulatory Actions and Marketing History

Atezolizumab is a new molecular entity and is not currently marketed in the U.S. and other parts of the world. There is no development program in non-malignant diseases.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

Major regulatory activities with FDA are summarized in Table 3. This summary focuses on activities relevant to the development program for atezolizumab in urinary tract malignancies, which was initiated in January of 2014. The initial IND (111271) for the same product was submitted in 2012.

**Table 3: Key Regulatory Activities during Clinical Development of Atezolizumab in Advanced Urothelial Carcinoma**

Jan. 2014	<ul style="list-style-type: none"> <li>• IND 120827 submitted for studies of MPDL3280A in urothelial carcinoma. This new IND was submitted secondary to an administrative split by tumor types.</li> <li>• Feedback was provided on differences between the proposed population, study patients with PD-L1 positive tumors and patients evaluable for PD-L1 expression. Feedback was also provided concerning the dose modifications plans for some immune-related adverse reactions and on the alternative treatments that should be included in the informed consent for patients ineligible for cisplatin-based chemotherapy in Cohort 1.</li> </ul>
Mar.-May, 2014	<ul style="list-style-type: none"> <li>• The sponsor’s requested Breakthrough Therapy designation of MPDL3280A for the treatment of patients with locally advanced or metastatic urothelial bladder cancer (UBC) that is PD-L1 positive, (b) (4) after progression on or intolerance to a platinum-containing chemotherapy regimen.</li> <li>• This request was granted based on preliminary evidence from 20 patients with locally advanced or metastatic UBC with a PD-L1 IHC score of 2 or 3 in their tumor specimens (as determined by the prototype PD-L1 assay). Confirmed objective response (per RECIST v1.1) rate was 50%. The median response duration was not reached (observed range: 2.9-7.5 months) at the data cutoff.</li> </ul>
June-Dec. 2014	<ul style="list-style-type: none"> <li>• Post Breakthrough Therapy designation meetings were held to discuss the development plans and regulatory approval pathways. The single-arm study GO 29293 was proposed to support potential accelerated approval, and a randomized active-controlled trial* to support conversion to regular approval if the results are positive. Both study designs were discussed and agreements were reached on stratification factors, efficacy measures and sample size</li> </ul>

	<p>determination.</p> <ul style="list-style-type: none"> <li>The <i>In vitro</i> diagnostic for the proposed PD-L1 assay was evaluated with CDRH and the sponsor planned to conduct analytical validation studies of PD-L1 of &lt;5% (IC0/1) vs. of ≥5% (IC2/3) (Section 4.6) and proposed to use clinical data from the two studies to perform clinical validation of the cutoff.</li> </ul>
Feb. 2015	<ul style="list-style-type: none"> <li>Evaluation of a new study** intended for adjuvant use of MPDL3280A in patients who have had radical cystectomy and whose tumor specimens test positive for PD-L1 (IC 2/3).</li> <li>Agreement reached on the design and analysis plan.</li> </ul>
May-Sep. 2015	<ul style="list-style-type: none"> <li>Pre-BLA submission meetings held.</li> <li>Agreements reached on the contents, format, and analyses for a BLA submission based on results from Cohort 2 of Study GO 29293 and supportive evidence from the Phase 1 UBC Cohort</li> <li>Additional follow up time requested by the review division for better assessment of response durability. The initial median follow up time was 7.1 months based on the topline results provided to the review division.</li> </ul>
Oct.2015-Feb. 2016	<ul style="list-style-type: none"> <li>Rolling submission of the BLA initiated, with the clinical datasets and study reports submitted on January 12, 2016.</li> <li>The BLA was designated for priority review at the filing meeting.</li> </ul>
Feb. 2016	<ul style="list-style-type: none"> <li>Submission of updated clinical datasets, which were used for this review.</li> </ul>
<p>* Ongoing (NCT02302807 at <a href="http://ClinicalTrials.gov">ClinicalTrials.gov</a>)</p> <p>**Ongoing (NCT02450331 at <a href="http://ClinicalTrials.gov">ClinicalTrials.gov</a>)</p>	

### 3.3. Foreign Regulatory Actions and Marketing History

None as of this review completion.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

For this new application for atezolizumab, the clinical team requested that OSI verify the integrity of the submitted clinical data from Cohort 2 of Study GO 29293. Three study sites

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

(Table 4) were selected based on the number of patients enrolled and the number of reported responders and adverse reactions. The Applicant or study sponsor was also audited by OSI.

There were no significant inspectional findings at the three sites and study sponsor. The interim classification of each site is listed in the last column of Table 4. Based on the available information, OSI concluded that data from Study GO29293 appears reliable in support of this application. For details, see Clinical Inspection Summary from OSI.

A few deviations were identified in Study Site 268646, including two patients enrolled prior to completion of all required screening studies and several laboratory assessments (e.g., urinalysis) were missed during study conduct.

In addition, Study Site 268278 had adverse reactions reported in the eCRFs which were not found in the submitted dataset. The Applicant was notified of these discrepancies. The Applicant's investigation found that this problem was secondary to delayed entry of adverse events into eCRFs by the study site. Adverse event entry occurred after the Applicant extracted data for the planned initial analysis. The same problem was identified in 17 other study sites. The Applicant found delayed entry of 242 AEs. Of the 242 AEs in which entry was delayed, 206 (85.1%) were Grade 1-2 events, 35 (14.5%) were Grade 3 and 1 (0.4%) was a Grade 4 event. Eight events were reported as serious from which the majority of patients recovered (7 out of 8 events). One event led to dose interruption and two events led to study drug withdrawal. There were no Grade 5 events among the delayed-entry AEs. The effect of those delayed-entry AEs was assessed and found to have no major impact on the safety profile.

**Table 4: OSI Inspected Sites and Inspectional Classification**

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Jonathan Rosenberg, M.D.</b> Memorial Sloan-Kettering Cancer Center 1275 York Avenue, Box 344 New York, NY 10065	Protocol: IMvigor210 (GO29293)  Site Number: 268278  Number of Subjects Enrolled: 30	March 10-15, 2016	Pending  Interim classification: NAI
<b>CI#2: Ani Balmanoukian, M.D.</b> The Angeles Clinic and Research Institute – W. LA Office 11818 Wilshire Blvd., Suite 200 Los Angeles CA 90025	Protocol: IMvigor210 (GO29293)  Site Number: 268794  Number of Subjects Enrolled: 12	March 22-24, 2016	Pending  Interim classification: NAI
<b>CI#3: Richard Joseph, M.D.</b> Mayo Clinic Cancer Center 4500 San Pablo Road Jacksonville FL 32224	Protocol: IMvigor210 (GO29293)  Site Number: 268646  Number of Subjects Enrolled: 12	February 23-29, 2016	Pending  Interim classification: VAI
<b>Sponsor: Hoffmann-La Roche, Inc./Genentech, Inc.</b> 1 DNA Way South San Francisco, California 94080-499	Protocol: IMvigor210 (GO29293)  Number of Sites: 26	March 9-16, 2016	Pending  Interim classification: NAI

## 4.2. Product Quality

No significant issues were identified regarding the CMC part of the application. A facility inspection was conducted for the site of drug substance manufacture. One citation, (b) (4) was found. The Applicant will correct this.

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Nonclinical Pharmacology/Toxicology

There are no data available on the use of atezolizumab in pregnant women. See the Pharmatox Review and CDTL review for details.

## 4.5. Clinical Pharmacology

There were no significant clinically related issues identified in the clinical pharmacology review.

### 4.5.1. Mechanism of Action

Atezolizumab is a humanized monoclonal antibody (IgG1) that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7.1 receptors. This results in a release of PD-L1/PD-1 mediated inhibition of the antitumor immune response. In mouse tumor models, inhibition of PD-L1 activity was associated with an increase in activated cytotoxic T cells and a decrease in tumor growth.

### 4.5.2. Pharmacodynamics

No issues identified.

### 4.5.3. Pharmacokinetics

Exposures to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 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 (C<sub>max</sub>) and trough concentration (C<sub>min</sub>) was 1.91, 1.46 and 2.75-fold, respectively.

## 4.6. Devices and (b) (4) Diagnostic Issues

The PD-L1 (SP142) IHC assay was submitted to CDRH for evaluation (b) (4)

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

(b) (4). This assay is intended for the qualitative immunohistochemical assessment of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial cancer tissue stained with a BenchMark ULTRA automated staining instrument. The scoring criteria rely on the percentage of PD-L1 stained immune cells (ICs) within the tumor area.

This assay was analytically validated to only support a single cutoff (b) (4). The evaluation from CDRH concluded that the inclusion of both cutoffs within the same scoring criteria is not consistent with how the assay was developed or validated. (b) (4)

(b) (4) Using the 5% cutoff is supported by the clinical data since response rates differ between the IC 0/1 group (<5%) and the IC 2/3 group ( $\geq 5\%$ ). (b) (4) which is not supported by the data.

For Study GO 29293, there was no IC3 score reported because pathologists who scored the slides were not instructed to differentiate between IC2 and IC3. The first pathologist would record  $\geq 5\%$  or  $< 5\%$  as the binary score (resulting in IC 0/1 vs IC 2, consistent with the 5% cutoff scoring criteria). If the percentage of stained ICs in the tumor area was  $< 5\%$ , a second pathologist would score it as  $\geq 1\%$  vs  $< 1\%$  (IC0 1 vs IC 1). The IC 3 was defined as  $> 10\%$  of stained ICs in the tumor area. Evidence submitted to CDRH showed that some samples in Study GO 29293 had  $> 10\%$  of stained ICs in the tumor area.

There is a discordance rate of 27% in PD-L1 positivity (IC 2/3) between primary tumors and the paired metastatic tumor tissue, with a slightly higher positivity in primary tumors than in metastatic tumors. Because PD-L1 positivity can be determined from either the metastatic or primary site, the discordance between the two types of tissue may introduce some uncertainty as to how to reliably interpret the result of the assay. Nevertheless, there was a similar association between PD-L1 status and ORR regardless of primary tissue or metastatic tissue used in the assay.

Due to the design of Study GO 29293 (all patients received atezolizumab without a control), it is not possible to assess whether the associations between PD-L1 IC status and ORR are prognostic and/or predictive of responses in advanced urothelial carcinoma. In patients with metastatic disease, PD-L1 expression in tumor infiltrating mononuclear cells appears associated with a better prognosis<sup>5</sup>. Data from the ongoing randomized trial may help clarify if the association between PD-L1 positive immune cells and ORR is predictive or prognostic.

Based on the clinical evidence presented in this BLA, the CDRH review team is in agreement with the clinical review team that the PD-L1 (SP142) assay should be used as a complementary

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<sup>5</sup> Bellmunt J. et al: Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. *Annals of Oncology* 2015; 26: 812–817

diagnostic [REDACTED] (b) (4).

#### **4.7. Consumer Study Reviews**

Not applicable.

## **5 Sources of Clinical Data and Review Strategy**

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### **5.1. Table of Clinical Studies**

Table 5 summarizes key information of the two studies [Study GO 29293 (or IMvigor 210) and Study PCD4989g] that supported this BLA submission. In February of 2016, the Applicant submitted updated datasets for both studies. These updates provided an additional follow up time for each study, constituting the basis for our analyses as described in this combined review. The data cutoff time for each study is listed in Section 6.

**Table 5: Clinical Studies Supporting BLA 761034 for Second-Line Use of Atezolizumab in Advanced Urothelial Carcinoma**

Study Identity	Trial Design	Study Population	Dosing Schedule	Key Study Objectives	No. of patients enrolled
GO 29293 (IMVIGOR 210)	Single-arm, two-cohort Phase 2*	Patients with progressive advanced UC who received prior platinum-containing chemotherapy	1200 mg atezolizumab administered intravenously every 3 weeks	Objective response as assessed by IRF per RECIST v1.1  Duration of Response	310 patients enrolled for Cohort 2
PCD4989g (UBC Cohort)	Single-arm Phase 1, including a UBC cohort**	Patients with incurable UC for which no standard treatments existed	atezolizumab administered intravenously at a dose 15 mg/kg every 3 weeks***	Objective response in UBC cohort, as assessed by IRF per RECIST v1.1  Duration of Response	94 patients enrolled in the UBC cohort

*\*Results from Cohort 2 were evaluated in this application. Cohort 1 was intended to assess the activity and safety of atezolizumab in patients unfit for cisplatin-based chemotherapy and the results were not relevant for the current proposed indication.*

*\*\*This UBC cohort was initially enriched with patients whose tumor specimens had a PD-L1 IHC score of 2 or 3 based on the prototype PD-L1 assay. As a result, the study population of this cohort may differ from the population of the Phase 2 study in terms of PD-L1 expression levels in tumor specimens.*

*\*\*\*Representing the dosing schedule used for 85 patients in the UBC cohort. Of the remaining 9 patients, one patient received atezolizumab at a dose of 20 mg/kg every 3 weeks, and 8 patients received a flat dose of 1200 mg every 3 weeks.*

*Note that Study GO29293 and IMvigor 210 represent the same study. The latter name was introduced after the study initiation.*

## 5.2. Review Strategy

Based on the study design and the reported findings from each study, the review team examined the study protocol and its amendments for each study, cross-examined the consistency of the submitted datasets, performed independent analyses based on the datasets, and examined the findings against the results presented in the Clinical Study Report and/or its amendments as well as the Applicant's responses to the review team's inquiries. The review team focused on examination of the submitted IRF-assessed response results and verified each responder with the reported assessment findings per RECIST v1.1. In addition, discordance rates between different assessors (e.g., IRF vs. Investigator) or different criteria (RECIST vs. Modified RECIST) were also evaluated. Sensitivity and subgroup analyses were performed as indicated (Section 6.2)

The clinical safety review focused on the 310 patients treated with atezolizumab in Cohort 2 of Trial GO29293-IMVigor 210 with additional analyses of adverse events of special interest (AESIs) including immune-mediated adverse events. This included detailed review and analysis of data including the CSR, CRFs, narratives and datasets. The safety review focused on data available as of the data cut-off of May 5, 2015. Adverse events that occurred within 30 days following discontinuation of atezolizumab were included.

The clinical review of safety was supplemented with an evaluation of AESIs in patients with urothelial carcinoma treated with atezolizumab in Cohort 1 of IMVigor 210 (119 patients) and PCD4989g (94 patients). Study PCD4989g was analyzed based on the data cut-off of August 7, 2015. Study PCD4989g provided limited ECG/QT data. The frequency of specific immune-mediated AEs were obtained from additional trials including BIRCH and POPLAR as well as the Applicant safety database, comprised of 1978 atezolizumab-treated patients.

Key analysis findings to be included in the label were conveyed to the Applicant during the labeling review, and agreements reached before the final labeling.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. Studies Supporting the BLA

#### 6.1.1. Study Design

##### Overview and Objective

This BLA is primarily based on findings from Cohort 2 of the Phase 2 study as listed in Table 5, with supportive evidence from the Phase 1 UBC cohort. Therefore, our review focused more on the data from the Cohort 2. Given the differences and similarity (e.g., IRF-assessed ORR as the

key efficacy parameter), we reviewed the design and listed each study cohort individually in this Section.

- **Cohort 2 of Phase 2 Study (GO 29293)**

### **Trial Design for GO29293**

GO29293 was a multicenter, open-label, two-cohort study of atezolizumab in patients with locally advanced or metastatic urothelial carcinoma. The key objectives were to evaluate the safety and antitumor activity of the product, as assessed by independent review per RECIST v1.1, and to evaluate the duration of response (DOR) according to the independent review as well as PFS and OS.

Cohort 1 enrolled previously untreated patients who were ineligible for cisplatin-based chemotherapy. This is not relevant to the current proposed indication.

Cohort 2 of the study was open to patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen in the metastatic setting or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients were required to have evidence of disease progression, measurable disease as per RECIST v1.1, an ECOG performance score of 0 or 1, and controlled tumor-related pain. In addition, patients had to have adequate tumor tissue for prospective testing and determination of tumor PD-L1 expression status at a central laboratory. See Section 4.6 about the classification of PD-L1 IC scores and grouping for this study. The results of PD-L1 expression status were blinded to patients, investigators and study site staff at the time of enrollment. The Sponsor was blinded to individual patient PD-L1 IC scores, but had access to aggregated level data in order to monitor the prevalence of PD-L1 expression.

This study excluded patients who had a history of autoimmune disease, HIV, active HBV/HCV, and tuberculosis, active or corticosteroid-dependent brain metastases, or had received a live, attenuated vaccine within 28 days prior to enrollment. It also excluded patients who had received systemic immunostimulatory agents, other PD-1/PD-L1 targeted products, or systemic immunosuppressive medications.

Patients received an intravenous infusion of 1200 mg of atezolizumab on Day 1 of a 3 week cycle until unacceptable toxicity, disease progression, or symptomatic progression. For patients who met RECIST v1.1 criteria for disease progression in Cohort 2, continued treatment with atezolizumab was allowed at the discretion of the Investigator if they met all of the following: 1) Absence of symptoms and signs (including worsening of laboratory values; e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease; 2) No decline in ECOG performance status from baseline; 3) Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions; 4)

Evidence of clinical benefit as assessed by the investigator.

Safety assessments were performed before each administration. See detailed safety monitoring plans and clinical tests specified for this study in Section 8.3.2 of this review.

Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter.

### Study Endpoints of GO29293

The primary study endpoints included confirmed ORR as assessed by IRF using RECIST v1.1 and confirmed ORR as assessed by the Investigator per modified immune-related RECIST criteria.

The modified RECIST criteria incorporate measurement of new lesions and confirmation by repeat assessments performed  $\geq 4$  weeks after the first criteria for response are first met. The modified criteria are intended to detect delayed responses that may be preceded by initial immunotherapy-induced radiographic progression, including the appearance of new lesions. Key differences between the conventional RECIST v1.1 and modified RECIST criteria are shown in Table 6.

**Table 6: Key Differences between RECIST v1.1 and Modified RECIST**

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of $\geq 20\%$ increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment $\geq 4$ weeks from the date first documented

*Adopted from the study protocol*

*Review Comments: From a regulatory perspective, use of RECIST v1.1 has been used to determine tumor responses to an investigational product and is accepted by practicing oncologists. Results generated with the modified RECIST criteria are considered exploratory. Section 6.2 discusses a few patients with advanced urothelial carcinoma who had “pseudo-progression” followed by tumor responses.*

Key secondary efficacy endpoints of this study included DOR and PFS as assessed by the IRF, and OS.

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

- DOR was defined as the time from the initially documented CR or PR until evidence of disease progression as determined by the IRF or death due to any cause, whichever occurred first.
- PFS was defined as the time from the first dose of atezolizumab to disease progression as assessed by IRF per RECIST v1.1 or death due to any cause on study, whichever occurred first.
- OS was defined as the time from the first dose of atezolizumab to the time of death from any cause on study.

*Review comments: PFS/OS results from a single-arm study are not interpretable because of the absence of a control.*

### Statistical Analysis Plan

This single-arm study was designed to characterize ORR in all study patients and to examine whether there was a statistically difference between the observed ORR and an assumed historical response rate of 10% in patients with advanced urothelial carcinoma. Cohort 2 planned to enroll approximately 300 patients, assuming a 30% prevalence rate of IC2/3 patients (n~100) in the overall locally advanced or metastatic UBC population. Comparison of ORR between atezolizumab treatment and the assumed historical response rate was to be tested for three patient populations using a hierarchical fixed-sequence procedure. The planned hierarchical tests are shown in Table 7.

**Table 7: Hierarchical Tests of Cohort 2 of GO 29293**

Test Order	Endpoint	Analysis Population <sup>a</sup>	Pre-Specified Hypothesis Test
1	IRF-assessed ORR per RECIST v1.1	Cohort 2, IC2/3 patients	H <sub>0</sub> : ORR = 10% vs. H <sub>a</sub> : ORR ≠ 10%
2	Investigator-assessed ORR per modified RECIST		
3	IRF-assessed ORR per RECIST v1.1	Cohort 2, IC1/2/3 patients	
4	Investigator-assessed ORR per modified RECIST		
5	IRF-assessed ORR per RECIST v1.1	Cohort 2, all patients	
6	Investigator-assessed ORR per modified RECIST		

IC = tumor-infiltrating immune cell; IRF = Independent Review Facility; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: The tests will be performed in a sequential order, i.e., the subsequent hypothesis will not be performed if the preceding test is not rejected. Each test is performed at a two-sided  $\alpha$  of 0.05 significance level.

<sup>a</sup> Objective response—evaluable.

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

*Review Comments: In general, a clinically meaningful effect on response rate with a reasonable duration of response and an acceptable safety profile can be considered for regulatory evaluation and approval.*

The exact 95% CIs using the Clopper-Pearson method for ORR were calculated. The ORR estimates in key subgroups based on PD-L1 expression status were to be assessed.

DOR was calculated as the time from the initial occurrence of documented CR or PR (whichever occurred first) until documented disease progression or death due to any cause, whichever occurred first. Patients who have not progressed or who have died at the time of analysis were censored at the last tumor assessment date. The Kaplan-Meier estimate of the median DOR was to be presented; along with the 95% CIs computed using the Brookmeyer and Crowley method.

For analysis of PFS, the Kaplan-Meier method was to be used. Patients who did not have evidence of disease progression or death at the time of analysis were to be censored to the time of the last tumor assessment showing no disease progression. Patients with no post-baseline tumor assessment were censored to the time of study treatment plus one day. The 95% CIs for median PFS were computed using the Brookmeyer and Crowley method.

The Kaplan-Meier method was also used to estimate OS. Patients who were alive at the time of analysis were censored to the time of their last study assessment for patients on active treatment or to the last date known to be alive for patients in the follow-up phase.

The study SAP outlined the following key analysis populations:

- The Intent-To-Treat (ITT) population including all enrolled patients who received any amount of study drug.
- The objective response-evaluable population as the primary efficacy dataset for ORR analyses, defined as ITT patients who had measurable disease per RECIST v1.1 at baseline.
- The safety population defined as enrolled patients who received any amount of study drug.

A futility interim analysis on the IC0/1 patients was planned after the first 100 patients had at least 18 weeks of follow-up. The futility interim analysis was based on the unconfirmed ORR as assessed by the investigator per RECIST 1.1. The stopping boundary was set as 5%. If the stopping boundary for futility was crossed (i.e., ORR  $\leq$  5%) at the interim analysis, the IDMC could recommend stopping recruitment of IC0/1 patients.

*Review Comments: The review team considered the ITT population as the primary efficacy analysis population for ORR analyses. The presumed historical ORR control of 10% for the statistical test is debatable in patients with advanced urothelial carcinoma. As shown in Section*

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

*2, response rates can vary in the reported studies of second-line treatments. This may be related to treatment types and/or the heterogeneity of study patients among the studies. For a single-arm, open-label study, a detected statistical significance, as compared to the debatable historical control, may not represent a true clinical improvement. Therefore, no statistical tests and P-values will be reported in this review. See Section 6.2 about the percentage of patients on study treatment with the data cutoff for the analysis of ORR.*

### Protocol Amendments

The study protocol was proposed in January 2014. Before its initiation and during the study, the protocol was amended with feedback from the Agency. There were 4 major amendments relevant to Cohort 2, which are summarized in Table 8. Overall, the amendments did not affect the integrity of the study but rather helped improve interpretation of the results.

**Table 8: Protocol Milestones and Amendments of Study GO 29293**

<b>Milestone</b>	<b>Date</b>	<b>Major Changes or Comments</b>
Original Protocol	01/03/2014	
Amendments 1	03/11/2014	<ul style="list-style-type: none"><li>• Clarified that study patients needed to have tumor specimens evaluable for PD-L1 expression assay. Study entry was no longer limited to patients positive for PD-L1 expression (IHC score 2 or 3)</li><li>• Clarified the dose modification guidelines for the management of immune-related adverse events (e.g., dermatologic toxicity, endocrine toxicity)</li><li>• Listed alternative treatment options in the Informed Consent for patients participating in the study</li></ul>
Protocol Initiation	05/24/2014	<ul style="list-style-type: none"><li>• First patient enrolled following the Breakthrough Therapy designation</li></ul>
Amendments 2	05/29/2014	<ul style="list-style-type: none"><li>• Specified that there was no need to stop treatment after one year if patients continued to respond or had no disease progression.</li><li>• Added that patients could continue study treatment, at the discretion of the Investigator, until symptomatic disease progression or decline in performance status.</li></ul>

<b>Milestone</b>	<b>Date</b>	<b>Major Changes or Comments</b>
Amendment 3	09/27/2014	<ul style="list-style-type: none"> <li>Replaced the internal monitoring committee with an Independent Data Monitoring Committee (IDMC)</li> <li>Added an interim futility analysis for negative PD-L1 expression (IHC 0 or 1) following the first 100 patients. The results were to be evaluated by the IDMC. The boundary for stopping enrollment of patients with an IHC score of 0 or 1 was set at an ORR of <math>\leq 5\%</math>.</li> <li>Specified the conduct an interim futility analysis in patients with a PD-L1 IC score 0/1 after the 100 patients have been followed for approximately 18 weeks.</li> </ul>
Amendment 4	02/06/2015	<ul style="list-style-type: none"> <li>Added an analysis of patients with an IHC score of 1/2/3 to the planned hierarchical analysis*</li> </ul>
Enrollment Completion	03/30/2015	<ul style="list-style-type: none"> <li>Last patient enrolled</li> </ul>
Study Report	01/12/2016	<ul style="list-style-type: none"> <li>Generated with a data cutoff date of 05/05/2015</li> <li>Updated analyses provided with a data cutoff date of 09/14/2015</li> </ul>
Updated Datasets	2/24/2016	<ul style="list-style-type: none"> <li>Provided updated datasets at the Agency's request (in the pre-BLA meeting) for a better assessment of DOR. The data cutoff date was 11/27/2015 for Cohort 2 of this study.</li> </ul>
<p><i>*This analysis was secondary to the analytical validation of the PD-L1 expression assay cutoff point of 1%. See Section 4.6 for information about the role of the PD-L1 assay in the use of atezolizumab in the intended patient population.</i></p>		

### Data Quality and Integrity: Sponsor's Assurance

The Applicant used an electronic data capture (EDC) system to gather all study patient details on eCRFs. The Applicant managed and examined the data quality using the standard procedures. All eCRFs were completed by designated, trained site staff, and were reviewed and electronically signed and dated by the investigator or sub-investigator. For discrepant data, the Applicant clarified the issue(s) with the study sites and resolved them through the EDC system.

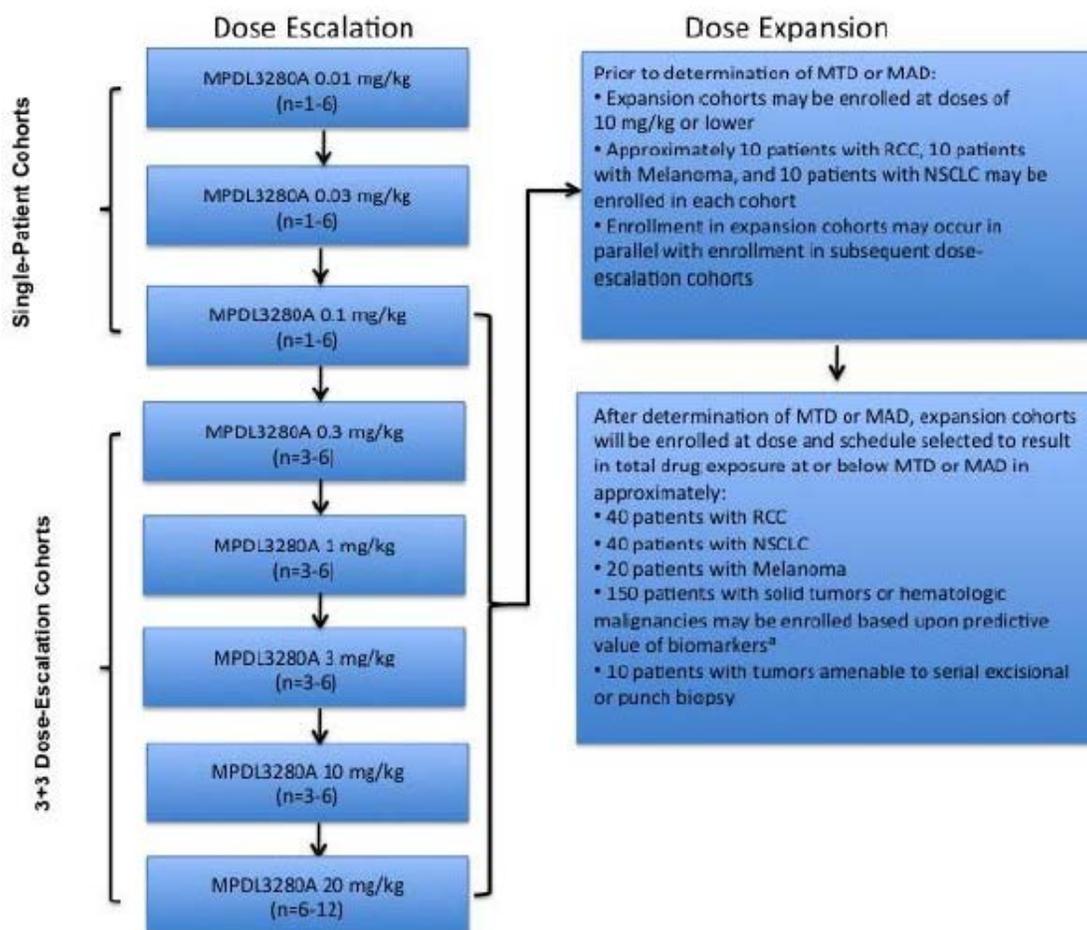
Study source documents required for verifying the validity and completeness of data entered into eCRFs were to be retained for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities.

- **UBC Cohort of Phase 1 Study**

**Trial Design for the Phase 1 UBC Cohort**

The UBC Cohort was one of numerous expansion cohorts included in Study PCD4989g. This Phase 1 study, conducted under IND 111271 since 2012, was initially designed to evaluate the safety and MTD of MPDL3280A (atezolizumab) in patients with locally advanced or metastatic solid tumors (Figure 1). After the dose-escalation stage in which no dose-limiting toxicities were observed at the 8 dose levels tested (up to 20 mg/kg), a number of expansion cohorts were initiated to better characterize the safety, tolerability, and activity in different malignancies, including advanced urothelial bladder cancer (UBC) following . Patients eligible for this study were required to have pathologically documented, incurable or metastatic tumor that had progressed since the last the anti-tumor therapy and for which no recognized standard curative therapy existed. For patients in expansion cohorts, the availability of archival tumor specimens needed to be confirmed prior to study entry.

**Figure 1: Design of Study PCD4989g**



## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

*(Adopted from the study protocol dated November 28, 2012, the version used for the initiation the UBC Cohort)*

Atezolizumab was administered intravenously every 3 weeks according to assigned dose levels in the study. At the time of enrollment of the UBC cohort, the dose levels were 15 mg/kg, 20 mg/kg, or a flat dose of 1200 mg (equivalent to 15 mg/kg based on an average body weight). Infusion of atezolizumab was performed in a setting with emergency medical facilities. The initial infusion was delivered over 60 ( $\pm$  15) minutes, with subsequent infusions over 30 ( $\pm$  10) minutes if the first infusion was tolerated. No premedication was allowed for the first infusion.

Tumor response assessments were performed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Study treatment continued, at the discretion of the investigator, until withdrawal, unacceptable toxicity, disease progression or symptomatic deterioration attributed to disease progression.

Design considerations were made to obtain preliminary safety, PK, and pharmacodynamic information in this patient population, and were not made with regard to explicit power and type I error considerations. The planned enrollment for this ongoing study was approximately (b) (4) patients, inclusive of approximately (b) (4) patients in the dose-escalation stage and up to approximately (b) (4) patients in the dose-expansion stage of this Phase 1 study.

### **Study Endpoints of the Phase 1 UBC Cohort**

The primary objective remained the evaluation of the safety and tolerability of atezolizumab. The secondary objectives were to characterize PK-related parameters and to assess the antitumor activity of atezolizumab monotherapy.

Key antitumor or efficacy measures included confirmed ORR and DOR, as assessed by IRF per RECIST v1.1. In addition, ORR, by PD-L1 status as assessed with the IUO assay, PFS and OS were included as exploratory endpoints.

### **Statistical Analysis Plan for the Phase 1 UBC Cohort**

A statistical analysis plan specific to the Phase 1 UBC cohort was finalized in May of 2015. Patients who received a dose of atezolizumab ( $\geq$  1 mg/kg) were considered evaluable for activity assessments.

ORR was analyzed in patients with measurable disease per RECIST v1.1 at baseline and with a minimum of 12 weeks of follow up from the first treatment with atezolizumab. In patients who achieved a CR or PR, DOR and time to onset of response (TTOR) analyses were also evaluated.

Exploratory analyses included ORR by PD-L1 expression status, PFS and OS.

### **Protocol Amendments Relevant to the UBC Cohort**

There were no specific amendments to the protocol relevant to the UBC cohort. Enrollment of patients with advanced UBC was introduced in Amendment 4 in August of 2012. Thereafter, revisions that may affect the analyses of the UBC cohort included increases in the number of patients for expansion cohorts in which antitumor activity was observed in multiple patients, addition of OS as an exploratory endpoint, and allowance of patients with an existing, low-risk second malignancy under surveillance to participate.

***Review Comments:** As listed in Section 5 of this review, all patients enrolled in the UBC Cohort received atezolizumab at a dose of >10 mg/kg and thus all treated patients were considered evaluable in both efficacy and safety analyses. The review team considered the all treated population as the efficacy population for analysis of ORR.*

## **6.1.2. Study Results**

### **Compliance with Good Clinical Practices**

The Applicant attested that the clinical trials were conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The Applicant also specified that the trials conducted under the relevant INDs complied with FDA regulations and applicable local, state, and federal laws in the United States.

To evaluate the Applicant's compliance, the Applicant and three study sites were selected for audit by OSI. There were no significant inspectional findings based on the clinical inspection summary. Based on the available audit information, OSI concluded that the submitted data from the key study GO29293 appear reliable in support of this BLA.

### **Financial Disclosure**

Disclosure of the financial interests of all the investigators involved in the two clinical trials was submitted in the FDA form 3454. The disclosure, certified by Eric Olson, Vice President of Regulatory Affairs of the Applicant, showed that investigators required to disclose a proprietary interest or a significant equity in the Applicant did not disclose any such interests and that no investigators listed in Form 3455 received significant payments of other sorts as defined in 21 CFR 54.2 (f).

Given that the key study supporting this BLA relied on independent-review determined objective responses, financial issues, if any, are less likely to affect the analyses that demonstrate the effectiveness of atezolizumab.

**Results from Cohort 2 of Study GO29293**

**Patient Disposition**

There were 310 patients enrolled in Cohort 2 of Study GO29293. With the data cutoff date of 11/27/2015, 19% patients were still on study treatment and 81% patients discontinued study treatment. As listed in Table 9, most patients discontinued due to disease progression. Since all the enrolled patients had their PD-L1 IC scores determined prospectively at a central laboratory and the Investigator and Sponsor were blinded to the PD-L1 status during the study, patients' disposition was also tabulated and listed by PD-L1 IC scores as reported from the central laboratory. As of the data cutoff time, the percentage of patients on study treatment was higher in the IC2 group than that in the IC 0 or 1 group, suggestive of either better responses or favorable disease characteristics in the IC2 group.

**Table 9: Patient Disposition in Cohort 2 of Study GO29293**

	All Patients	Patient Subgroups by PD-L1 IC Score		
	(all IC scores)	IC 0	IC1	IC2***
<b>N</b>	<b>310</b>	<b>103</b>	<b>107</b>	<b>100</b>
On-Study Treatment	59 (19%)	12 (12%)	15 (14%)	32 (32%)
Off-Study Treatment	251 (81%)	91 (88%)	92 (86%)	68 (68%)
<u>Reasons for Discontinuation</u>				
Disease Progression	216	80	79	57
Death	2	1	0	1
Adverse Reaction	13	1	8	4
Withdrawal*	9	5	2	2
Other**	11	4	3	4
*Withdrawal by study patient.				
**Other: Including non-compliance and Investigator's decision.				
***Tabulated as reported. This subgroup might contain a few patients whose PD-L1 expression was $\geq 10\%$ in tumor infiltrating immune cells (See Section 4.6)				

**Protocol Violations/Deviations**

**Table 10: Major Protocol Violations/Deviations in Cohort 2 of Study GO29293**

	All Patients
<b>N</b>	<b>310</b>
Protocol violations	60 (19%)
Eligibility Criteria Unmet	1*
No Signed ICF	7
Procedural Deviations Affecting Safety	20
Missing Scheduled Assessments	14
Other	20
<i>Note that some patients had &gt;1 violations and/or deviations. This table is based on the DV dataset submitted in April of 2016.</i>	
<i>* Received radiotherapy prior to study entry.</i>	
<i>Other: Including use of prohibited concomitant medicine, use of expired or quarantined study medicine (in 5 patients, one each in July-August of 2015), missing study medicine, and assessment out of the specified window time period.</i>	

Based on the review of the reported violation types, key protocol violations that may affect overall efficacy assessments were identified in 34 patients. These violations include radiotherapy prior to study treatment, missed protocol-scheduled protocol assessments, and those listed under “Other” in Table 10.

#### Table of Demographic Characteristics

Key baseline demographics and disease characteristics of Cohort 2 are summarized in Tables 11 and 12. As shown, the median age was 66 years, 78% were male, 91% patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had metastases to the lungs, liver and bone. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received  $\geq 2$  prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

**Table 11: Baseline Demographics of Cohort 2 of Study GO29293**

	All Patients	Patient Subgroups by PD-L1 IC Score		
	(all IC scores)	IC 0	IC1	IC2**
<b>N</b>	<b>310</b>	<b>103</b>	<b>107</b>	<b>100</b>
Age Median (mos) (Range)	66 (32, 91)	65 (36, 88)	68 (32, 91)	66 (41, 84)
Sex				
Male (%)	241 (78%)	81 (79%)	82 (77%)	78 (78%)
Female (%)	69 (22%)	22 (21%)	25 (23%)	22 (22%)
Race				
Caucasian	282 (91%)	98 (95%)	97 (91%)	87 (87%)
Black	6 (2%)	0 (0%)	4 (4%)	2 (2%)
Asian	7 (2%)	3 (3%)	0 (0%)	4 (4%)
Other*	15 (5%)	2 (2%)	6 (6%)	7 (7%)
ECOG Score				
0	117 (38%)	34 (33%)	41 (38%)	42 (42%)
1	193 (62%)	69 (67%)	66 (62%)	58 (58%)
<i>*Other: Including American Indian, Native Hawaiian, and Unknown</i>				
<i>**Tabulated as reported. See Table 9 for more details.</i>				

**Table 12: Disease Characteristics of Cohort 2 of Study GO29293**

	All Patients	Subgroups by PD-L1 IC Score		
	(all IC scores)	IC 0	IC1	IC2
<b>N</b>	<b>310</b>	<b>103</b>	<b>107</b>	<b>100</b>
UC Primary Site				
Bladder (%)	230 (74%)	71 (69%)	80 (75%)	79 (79%)
Non-Bladder (%)	80 (26%)	32 (31%)	27 (25%)	21 (21%)

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Disease Extent				
Metastatic	290 (94%)	97 (94%)	101(94%)	92 (92%)
Locally advanced	20 (6%)	6 (6%)	6 (6%)	8 (8%)
Metastasis Site				
Lymph Node Only	43 (14%)	4 (4%)	15 (14%)	24 (24%)
Visceral Metastases	243 (78%)	91 (88%)	86 (80%)	66 (66%)
Liver	96	35	34	27
Lung	135	50	54	31
Bone	59	20	23	16
Other	24 (8%)	8 (8%)	6 (6%)	10 (10%)
Number of Prior Systemic Regimens				
One Line	118 (38%)	41 (40%)	39 (36%)	38 (38%)
≥2 Lines	192 (62%)	62 (60%)	68 (64%)	62 (62%)
Number of Prior Therapy for Metastatic Disease				
One Line	182 (59%)	57 (56%)	65 (61%)	59 (59%)
≥2 Lines	128 (41%)	45 (44%)	42 (39%)	41 (41%)
Time from Last Systemic Therapy				
≤3 months	121 (39%)	34 (33%)	44 (41%)	43 (43%)
>3 months	189 (61%)	69 (67%)	63 (59%)	57 (57%)
Prior Therapy				
Cisplatin-Based	227 (73%)	66 (64%)	78 (73%)	83 (83%)
Carboplatin-Based	80 (26%)	37 (36%)	26 (24%)	17 (17%)
Other	3 (1%)	0 (0%)	3 (3%)	0 (0%)
Prior Neoadjuvant or Adjuvant	59 (19%)	17 (17%)	18 (17%)	24 (24%)

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Therapy (%)				
Prior Intravesical BCG Treatment (%)	73 (24%)	27 (26%)	31 (29%)	15 (15%)
Cystectomy				
Yes	116 (37%)	33 (32%)	39 (36%)	44 (44%)
No	194 (63%)	70 (68%)	68 (64%)	56 (56%)
HgB <10 g/dL	69 (22%)	19 (18%)	26 (24%)	24 (24%)
Cr CL<60 mL/Min	110 (35%)	41 (40%)	29 (27%)	40 (40%)
<p><i>Non-bladder UC: Including UC from the ureter, renal pelvis, urethra, and Other.</i></p> <p><i>Prior Neoadjuvant or Adjuvant Therapy: Including 2 patients who had their first disease progression 12 months after systemic therapy. All other patients had disease progression within 12 months following systemic therapy.</i></p> <p><i>Visceral disease: Some patients had &gt;1 sites of visceral metastases in the liver, lungs, and/or bone. Sixty-two percent (150/243) of patients with visceral disease also had metastases to lymph nodes. There were no patients with bone-only metastases.</i></p>				

**Efficacy Results – Primary Endpoint**

The key primary endpoint was confirmed, IRF-assessed ORR per RECIST v1.1 in all patients. As shown in Table 13, the confirmed ORR was 14.8% (95% CI: 11.1%, 19.3%) in all treated patients. Both CRs and PRs were observed. Note that this ORR was based on the submitted dataset with the cutoff date of November 27, 2015, which was associated with a median follow-up time of 14.4 months for Cohort 2.

ORR was also evaluated by the PD-L1 expression status, which was prospectively assayed in tumor specimens at a central laboratory. Two PD-L1 IC subgroups were classified as “PD-L1 expression of < 5%” and “PD-L1 expression of ≥ 5%” of stained tumor-infiltrating immune cells in the tumor area. The PD-L1 expression of < 5% corresponded to IC 0/1 and PD-L1 expression of ≥ 5% corresponded to IC 2/3. As shown in Table 13, the confirmed ORR was 9.5% (95% CI: 5.9%, 14.3%) in 210 patients with PD-L1 expression of <5% in ICs (IC0/1), and 26.0% (95% CI: 17.7%, 35.7%) in 100 patients with PD-L1 expression of ≥5% in ICs (IC2/3).

**Table 13: Confirmed ORR as Assessed by IRF in Cohort 2 of Study GO29293**

	All Patients  N = 310	PD-L1 Expression Subgroups	
		PD-L1 Expression of <5% in ICs <sup>1</sup> (N=210)	PD-L1 Expression of ≥5% in ICs (N=100)
<b>Number of IRF-assessed Confirmed Responders</b>	46	20	26
<b>ORR % (95% CI)</b>	<b>14.8 % (11.1, 19.3)</b>	<b>9.5% (5.9, 14.3)</b>	<b>26.0% (17.7, 35.7)</b>
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
<sup>1</sup> PD-L1 expression in tumor-infiltrating immune cells (ICs)			

There were 3 PD-L1 IC scores (IC0, IC1, and IC2) reported for this study. To further understand the effect of PD-L1 status on tumor responses, ORR was further evaluated by individual PD-L1 IC score (Table 14). The results show a similar ORR in patients with a PD-L1 IC score of 0 or 1. The ORR was about 16% higher in the IC 2 subgroup.

**Table 14: Confirmed, IRF-Assessed ORR by Individual PD-L1 IC Score**

	Patient Subgroups by PD-L1 IC Score		
	IC 0	IC1	IC2

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

n/N	8/103	12/107	26/100
ORR (%)	7.8%	11.2%	26.0%
(95% CI)	(3.4, 14.7%)	(5.9, 18.8%)	(17.7, 35.7%)
CR (%)	2.9%	1.9%	12.0%
PR (%)	4.9%	9.3%	14.0%

The impact of major protocol violations on ORR was assessed in all enrolled patients. Exclusion of the 34 patients resulted in an ORR of 14.5% (95% CI: 10.6%, 19.2%) in the rest of the study population. This ORR is similar to that reported in the overall population of Cohort 2 (Table 13), suggesting that the detected ORR in all patients is sustainable.

Investigator-assessed ORR per Modified RECIST was evaluated and the results are shown in Table 15. The ORR in this analysis was slightly higher in the all patient group or in each PD-L1 subgroup than that assessed per RECIST v1.1 (Table 13). The small difference was likely due to different readers and the use of different response criteria. Nevertheless, the results listed in Table 15 are considered exploratory (See Review Comments in Section 6.1).

**Table 15: ORR as Assessed by Investigator per Modified RECIST in Cohort 2 of Study GO29293**

	All Patients	PD-L1 Expression Subgroups	
	N = 310	PD-L1 Expression of <5% in ICs <sup>1</sup> (N=210)	PD-L1 Expression of <5% in ICs <sup>1</sup> (N=210)
<b>Number of Confirmed Responders per Modified RECIST</b>	60	31	29
<b>ORR % (95% CI)</b>	<b>19.4 % (15.1, 24.2)</b>	<b>14.8% (10.3, 20.2)</b>	<b>29.0% (20.4, 38.9)</b>
Complete Response (CR) (%)	5.8%	4.8%	8.0%
Partial Response (PR) (%)	13.5%	10%	21.0%
<sup>1</sup> PD-L1 expression in tumor-infiltrating immune cells (ICs)			

Discordances between Tables 13 and 15 were investigated and the findings are shown in Table 16. Overall, the discordance rates were approximately 10% or less. Note that due to differences in readers and use of response criteria, this investigation of discordances may have a high level of bias and/or irrelevance.

**Table 16: Discordance between IRF Assessment per RECIST 1.1 and Investigator Assessment per Modified RECIST**

INV modified RECIST	IRF RECIST 1.1		Discordance Rate
	Responder	Non-Responder	
	Overall (n=310)		
Responder	40	20	26/310=8.4%
Non-Responder	6	244	
	IC0 (n=103)		
Responder	8	5	5/103=4.9%
Non-Responder	0	90	
	IC1 (n=107)		
Responder	10	8	10/107=9.3%
Non-Responder	2	87	
	IC2 (n=100)		
Responder	22	7	11/100=11%
Non-Responder	4	67	

*Note: Selection of different indexed lesions and use of Modified RECIST criteria likely contribute to the discordance.*

To understand whether atezolizumab treatment was associated with pseudo-progression in advanced urothelial carcinoma, we examined the number of patients who had disease progression per RECIST v1.1 but who were considered responsive by Investigator per modified RECIST criteria. Seven patients were identified (Table 17). After examining the reported response data for each patient, we found that after treatment initiation, two patients had early increases of  $\geq 20\%$  (relative to baseline) in the sum of the indexed lesions, followed by decreases of  $>30\%$  in the sum of the indexed lesion. This suggests that pseudo-progression occurred in few patients. The remaining 5 patients who were considered responsive per modified RECIST had no increases of  $\geq 20\%$  in the sum of the indexed lesions after treatment initiation. These patients might have had non-evaluable disease or new lesions considered disease progression by IRF per RECIST v1.1.

**Table 17: Difference in Tumor Responses between IRF-Assessed per RECIST v1.1 and Investigator-Assessed per Modified RECIST**

Investigator-assessed per Modified RECIST	IRF Assessed per RECIST v1.1					
	CR	PR	SD	PD	NE	Missing
CR	9	5	0	3	1	0
PR	7	19	11	4	1	0
SD	1	5	44	40	0	0
PD	0	0	5	104	1	
NE	0	0	0	5	2	1
Missing	0	0	0	1	2	39

*NE: non-evaluable as reported.*

### Data Quality and Integrity – Reviewers’ Assessment

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent and variables are clearly labeled and or explained. The tumor response datasets included all assessment values and time points. In addition, the Applicant responded to numerous information inquiries in a timely manner and resolved identified issues and/or review questions satisfactorily. Based on the submitted data and reports, the reviewers believe that analyses and results are reliable for regulatory decision making.

### Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was DOR. With the data used for the ORR analysis shown in Table 13, median DOR in responders was not reached and the observed response durations ranged from 2.1+ to 13.8+ months (Table 18). Of the responders, 37 had ongoing responses of  $\geq 6$  months and 6 had ongoing responses of  $\geq 12$  months. Response durations were also tabulated by the PD-L1 subgroups and the results are similar to those in all patients.

**Table 18: Response Duration in Responders of Cohort 2 of GO 29293**

	All Patients (N=310)	PD-L1 Expression Subgroups	
		PD-L1 Expression of <5% in ICs (IC 0/1) (N=210)	PD-L1 Expression of $\geq 5\%$ in ICs (IC2/3) (N=100)
Number of Responders (IRF)	46	20	26
DOR Median (mos) (Range)	NR (2.1+, 13.8+)	12.7 (2.1+, 12.7)	NR (4.2, 13.8+)
Number of Patients Responding for $\geq 6$ months (%)	37/46 (80.4%)	14/20 (70%)	23/26 (88.5%)
Number of Patients Responding for $\geq 12$ months (%)	6/46 (13.0%)	2/20 (10%)	4/26 (15.4%)
+: denotes a censored value NR= Not reached			

Other important secondary endpoints included ORR and DOR as assessed by Investigator per RECIST v1.1. The analysis findings are shown in Table 19. These are similar to the results based on the IRF assessments using the same criteria (Table 13).

**Table 19: Investigator-Assessed ORR and DOR per RECIST v1.1 in Cohort 2 of GO 29293**

	All Patients (N=310)	PD-L1 Expression Subgroups	
		PD-L1 Expression of <5% in ICs (IC0/1) (N=210)	PD-L1 Expression of ≥5% in ICs (IC2/3) (N=100)
n/N	50/310	25/210	25/100
ORR (%)	16.1%	11.9%	25.0%
(95% CI)	(12.2, 20.7%)	(7.9, 17.1%)	(16.9, 34.7%)
CR (%)	5.5%	4.3%	8.0%
PR (%)	10.6%	7.6%	17.0%
DoR Median (mos) (Range)	NR (2.1+, 13.8+)	NR (2.1+, 12.2+)	NR (4.2, 13.8+)
Number of Patients Responding for ≥6 months (%)	44/50 (88%)	21/25 (84%)	23/25 (92%)
Number of Patients Responding for ≥12 months (%)	4/50 (8%)	1/25 (4%)	3/25 (12%)

*NR: Not reached*

We further evaluated discordances between IRF- and Investigator-assessed responses per RECIST v1.1 and found generally lower discordance rates (Table 20) when the same response criteria were used.

Similarly, we explored Investigator-assessed responses between the RECIST v1.1 and modified RECIST and the findings are listed in Table 21. Relative to the results in Table 17, it seems that discrepancies were less frequent with the same reader despite the use of two different criteria.

We examined the 6 patients with Investigator-assessed disease progression per RECIST v1.1 who had a response per modified RECIST (Table 21), and found that after treatment initiation, three patients had early increases of ≥20% (relative to baseline) in the sum of the indexed lesions, followed by decreases of >30% in the sum of the indexed lesion. Two of the three patients were the same as those identified in the examination of the differences between IRF-assessed per RECIST v1.1 and Investigator-assessed per modified RECIST. The third patient had early increases of ≥20% in the sum of the lesions as assessed by the Investigator per RECIST

v1.1, followed by decreases of >30%. For this patient, the best response, according to the IRF assessments, was stable disease. This discrepancy might be due to selection of different target lesions. Overall, these observations suggest that pseudo-progression occurred occasionally in patients with advanced urothelial carcinoma who received atezolizumab monotherapy.

**Table 20: Discordance between IRF- and Investigator-Assessed Responses per RECIST v1.1**

Per IRF assessment	Per INV assessment		Discordance rate
	Responder	Non-Responder	
	Overall (N=310)		
Responder	39	7	18/310=5.8%
Non-Responder	11	253	
	IC0 (N=103)		
Responder	8	0	4/103=3.9%
Non-Responder	4	91	
	IC1 (N=107)		
Responder	10	2	5/107=4.7%
Non-Responder	3	92	
	IC2 (N=100)		
Responder	21	5	9/100=9.0%
Non-Responder	4	70	

**Table 21: Difference in Distribution of Investigator-Assessed Tumor Responses between RECIST v 1.1 and Modified RECIST**

Modified RECIST	INV RECIST 1.1					
	CR	PR	SD	PD	NE	Missing
CR	17	0	0	1	0	0
PR	0	33	4	5	0	0
SD	0	0	65	25	0	0
PD	0	0	0	110	0	0
NE	0	0	0	4	4	0
Missing	0	0	0	2	0	40

Relevant to the proposed indication for use of atezolizumab in patients who have disease progression within 12 months of neoadjuvant or adjuvant therapy, we also analyzed ORR and DOR in this subpopulation. The results are shown in Table 22, indicating that atezolizumab is active in this subpopulation.

Table 22 also contains results from other subgroup analyses based on key baseline disease characteristics. None of these analyses were pre-specified. Overall, atezolizumab is active in all the subgroups. Prior BCG treatment does not appear to increase responses to atezolizumab.

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Patients with non-bladder urothelial carcinoma had a low response rate relative to other subgroups. In contrast, patients with lymph node only metastases had a higher response rate relative to patients with visceral metastases, suggesting that tumor burden and location may affect the treatment effect of atezolizumab.

**Table 22: ORR and DOR in Important Subgroups in Cohort 2 of Study GO29293**

Subgroup	Disease Progression Following Neoadjuvant or Adjuvant Treatment	Prior BCG Treatment	With Non-bladder UC	With Visceral Metastases	Lymph Node Only Metastases
n/N	13/59	10/73	6/80	24/243	13/43
ORR (%)	22.0%	13.7%	7.5%	9.9%	30.2%
(95% CI)	(12.3, 34.7%)	(6.8, 23.8%)	(2.8, 15.6%)	(6.4, 14.3%)	(17.2, 46.1%)
CR (%)	11.9%	1.4%	0%	2.1%	20.9%
PR (%)	10.2%	12.3%	7.5%	7.8%	9.3%
DoR Median (mos) (Range)	12.7 (4.1, 12.7)	NR (4.2+, 12.2+)	NR (2.1+, 13.7+)	12.7 (4.1, 13.7+)	NR (2.1+, 13.8+)
Number of Responding Patients Still on Treatment (%)	11/13 (84.6%)	7/10 (70%)	3/6 (50%)	16/24 (66.7%)	11/13 (84.6%)
Number of Patients Responding for ≥6 months (%)	10/13 (77%)	6/10 (60%)	5/6 (83%)	13/24 (54%)	11/13 (85%)
Number of Patients Responding for ≥12 months (%)	1/13 (8%)	1/10 (10%)	1/6 (17%)	4/24 (17%)	1/13 (8%)

NR: Not reached

Note that 35% of patients (7/20) with locally advanced disease without metastases had IRF-confirmed responses. In addition, 7.4% of patients (2/27) with transitional cell carcinoma with mixed histology had IRF confirmed responses.

Regarding time from the last chemotherapy, 10.7% of patients (13/121) with ≤3 months from the last

*chemotherapy had IRF confirmed responses versus 17.5% of patients (33/189) with >3 months from the last chemotherapy.*

*There are overlapping patients among the listed subgroups due to coexisting characteristics.*

Other important secondary endpoints were PFS and OS. Table 23 shows the results of PFS and OS in Cohort 2. The median PFS in all patients was 2.1 months. This is consistent across all the PD-L1 subgroups. The median OS was 7.9 months in all patients. While the median in the IC 0/1 groups was similar, the median OS in the IC 2 group appears longer. The reason for this observed difference may be related to the baseline disease characteristics and/or better responses in the IC2 subgroup. Nevertheless, having considered that time-to-event endpoints are difficult to interpret in single arm trials, implications of the observed OS and PFS in this study are not clear and no conclusions can be reliably made based on the results shown Table 23.

**Table 23: Estimated PFS and OS in Cohort 2 of Study GO 29293**

	All Patients	Patient Subgroups by PD-L1 IC Score		
	(all IC scores)	IC 0	IC1	IC2
<b>N</b>	<b>310</b>	<b>103</b>	<b>107</b>	<b>100</b>
PFS				
# of events (%)	266 (85.8%)	94 (91.3%)	95 (88.8%)	77 (77%)
Median (mos)	2.1	2.1	2.1	2.1
(95% CI)	(2.1, 2.1)	(2.0, 2.3)	(2.0, 2.1)	(2.1, 4.1)
OS				
# of events (%)	204 (65.8%)	77 (74.8%)	77 (72.0%)	50 (50.0%)
Median (mos)	7.9	6.5	6.7	11.9
(95% CI)	(6.6, 9.3)	(4.2, 8.1)	(5.1, 8.8)	(7.6, NE)

### Dose/Dose Response

All patients in this cohort received a fixed dose of 1200 mg atezolizumab.

### Durability of Response

See Tables 18 regarding the response durability. The median of DOR was not reached at the data cutoff time for ORR analysis of the overall patient population. The majority of responders

maintained their responses for 6 months or more.

### Persistence of Effect

Given the above findings, the treatment effect in responding patients appear persistent; however, the current estimate in all patients or in each PD-L1 subgroup may not be dependable as the data is not mature. To better assess the persistence of treatment effect in responders, the review team recommended that the applicant fulfill a PMC to provide mature datasets and estimates of DOR (See Section 12).

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### **Results from Phase 1 UBC Cohort**

Phase 1 UBC Cohort provides supportive evidence to this BLA for the proposed indication. As discussed in Section 6.1.1, this cohort was generated from a large expansion of the Phase 1 study that was designed to primarily assess the safety and MTD of atezolizumab in multiple solid tumors and hematological malignancies. The cohort started to enroll patients from March of 2013 and initially focused on recruiting patients with a PD-L1 IHC score of 2 or 3 in tumor specimens as determined by the prototype PD-L1 assay. From September of 2013, this cohort was open to patients with a PD-L1 IHC score of 0 or 1 in their tumor specimens. There were a total of 94 patients enrolled in this cohort from March 2013 to December 2014. Table 24 shows patients' enrollment distribution by time periods and PD-L1 IHC status according to the prototype PD-L1 assay. Given that 53% of patients had an original PD-L1 IHC score of 2 or 3 at enrollment, the population of this cohort is not the same as the patient population in Study GO 29293.

**Table 24: Enrollment of Patients by Time Periods and Preliminary PD-L1 Scores in the UBC Cohort**

Time Period	Mar-Aug. 2013	Sep-Dec. 2013	Jan-Apr. 2014	May-Dec. 2014	Total
IHC 0/1	0	37	0	7	44 (47%)
IHC 2/3	21	10	10	9*	50 (53%)
*Two of the 9 patients had their PD-L1 score determined with both the prototype and IUO PD-L1 assay.					
IUO: Investigation use only					

For patients with additional evaluable tumor specimens, PD-L1 expression scores were later

reassessed per the IUO PD-L1 assay that was submitted to CDRH for its analytical validation evaluation (Section 4.1.6). The results are summarized in Table 25. Twenty five patients had their PD-L1 IC scores reported as “Unknown” in this reassessment, including 14 patients from the “preliminary IC 2/3” group and 9 from the “preliminary IC 0/1” group. The new IC scores per IUO assay as listed in the table were used to explore differences in ORR and DOR in this cohort.

**Table 25: PD-L1 Expression Status in Reanalysis with PD-L1 IUO Assay**

	Enrolled Patients	PD-L1 IC Score per IUO				
		PD-L1 Expression of <5% in ICs		PD-L1 Expression of ≥5% in ICs		PD-L1 Expression Unknown
		IC 0	IC1	IC2	IC3	
<b>IC Scores per Prototype Assay</b>	94	18	30	17	4	25
IHC 0/1	44 (47%)	15	16	1	1	11
IHC 2/3	50* (53%)	3	14	16	3	14

*\*Including two patients whose PD-L1 expression was assessed with both the prototype and IUO PD-L1 assay.*

*Note: PD-L1 IC Score per IUO was based on the retrospective assessment of evaluable tumor specimens using the PD-L1 assay submitted to CDRH for a PMA. IC Scores per Prototype Assay represent those determined with the prototype assay during the study.*

#### Patient Disposition in the Phase 1 UBC Cohort

Patient disposition in the UB cohort was examined with the data cutoff date of August 7, 2015 and the results are shown in Table 26. Twenty-eight percent of patients were on study treatment while 72% of patients discontinued from study treatment. The majority of the patients came off the study because of disease progression.

**Table 26: Patient Disposition in the Phase 1 UBC Cohort**

	Enrolled Patients
<b>N</b>	<b>94</b>
On-Study Treatment	26 (28%)

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Off-Study Treatment	68 (72%)
<u>Reasons for Discontinuation</u>	
Disease Progression	60
Death	1
Adverse Reaction	1
Withdrawal	2
Other*	4
<i>Other: Including non-compliance, lost to follow-up, and Investigator's decision.</i>	

**Protocol Violations/Deviations in the UBC Cohort**

Major protocol violations and/or deviations were investigated and the results are summarized in Table 27. These included unmet eligibility criteria, delayed consent of patients and delayed reporting of serious adverse events. The reasons for “eligibility criteria unmet” were hemoglobin levels less than the required level of 9 g/dL in two patients, active infection within 2 weeks before the first dose in 1 patient, and radiotherapy within 2 weeks prior to the first dose in 1 patient.

The impact of key deviations such as eligibility criteria unmet and study procedure deviations, which might affect the treatment effect assessment, was evaluated in a sensitivity analysis and the results are included in the following result section for this UBC cohort.

**Table 27: Major Protocol Violations/Deviations in the Phase 1 UBC Cohort**

	All Patients
<b>N</b>	<b>94</b>
Protocol violations	20 (21%)
Eligibility Criteria Unmet	4 (4%)
Delayed ICF and/or Not Re-consented per Protocol	7 (7%)
Delayed Reporting of SAEs	4 (4%)
Other*	10 (11%)
<i>*Other: Including laboratory criteria not met, study procedure deviations, and dosing deviations (e.g., one time of 2 week dosing interval instead of the protocol required 3 week interval).</i>	
<i>Note that some patients had &gt;1 violations and/or deviations.</i>	

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Baseline characteristics of patients in this cohort were evaluated and key findings are listed in Tables 28 and 29. Seventy percent of patients had visceral metastases and 98% received prior platinum-containing chemotherapy. Eight percent of patients had systemic chemotherapy for metastatic disease. Overall, the baseline characteristics appear similar to those in Study GO 29293, but are not the same as those in Study GO29293 in that there were more patients (~47%) who received prior adjuvant treatment besides the enrichment with a PD-L1 IHC score of 2/3 (Table 24).

**Table 28: Demographic Characteristics in the UBC Cohort**

	All Patients
<b>N</b>	<b>94</b>
Age Median (mos) (Range)	66 (36, 89)
Sex Male (%) Female (%)	71 (76%) 23 (34%)
Race Caucasian Black Asian Other*	74 (79%) 1 (1%) 2 (2%) 17 (18%)
ECOG Score 0 1	37 (39%) 57 (61%)
<i>*Other: Including American Indian, Native Hawaiian, and Unknown</i>	

**Table 29: Disease Characteristics in the Phase 1 UBC Cohort**

	All Patients
<b>N</b>	<b>94</b>

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Primary UC Site	
Bladder (%)	75 (80%)
Non-Bladder* (%)	19 (20%)
Metastasis Site**	
Lymph Node Only	15 (16%)
Visceral Metastases	74 (79%)
Liver	31
Lung	46
Bone	13
Other	15 (16%)
Prior Therapy	
Cisplatin-Based	72 (77%)
Carboplatin-Based	36 (38%)
Other	2 (2%)
Number of Prior Systemic Therapy for Metastatic Disease	
≥2 Lines	70 (74%)
1 Line	6 (6%)
None	18 (19%)
Prior Adjuvant Therapy (%)	44 (47%)
Prior Cystectomy or Nephrectomy	
Yes	65 (69%)
No	29 (31%)
Hgb <10g/dL	17 (18%)
*Non-bladder UC: Including UC from the ureter, renal pelvis, and urethra.	
** Patients could have more than one sites of metastases	
Visceral disease: Some patients had >1 sites of visceral metastases in the liver, lungs, and/or bone.	

**Efficacy Results from the UBC Cohort**

Confirmed ORR as assessed by IRF per RECIST v1.1 was 25.5% (95% CI: 17.1%, 35.6%) in the whole cohort, with 9 CRs and 15 PRs reported (Table 30). For this ORR analysis, the median duration of survival follow-up in this UBC cohort was 20 months.

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Median DOR per IRF-RECIST v1.1 in all responders was not reached, with ongoing responses of  $\geq 6$  months observed in 22 responders and of  $\geq 12$  months in 14 responders.

Based on the reported retrospective PD-L1 expression IC scores per IUO assay in this cohort, the confirmed ORR was 20.8% (95% CI:10.5%, 35.0%) in 48 patients with PD-L1 expression negative in ICs, 33.3% (95% CI: 14.6%, 57.0%) in 21 patients with PD-L1 expression positive in ICs, and 28.0% (95% CI: 12.1%, 49.4%) in 25 patients with PD-L1 expression “Unknown”. The percentages of patients who maintained their responses for  $\geq 6$  months or  $\geq 12$  months in the subgroups seems similar to those in the all enrolled patients in this UBC cohort. Given the initial enrichment of this cohort for PD-L1 expression and the small sample size, the ORRs along with the listed duration response information in the overall enrolled population should be interpreted with caution.

**Table 30: Confirmed ORR and DOR as Assessed by IRF in the UBC Cohort**

	Enrolled Patients (N=94)	Retrospectively-Determined IC Subgroups		
		PD-L1 Expression of <5% in ICs (IC 0/1) (N=48)	PD-L1 Expression of $\geq 5\%$ in ICs (IC 2/3) (N=21)	PD-L1 Expression Unknown (N=25)
<b>Number of IRF- assessed Confirmed Responders*</b>	24	10	7	7
<b>ORR % (95% CI)</b>	<b>25.5 % (17.1, 35.6)</b>	<b>20.8% (10.5, 35.0)</b>	<b>33.3% (14.6, 57.0)</b>	<b>28.0% (12.1, 49.4)</b>
Complete Response (CR) (%)	9.6%	6.3%	14.3%	12.0%
Partial Response (PR) (%)	16.0%	14.6%	19.0%	16.0%
Number of Patients Responding for $\geq 6$ months (%)	22/24 (91.7%)	8/10 (80%)	7/7 (100%)	7/7 (100%)
Number of Patients Responding for $\geq 12$ months (%)	14/24 (58.3%)	5/10 (50%)	5/7 (71%)	4/7 (57.1%)
<i>*The minimum follow up time was 24 weeks for all the enrolled patients.</i>				

The impact of major protocol violations was also evaluated for this cohort. Exclusion of 8 patients whose protocol violations (eligibility criteria unmet and study procedure deviations), which might affect the treatment effect assessment may affect ORR, resulted in an ORR 23.3% (95% CI: 14.8%, 33.6%). This is similar to that shown in Table 30, supporting the observed ORR in all enrolled patients.

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

We further explored ORR and DOR by each reported IC score per the IUO assay, the findings are listed in Table 31. Except for patients with an IC score of 0, patients with other IC score appear to have comparable ORRs (25%-35%). This also includes patients “unknown” for PD-L1 expression.

**Table 31: ORR and DOR by Individual IC score per the IUO assay in the UBC Cohort**

	PD-L1 IC Score per IUO Assay				
	IC 0	IC1	IC2	IC3	Unknown
n/N	2/18	8/30	6/17	1/4	7/25
ORR (%)	11.1%	26.7%	35.3%	25.0%	28.0%
(95% CI)	(1.4, 34.7%)	(12.3, 45.9%)	(14.2, 61.7%)	(0.6, 80.6%)	(12.1, 49.4%)
CR (%)	5.6%	6.7%	11.8%	25.0%	12.0%
PR (%)	5.6%	20.0%	23.5%	0%	16.0%
DoR Median (mos) (Range)	NR  (16.1+, 18.1+)	9.6  (2.9, 21.4+)	NR  (9.2, 24.0+)	NR  (21.9+)	17.5  (7.0, 26.3+)
Number of Patients Responding for ≥6 months (%)	2/2 (100%)	6/8 (75%)	6/6 (100%)	1/1 (100%)	7/7 (100%)
Number of Patients Responding for ≥12 months (%)	2/2 (100%)	3/8 (37.5%)	4/6 (66.7%)	1/1 (100%)	4/7 (57.1%)

+Censored value. NR=Not reached

The results are based on the updated dataset with a data cutoff date of August 7, 2015.

Overall survival and PFS of patients in the cohort were evaluated in all the enrolled patients and PD-L1 subgroups (Table 32). The median survival in all the patients was 10.6 months while the median PFS was about 2 months. It seems that patients in the PD-L1 expression “unknown” group had a median OS of ~18 months. Given the limitations related to this cohort in a single arm study, interpretation of the OS and PFS in the PD-L1 subgroups is very difficult.

**Table 32: PFS and OS in the Phase 1 UBC Cohort**

	All Enrolled Patients	PD-L1 IC Subgroups		
		PD-L1 Expression of <5% in ICs (IC 0/1) (N=48)	PD-L1 Expression of ≥5% in ICs (IC 2/3) (N=21)	PD-L1 Expression Unknown (N=25)
PFS*				
# of events (%)	74 (79%)	39 (81%)	16 (76%)	19 (76%)
Median (mos)	1.8	1.6	2.7	1.5
(95% CI)	(1.4, 4.0)	(1.4, 4.0)	(1.4, 10.6)	(1.3, 8.2)
OS				
# of events (%)	52 (55%)	27 (56%)	12 (57%)	13 (52%)
Median (mos)	10.6	9.9	11.2	17.9
(95% CI)	(7.3, 17.9)	6.0, 19.6)	(4.4, NE)	(4.6, NE)

\*Tumor response assessments were performed every 6 weeks in this UBC cohort.

**Review Comments:** The above results from this UBC cohort are considered supportive of this BLA for the proposed indication. The noticeable difference in the patient population between this cohort and Cohort 2 of Study GO 29293 likely explains the observed, relatively higher response rate in the Phase 1 UBC cohort, which may not represent the response rate in a PD-L1 unselect, general patient population. On the other hand, the key measures of antitumor activity in this UBC cohort may be suggestive of a possibly higher response rate to atezolizumab in patients with a PD-L1 expression IC score of 2 or 3. Nevertheless, the predictive value of PD-L1 IC positivity appear low and additional studies of other biomarkers are clearly needed to select patients who are likely to benefit more from atezolizumab.

#### Additional Analyses Conducted on the Individual Trial

**Cohort 2 of Study GO29293:** PD-L1 expression on tumor cells (TCs) was also collected at the central laboratory without analytical validation. To explore whether the detected ORR was association with PD-L1 expression in TCs, we evaluated ORR by the reported PD-L1 TC scores. The results, as shown in Table 33, suggest no association of ORR with the reported PD-L1 TC scores in this study cohort.

**Table 33: Exploratory Evaluation of ORR by the Reported PD-L1 TC Scores in Cohort 2 of Study GO 29293**

TC Score*	All Patients	Patients Subgroup by PD-L1 IC Score		
	(All IC Scores)	IC0	IC1	IC2
<b>TC0 (n= 248)</b>	36/248 (14.5%)	6/98 (6.1%)	11/85 (12.9%)	19/65 (29.2%)
<b>TC1 (n= 22)</b>	3/22 (13.6%)	2/4 (50%)	1/14 (7.1%)	0/4 (0%)
<b>TC2 (n= 28)</b>	5/28 (17.9%)	0/1 (0%)	0/7 (0%)	5/20 (25%)
<b>TC3 (n= 12)</b>	2/12 (16.7%)	0	0/1 (0%)	2/11 (18.2%)

\* The TC scoring system was not analytically validated based on the Applicant's development plan and submitted data for the PMA. The reported TC scores may be uninterpretable and the results as shown are solely exploratory.

**The Phase 1 UBC Cohort:** As illustrated in Table 24, this initial study cohort in patients with advanced urothelial carcinoma was enriched with those whose tumor specimens tested positive for PD-L1 expression (IHC 2/3) per the prototype assay. The percentage of those patients was 53% in this cohort, which about 20% higher than that of patients with a PD-L1 IC score of 2/3 in Cohort 2 of Study GO 29293 that enrolled patients without selection by PD-L1 status. As such, we also explored ORR of this cohort by the prototype assay determined PD-L1 IHC score subgroups. As shown in Table 34, the results suggest that patients “positive” for PD-L1 expression in ICs (IHC 2/3) in the original assay appear to have considerably higher response rates regardless of the groups (all enrolled group, IC subgroups, or unknown as determined with the IUO assay). This may explain why the ORR in this small cohort was higher than that in Cohort 2 of Study GO 29293. Given this reason, the overall ORR of 25.5% in this selected UBC cohort (Table 30) appears inflated, and may not represent the response rate to be observed in the intended patient population for this BLA.

**Table 34: Exploratory Evaluation of ORR per PD-L1 Expression Status as Reported with Prototype Assay in the Phase 1 UBC Cohort**

	Enrolled Patients	PD-L1 IC Subgroups per IUO Assay		
		PD-L1 Expression of <5% in ICs (IC 0/1)	PD-L1 Expression of ≥5% in ICs (IC 2/3)	PD-L1 Expression in ICs (Unknown)
<b>IHC Subgroups per Prototype Assay*</b>	94	48	21	25
IHC 0/1	5/44 (11.4%)	3/31 (9.7%)	0/2 (0%)	2/11 (18.2%)
IHC 2/3	19/50 (38.0%)	7/17 (41.2%)	7/19 (36.8%)	5/14 (35.7%)
*Note that the PD-L1 prototype assay was not submitted for analytical validation. See Table 25 about the retrospective re-determination of PD-L1 IC scores using the IUO assay for PD-L1 expression in this cohort.				

## 7 Integrated Review of Effectiveness

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## 7.1. Assessment of Efficacy Across Trials

### 7.1.1. Primary Endpoints

Demonstration of the effectiveness of atezolizumab for the proposed indication is based on the results of Cohort 2 of Study GO29293, with supportive evidence from the UBC Cohort of the Phase 1 Study PCD4989g. In both cohorts, the key efficacy measures were ORR and DOR as assessed by IRF per RECIST v1.1. These measures serve as surrogates of effectiveness.

ORRs from the two cohorts are summarized in Table 35. These ORRs show that approximately 15-25% of study patients with advanced urothelial carcinoma who had received prior platinum-containing chemotherapy responded to atezolizumab monotherapy. This most likely represents a clinically important improvement relative to the chemotherapeutics used off-label in the treatment of the disease. Most importantly, many patients had durable responses (Table 36). Given the limited treatment options in the disease setting and the relatively favorable tolerability and safety profile of atezolizumab (Section 8), the demonstrated effectiveness provides adequate evidence to support use of atezolizumab as a second-line treatment in patients with advanced urothelial carcinoma who have received prior platinum-containing chemotherapy.

The difference in ORR between the two study cohorts may be due to the difference in the enrolled patients, the small sample size, and/or the heterogeneity of the study disease. As discussed earlier (Tables 24 and 25), the Phase 1 UBC cohort was enriched with patients whose tumor specimens had a PD-L1 expression IHC score of 2 or 3. Since PD-L1 expression status appears to be associated with ORR in both study cohorts, we further evaluated ORR by PD-L1 subgroups in a pooled analysis. As shown in Table 35, ORR was 11.6% in the IC 0/1 group and 27.3% in the IC2/3 group. These are similar to the results (Table 13) in Cohort 2 of Study GO 29293, suggesting that patients with a PD-L1 IC score of 2 /3 may have a 15% higher response rate than those with a PD-L1 IC score of 0/1. Nevertheless, the observed ORR and durable responses in the PD-L1 IC 0/1 group remain clinically important because of the limited treatment options and their uncertain benefit-risk profiles (Table 2).

**Table 35: ORR as Assessed by IRF per RECIST v1.1 in the Two Study Cohorts and Pooled PD-L1 Subgroups**

	Cohort 2 of Study GO 29293  (n=310)	Phase 1 UBC Cohort  (n=94)	Pooled PD-L1 Subgroups*	
			PD-L1 Expression of <5% in ICs (IC 0/1) (N=258)	PD-L1 Expression of ≥5% in ICs (IC 2/3) (N=121)
<b>Number of IRF- assessed</b>				

<b>Confirmed Responders</b>	46	24	30	33
<b>ORR %</b>	14.8%	25.5%	11.6%	27.3%
<b>(95% CI)</b>	(11.1%, 19.3%)	(17.1%, 35.6%)	(8.0%, 16.2%)	(19.6%, 36.1%)
<b>CR (%)</b>	5.5%	9.6%	3.1%	12.4%
<b>PR (%)</b>	9.4%	16.0%	8.5%	14.9%
*Based on the reported IC scores with the IUO PD-L1 assay from the same central laboratory. The data cutoff time was 11/27/2015 in Cohort 2 of Study GO 29293 and 8/7/2015 in the Phase 1 UBC Cohort.				

### 7.1.2. Secondary and Other Endpoints

DOR was the key secondary endpoint. Table 36 summarizes DOR from the two cohorts along with the other endpoints PFS and OS.

Median DOR was not reached in either cohort as of the data cutoff for the ORR analysis. Some patients had durable responses for  $\geq 1$  years. This is consistent with the findings shown in Tables 18 and 30. Similarly, we explored DOR by PD-L1 expression status. The results suggest no noticeable differences in responders.

Table 36 also shows the analyses of PFS and OS. Given the non-randomized study design for each cohort, the interpretation of the findings is limited. One common finding is that the observed PFS appears similar either between the two study cohorts or between the PD-L1 IC subgroups. While the OS appears longer in the IC2/3 group than in the IC0/1 group, this finding is not interpretable. Whether the difference in OS is secondary to prognostic and/or predictive value of the IC scores needs to be examined in a randomized clinical trial.

**Table 36: Other Efficacy Measurements in the Two Studies and Relevant Subgroups**

	Phase 2 Cohort 2 (n=310)	Phase 1 UBC Cohort (n=94)	Pooled PD-L1 Subgroups*	
			PD-L1 Expression of <5% in ICs (IC 0/1) (N=258)	PD-L1 Expression of $\geq 5\%$ in ICs (IC 2/3) (N=121)
<b>DOR</b>				
# of Responders	46	24	30	33
# of Events** (%)	9 (20%)	8 (33%)	9 (30%)	6 (18%)
Median (mos)				

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

(min, max)	NR (2.1+, 13.8+)	NR (2.9, 26.3+)	NR (2.1+, 21.4+)	NR (4.2, 24.0+)
<b>PFS (IRF)</b>				
# of events (%)	266 (85.8%)	74 (78.7%)	228 (88%)	93 (77%)
Median (mos) (95% CI)	2.1 (2.1, 2.1)	1.8 (1.4, 4.0)	2.1 (2.0, 2.1)	2.2 (2.1, 4.1)
<b>OS</b>				
# of events (%)	204 (65.8%)	52 (55.3%)	154 (73%)	50 (50%)
Median (mos) (95% CI)	7.9 (6.6, 9.3)	10.6 (7.3, 17.9)	6.7 (5.4, 8.0)	11.9 (7.6, NE)
+ Censored value; NR=Not reached; NE=Not estimable				
*Based on the reported IC scores with the IUO PD-L1 assay from the same central laboratory.				
**Including patients whose disease progressed or who died.				
The data cutoff time was 11/27/2015 in Cohort 2 of Study GO 29293 and 8/7/2015 in the Phase 1 UBC Cohort.				

### 7.1.3. Subpopulations

In addition to the subgroup analyses shown in Table 22, we evaluated ORR in key demographic subgroups of the two study cohorts. Table 37 shows that responses were observed regardless of age, sex, performance status, and region, suggesting that the activity of atezolizumab in advanced urothelial carcinoma is not limited to a particular patient group. The observed differences in ORR may be due to the small numbers of responders rather than treatment effect differences. The differences in response rate by sex or ECOG status are noticeable in both studies and are of concern. Additional data from other studies in urothelial carcinoma may help in the interpretation of these differences.

**Table 37: Analysis of ORR in Key Subgroups in the Two Cohorts**

ORR n/N % (95% CI)	Cohort 2 of GO29293 (N=310)	Phase 1 UBC Cohort (N=94)
Age <65	17/127 13.4% (8.0%, 20.6%)	8/39 20.5% (9.3%, 36.5%)

Age >=65	29/183 15.8% (10.9%, 22.0%)	16/55 29.1% (17.6%, 42.9%)
Male	40/241 16.6% (12.1%, 21.9%)	21/71 29.6% (19.3%, 41.6%)
Female	6/69 8.7% (3.3%, 18.0%)	3/23 13.0% (2.8%, 33.6%)
ECOG PS 0	30/117 25.6% (18.0%, 34.5%)	17/37 46.0% (29.5%, 63.1%)
ECOG PS 1	16/193 8.3% (4.8%, 13.1%)	7/57 12.3% (5.1%, 23.7%)
US	28/210 13.3% (9.1%, 18.7%)	17/52 32.7% (20.3%, 47.1%)
Non-US	18/100 18.0% (11.0%, 27.0%)	7/42 16.7% (7.0%, 31.4%)

#### 7.1.4. Dose and Dose-Response

Almost all patients in the two cohorts received a fixed dose of 1200 mg atezolizumab or a dose similar to 1200 mg (e.g., 15 mg/kg) in the Phase 1 UBC cohort. One patient received a higher dose of atezolizumab (20 mg/kg). Therefore, no dose-response relationship can be explored.

#### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

Time to onset of responses was evaluated in both cohorts. Since the activity assessment schedules differ in the two cohorts, the findings are listed individually in Tables 38 and 39.

Median time to response onset was 2.1 months in all patients of Cohort 2 of the Phase 2 study and 1.4 months in the Phase 1 UBC Cohort. This is likely due to differences in the timing of the first assessment, 9 weeks in Cohort 2 and 6 weeks in the Phase 1 UBC Cohort. The observed ranges were up to 8 months, suggesting that some patients had delayed onset of responses. The time to onset did not appear associated with PD-L1 IC status in both cohorts or with PD-L1 IC unknown in the UBC cohort.

For response duration and durability, see Section 7.1.2 and the results listed in Tables 18 and 30. Given that the median DOR was not reached in either cohort at the time for the ORR analysis, the review team recommended that the Applicant conduct a PMC study and submit mature data and analyses in all responders in Cohort 2 of Study GO29293.

**Table 38: Time to Onset of Responses in Cohort 2 of Study GO 29293**

	All Patients (N=310)	PD-L1 Subgroups	
		PD-L1 Expression of <5% in ICs (IC 0/1) (N=210)	PD-L1 Expression of ≥5% in ICs (IC 2/3) (N=100)
Number of IRF- assessed Confirmed Responders	46	20	26
Time to onset of response* (IRF) Median (Min, Max), months	2.1 (1.6, 8.3)	2.1 (1.9, 8.3)	2.0 (1.6, 6.2)

*\*Responses were assessed every 9 weeks.*

**Table 39: Time to Onset of Responses in the Phase 1 UBC Cohort**

	Enrolled Patients (N=94)	Retrospectively-Determined IC Subgroups		
		PD-L1 Expression of <5% in ICs (IC 0/1) (N=48)	PD-L1 Expression of ≥5% in ICs (IC 2/3) (N=21)	PD-L1 Expression Unknown (N=25)
Number of IRF- assessed Confirmed Responders	24	10	7	7
Time to onset of response* (IRF) Median (Min, Max), months	1.4 (1.0, 8.1)	1.4 (1.3, 3.3)	1.4 (1.2, 8.1)	1.3 (1.0, 2.5)

*\*Responses were assessed every 6 weeks.*

## 7.2. Additional Efficacy Considerations

### **7.2.1. Considerations on Benefit in the Postmarket Setting**

Not Applicable.

### **7.2.2. Other Relevant Benefits**

Not Applicable

## **7.3. Integrated Assessment of Effectiveness**

In 310 patients with locally advanced or metastatic urothelial carcinoma who had prior platinum-containing chemotherapy, treatment with atezolizumab elicited a confirmed ORR of 14.8% (95% CI: 11.1%, 19.3%) as assessed by IRF per RECIST v1.1. The detected responses appear durable. At the time for the ORR analysis median DOR in responders was not reached (range: 2.1+ to 13.8+ months). Of the responders, 37 patients had ongoing responses of  $\geq 6$  months and 6 had ongoing responses of  $\geq 12$  months.

The confirmed ORR was 9.5% (95% CI: 5.9%, 14.3%) in 210 patients with a PD-L1 IC score of 0/1, and 26.0% (95% CI: 17.7%, 35.7%) in 100 patients with a PD-L1 IC score of 2/3. Response durations in the PD-L1 subgroups were similar to those in the 310 patients.

Similar results were found in another study cohort that enrolled 94 patients with advanced urothelial carcinoma for which no standard treatments existed. The majority of the patients had received prior platinum-containing chemotherapy, which was not an entry requirement. The results from the 94 patients provide supportive evidence for this BLA.

Overall, the atezolizumab-induced ORR and DOR represent a clinically meaningful improvement over existing chemotherapeutics used off-label in this disease setting (Table 2). To the review team, these improvements, along with the safety profile (Section 8), provide substantial evidence to support accelerated approval of atezolizumab for the proposed indication.

The benefit as reflected by the improvement in the above surrogates should be verified after accelerated approval. An ongoing randomized, active controlled trial of atezolizumab versus the Investigator's choice of a chemotherapeutic (NCT02302807) may provide confirmatory evidence. This trial, conducted in the same study patient population, has overall survival as the primary endpoint. The estimated completion time will be in 2017.

## 8 Review of Safety

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### 8.1. Safety Review Approach

The safety of atezolizumab was primarily evaluated in Trial IMvigor 210, a multi-center, single-arm trial of atezolizumab monotherapy in patients with locally advanced or metastatic urothelial bladder cancer. Patients were divided into two cohorts. Cohort 1 included only patients with no prior chemotherapy for locally-advanced or metastatic urothelial carcinoma who were deemed cisplatin-ineligible. Cohort 2 included patients with disease progression during or following treatment with at least one platinum-containing regimen; the maximum number of regimens was unrestricted. This review focused on the 310 patients in Cohort 2 treated with atezolizumab with a data cut-off of May 5, 2015. Of note, the initial dataset provided by the Sponsor included Subject 1008 in Cohort 1 and Subjects 4024 and 1279 in Cohort 2, however in an updated analysis from September 2015, but still using the May 2015 data cutoff, these patients were reassigned to the other cohort based on re-review of their eligibility for each cohort.

The safety review was supplemented with a pooled evaluation of the following trials:

1. Cohort 1 of IMvigor 210 (119 cisplatin-ineligible patients) [Data cut-off May 5, 2015]
2. PCD4989g: a Phase I, multicenter, first-in-human dose-escalation study of atezolizumab in patients with locally advanced or metastatic solid tumors or hematologic malignancies. (481 patients of whom 94 were patients with metastatic urothelial carcinoma) [Data cut-off August 7, 2015]
3. FIR: a Phase 2 multi-center, single-arm trial of atezolizumab in patients with locally advanced or metastatic PD-L1-positive non-small cell lung cancer (NSCLC). (137 patients). [Data cut-off January 7, 2015]
4. BIRCH: a Phase 2 multi-center, single-arm study of atezolizumab in patients with PD-L1-positive locally advanced or metastatic non-small cell lung cancer. (667 patients). [Data cut-off May 28, 2015]
5. POPLAR: a Phase 2 multi-center open-label randomized study of atezolizumab compared to docetaxel in patients with PD-L1-positive locally advanced or metastatic NSCLC. (142 patients) (144 patients) [Data cut-off May 8, 2015]

Adverse events of special interest were closely evaluated due to class effect of immune-mediated events in checkpoint inhibitors.

### 8.2. Review of the Safety Database

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

The safety database included 310 patients who received at least one infusion of atezolizumab. As discussed in Section 8.1, the patients included in this database differed from the initial May 5 2015 dataset. Analysis of Cohort 2 was performed using the May 2015 cutoff with the correct reassigned patients (N=310).

The Applicant mapped and coded verbatim adverse events (AE) terms for Trial IMvigor 210 using MedDRA version 18.0.

### Reviewer comments:

1. There were no significant discrepancies identified between the dataset and the information provided in the Clinical Study Report.
2. The Applicant's categorization of data and coding methods were deemed appropriate.
3. Pooled safety data regarding immune-mediated adverse events for mUC and all patients treated with atezolizumab were examined in an integrated manner (see section 8.4)
4. The clinical review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the IMvigor 210 raw AE data set. The review used manual matching of all verbatim and MedDRA PTs to assess the acceptability of the Applicant mapping from the verbatim term to MedDRA PT. The PTs listed in the dataset adequately represented the investigator-recorded term and did not raise any significant issues.
5. A random audit of 5% of the AE case report forms to assess the completeness and verify the accuracy of the raw AE datasets did not raise any significant issues.
6. To review the AE datasets, the following terms were pooled:

**Table 40: Pooled terms**

Pooled term	Preferred Terms
Diarrhea	Colitis Colitis microscopic Diarrhea Frequent bowel movements
Abdominal pain	Abdominal pain Abdominal pain upper Abdominal pain lower Flank pain
Fatigue	Asthenia Fatigue Decreased activity

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

	Lethargy Malaise
Peripheral edema	Generalized oedema Oedema Oedema genital Oedema peripheral Penile oedema Peripheral swelling Scrotal oedema Swelling
Urinary tract infection	Cystitis Kidney infection Pyelonephritis Urinary tract infection Urinary tract infection bacterial Urinary tract infection pseudomonal Urosepsis
Decreased appetite	Appetite disorder Decreased appetite Early satiety Hypophagia
Back pain	Back pain Neck pain
Rash	Rash Rash maculopapular Rash pruritic Rash papular Rash pustular Skin toxicity Eczema Erythema Erythema multiforme Rash erythematous Acne Lichen planus
Cough	Cough Productive cough
Sepsis	Sepsis Bacteremia
Pneumonia	Pneumonia Lobar pneumonia Lung infection

	Pulmonary sepsis
Intestinal obstruction	Small intestinal obstruction Intestinal obstruction Ileus Subileus Large intestinal obstruction
Dehydration	Dehydration Hypovolemia
Urinary obstruction	Ureteric obstruction Hydroureter Obstructive uropathy Urinary tract obstruction
Venous thromboembolism	Pulmonary embolism Deep vein thrombosis Embolism

### 8.2.1. Overall Exposure

In Cohort 2, the median number of doses received was 5 (1 to 16) and the median duration of therapy was 12.3 weeks (0-46 weeks) as of the May 2015 cutoff date (Table 41). All 310 subjects received at least one dose of atezolizumab.

**Table 41: Safety Population, Size and Denominators**

Clinical Trial Groups	Atezolizumab Cohort 2: n=310
<b>Number of doses received</b>	
Mean (SD)	6.2 (4.3)
Median (Min, Max)	5 (1-16)
<b>Treatment duration (weeks)</b>	
Mean (SD)	16 (13.1)
Median (Min, Max)	12.3 (0-46)
<b>Cumulative dose (mg)</b>	
Mean (SD)	7408 (5101)
Median (Min, Max)	6000 (1200-19200)
<b>Treatment duration (weeks)</b>	
0-13	161 (51.8%)
>13-26	52 (16.7%)
>26-39	81 (26.0%)

>39-52	17 (5.5%)
<b>Dose Interruptions/Delays</b>	
Any delay	62 (19.7%)
Delay due to AE	54 (17.4%)
Missed dose	12 (3.9%)

Data cut-off 5-5-15: Source AEX.xpt

Note that per AE.xpt dataset, 83/310 (26.8%) patients experienced an AE leading to dose interruption.

At the time of the database lock, 32% of patients were continuing with study treatment in Cohort 2.

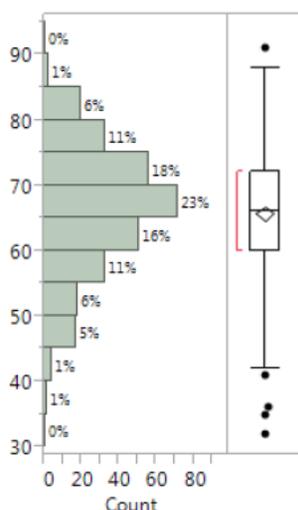
Reviewer comments: Overall, the size of the safety population and the extent of exposure were adequate and generally allowed sufficient characterization of AEs associated with atezolizumab in the target population.

### 8.2.2. Relevant characteristics of the safety population:

The safety and efficacy populations were similar. Refer to Section 6.1.2 for additional details regarding the efficacy population.

The demographics and baseline characteristics of the safety population of Cohort 2 are shown in Figure 2 and Table 42:

**Figure 2: Safety Population Age**



**Table 42: Safety Population Demographics**

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

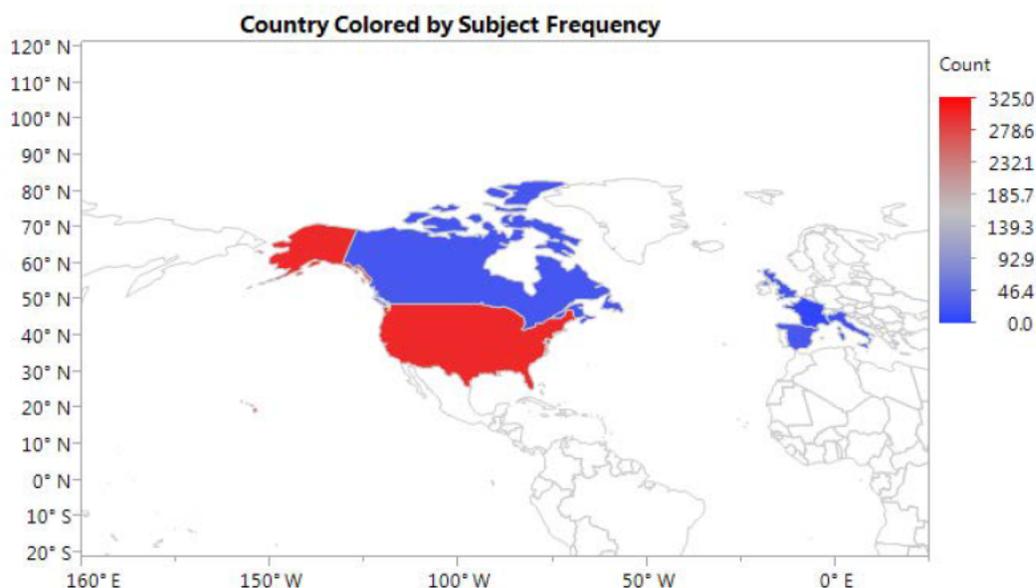
BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

N	310
Mean	65.6 (SD 10.1)
Minimum	32
Maximum	91
Median	66
Interquartile Range	12

		Count	%
Age Group	Age under 65 years	127	41
	65 <= Age <75	126	41
	Age 75 and over	57	18
Sex	Female	69	22
	Male	241	77
Race	Asian	7	2
	Black Or African American	6	2
	White	282	91
	Other/unknown	15	5
Ethnicity	Not Hispanic Or Latino	284	92
	Latino	10	3
	Hispanic Or Latino		
	Unknown/Not Reported	16	5

Study subjects were majority US patients (67%) (Figure 3):

**Figure 3: Safety Population Geography**



The trial excluded patients with a history of autoimmune disease with the exception of patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen. Additionally, the trial excluded patients with a history of pulmonary fibrosis or pneumonitis, although radiation pneumonitis in a radiation field was permitted.

Reviewer note: The safety database was adequate to represent the expected target population of U.S. patients with bladder cancer who have progressed following platinum-based therapy. Of note, as discussed above, this trial did not include those with a history of autoimmune disease. The trial did not enroll extensively in non-US countries. The trial did not enroll large numbers of non-Caucasian patients. Cohort 2 did not enroll patients who were deemed ineligible for platinum-based therapies. Thus, the safety results may not extend to these populations.

### **8.2.3. Adequacy of the safety database:**

The size of the safety database and duration of atezolizumab exposure were sufficient to characterize the safety of atezolizumab for treatment of a serious and life-threatening condition with the expectation of updated safety data from this trial and from the ongoing randomized phase III study, IMvigor 211. IMvigor 211 will evaluate atezolizumab compared with chemotherapy in UBC patients who have progressed during or following a platinum-containing regimen.

Demographics and disease characteristics of the study subjects were adequately representative of the target population of patients with UBC that has progressed during or following a platinum-containing regimen. The safety database is not yet adequate to evaluate the safety of

atezolizumab in patients not fit for platinum chemotherapy, including those considered too frail or without sufficient renal function.

### **8.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

On 4-5-2016, the Office of Scientific Investigations reported that there were several adverse events that were documented in source at an inspected site but were not included in the safety database. A teleconference was held with the Applicant on 4-14-2016. The Applicant reported that several adverse events were entered late by the site. They plan to send targeted information from the audit reports that outline the relevant information regarding late-entry by 4-22-2016. Based on this report, a more complete audit by Genentech along with submission of corrected datasets may be mandated.

#### **8.3.2. Categorization of Adverse Events**

Safety and tolerability assessment was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using random audit. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. Adverse events and laboratory values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

The Applicant identified adverse events of special interest (AESIs) based on pre-defined criteria based on the known mechanism of action of atezolizumab. See section 8.5 for more details regarding these events.

The Applicant further identified immune-mediated AEs based on the following pre-defined criteria: patients who required the use of systemic corticosteroids within 30 days after the AE onset date (based on the concomitant medication CRF) with no clear alternate etiology. Systemic corticosteroids specifically excluded steroids administered via the following routes: inhaled, intranasal, intravitreal, ophthalmic, otic, per vagina, and topical.

Safety data was available only for the 30-day post-discontinuation time point.

Immune-mediated adverse events (IMAE) were defined as AEs within 30 days prior to initiation of systemic corticosteroid therapy that did not resolve within that time period.

*Reviewer note: The Applicant's definition of AEs of special interest and immune-mediated AEs were pre-defined and adequate to evaluate class effect AEs. See section 8.1 for terms that were pooled for the purpose of this review.*

### **8.3.3. Routine Clinical Tests**

In IMvigor 210 (GO 29293), the following assessments were planned starting on Cycle 1 Day 1 and continued at regular intervals as needed:

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also amount of supplemental oxygen if applicable) within 72 hours of dosing.
- AEs continuously throughout the study.
- Physical examination and physical measurements including weight, and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results were to be obtained prior to dosing on infusion days).
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose and LDH), (results were to be obtained prior to dosing on infusion days).
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results were to be obtained prior to dosing on infusion days).

The following were performed only at screening and treatment discontinuation:

- Thyroid function testing including TSH (obtain free T3 and free T4 if abnormal result).
- Coagulation panel

Pregnancy screening was performed only prior to Cycle 1 for women of childbearing potential.

- Pregnancy test performed every 6 weeks on study or more frequently as per local standards.

Patients were assessed for toxicity prior to each dose. All visits had to occur within 3 days of the schedule date. All AEs were collected until 30 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurred first. Patients were contacted at 30 days after the last dose of study treatment to determine if any new AEs had occurred. After this period, investigators reported any death, serious adverse event, or any other adverse event of concern that were considered to be related to prior study treatment. All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

**Reviewer note:**

*Routine clinical testing of patients enrolled in the trial, including efforts to elicit adverse event data by monitoring laboratory tests, vital signs, and oxygen saturation appear to have been adequate with the exception of thyroid function. Thyroid function testing, which included thyroid stimulating hormone (TSH), free T3, and free T4 levels, was routinely performed in IMvigor 210 only at screening and at treatment discontinuation. Immune checkpoint therapy, including ipilimumab, nivolumab, and pembrolizumab, has been associated with a high frequency of endocrine events with thyroiditis/hypothyroidism. Other studies of checkpoint inhibitors have measured thyroid function more frequently (e.g. every 3 cycles [6 weeks] in Study CA209057 of nivolumab in non-squamous non-small cell lung cancer). Thus, the frequency of thyroid adverse events in IMvigor 210 may underestimate the true incidence of thyroiditis/hypothyroidism.*

## 8.4. Safety Results

Table 43 presents the overview of safety in Cohort 2, the metastatic urothelial carcinoma population (including Cohort 1 and the mUC population of PCD4989g) and the pooled safety population including all patients on PCD4989g and the atezolizumab-treated patients in FIR, BIRCH, and POPLAR.

**Table 43: Integrated Summary of Safety**

Total number of patients with at least one:	Cohort 2 (n = 310)	All mUC (n = 523)	All patients (n = 1189)
Grade 5 AE	5 (1.6%)	9 (1.7%)	35 (2.9%)
Grade 3-4 AE	153 (49%)	235(45%)	530 (45%)
SAE	141 (45%)	222 (43%)	480 (40%)
AE leading to treatment discontinuation	10 (3.2%)	19 (3.6%)	103 (8.7%)
imAE	20 (6%)	34 (7%)	93 (8%)

### 8.4.1. Deaths

Table 44 summarizes total deaths in Cohort 2. Listed deaths include deaths during treatment

and occurring up to 100 days of the last dose of study drug as of the database lock date (May 5, 2015).

**Table 44: Cohort 2 Deaths on Study**

	Cohort 2 (N = 310)
Total deaths	141 (45%)
Deaths within 30 days of last dose	34 (11%)
Death attributed to disease progression	137 (44%)
Death attributed to other/unknown/toxicity (including those occurring up to 100 days after last dose of study drug)	5 (1.6%)

Death associated with atezolizumab occurred in 3 patients (0.9%) due to sepsis, pneumonitis, and intestinal obstruction. Due to the potential for late-onset immune-related toxicity, deaths occurring up to 100 days after the last dose of atezolizumab were studied. Two patients (1167 and 4017) with deaths occurring between 30-100 days and attributed to “other/unknown” were deemed as unlikely to have died due to study drug toxicity. The reviewer did not agree with the Applicant on the attribution of death in patient 1087; the attribution of death was changed to pneumonitis (see narrative for patient 1087.) Brief summary narratives for these patients are provided in Table 45.

**Table 45: Brief Summaries of Related Deaths**

Adverse event	Brief case description	Days from death to last dose
<b>Pulmonary sepsis</b> Patient 8009  <i>Reviewer note: Increased incidence of infection was noted with atezolizumab, thus it is plausible that pulmonary sepsis related to atezolizumab was the</i>	An 80 year-old man with metastatic disease to the groin lymph nodes and right groin and with five prior lines of therapy was hospitalized with fever and altered mental status 14 days after his first dose of study drug. CT of the chest demonstrated no metastatic disease in the lung, while chest x-ray showed “cotton-pattern” infiltrates in the right lung base. Physical	<b>16</b>

<p><i>cause of death in this patient.</i></p>	<p>exam demonstrated right inguinal adenopathy with unspecified signs of infection. He was treated with broad-spectrum intravenous antibiotics, however died on Study Day 16. The narrative notes a potential infectious focus of right inguinal adenopathy with ulcerative and necrotic zones. No autopsy was performed. Blood culture results were not reported. The putative cause of death was “pulmonary sepsis.” The investigator considered pulmonary sepsis to be unrelated to atezolizumab.</p>	
<p><b>Pneumonitis</b> Patient 1087</p> <p><i>Reviewer note: Pneumonitis is a known toxicity from anti-PD-1 and anti-PD-L1 drugs. The patient’s death due to septic shock and respiratory failure, occurred in close temporal proximity to pneumonitis. Thus, it is plausible that this patient’s death was attributable to toxicity from the study drug.</i></p>	<p>A 68 year-old man with metastatic disease to the lung (with multiple bilateral pulmonary nodules), left lower abdominal wall, and right renal fossa with one prior line of therapy developed disease progression on Study Day 62, but continued to receive study drug per protocol guidance. On Study Day 100, the patient developed reticulo-nodular opacities throughout the left lung as well as demonstration of multiple patchy opacities in the right lung, felt to be consistent with pulmonary metastases. However, on Study Day 101, he presented with worsening shortness of breath and cough, felt to represent Grade 4 pneumonitis. He was intubated and placed on continuous renal replacement therapy due to acute kidney injury and hypotension. He developed septic shock and worsening hypoxic respiratory failure and subsequently died on Study Day 108. No autopsy was performed.</p>	<p><b>25</b></p>
<p><b>Subileus</b> Patient 8013</p> <p><i>Reviewer note: Anti-PD-1/PD-L1 drugs can induce</i></p>	<p>An 83 year-old man with metastatic disease to the left infraclavicular and external iliac lymph nodes, pelvis, and peritoneum who had received two prior</p>	<p><b>27</b></p>

<p><i>colitis, which may plausibly predispose to volvulus. Although this patient had other risk factors for volvulus, including prior abdominal surgery and peritoneal metastases, volvulus and interstitial that led to death may have been related to atezolizumab.</i></p>	<p>lines of therapy and had undergone prior bilateral inguinal herniorrhaphy presented with abdominal pain and distension on Study Day 8. Abdominal x-ray demonstrated volvulus of the colon. The patient subsequently underwent sigmoidectomy and colostomy. On Study Day 18, the patient developed fever and discharge from the wound with generalized edema. His condition deteriorated and he died on Study Day 27. No autopsy was performed. The putative cause of death was “sub-ileus.”</p>	
<p><b>“Unknown”</b> Patient 1167</p> <p><i>Reviewer note: This patient likely died from disease progression although the Applicant reports cause as “unknown.”</i></p>	<p>60 year old man with prior vertebral resection who developed lower limb paralysis on Day 46 with likely T12 cord compression. He was discharged to hospice without followup and died of unknown cause.</p>	<b>43</b>
<p><b>Intracranial bleed</b> Patient 4017</p> <p><i>Reviewer note: Severe thrombocytopenia likely led to intracranial bleed, however the most likely etiology of thrombocytopenia was radiation therapy.</i></p>	<p>73 year old woman who withdrew consent following on-study external beam radiation to the tumor bed and lumbar paraspinal lymph nodes and subsequent thrombocytopenia. Severe thrombocytopenia (platelets of 16 g/L) persisted through Day 153 (last day of laboratory collection). The patient died 37 days later due to intracranial bleed.</p>	<b>85</b>

Thirty-four patients were reported to have died within 30 days after their last dose of study drug due to disease progression. Review of these narratives found one patient, 269145-1122, who may have died of pneumonia rather than disease progression.

### 8.4.2. Serious Adverse Events

Non-fatal serious adverse events (SAEs) occurred in 45% of patients. The most frequent serious adverse reactions (>2% of patients) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and altered mentation. Table 46 summarizes these common SAEs.

**Table 46: Serious Adverse Events (Cohort 2) [Database cut-off 5-5-15]**

Pooled term	N (%)
Urinary tract infection	27 (9%)
Hematuria	10 (3.2%)
Acute kidney injury	10 (3.2%)
Intestinal obstruction	10 (3.2%)
Venous thromboembolism	9 (2.9%)
Urinary obstruction	9 (2.9%)
Pyrexia	8 (2.6%)
Pneumonia	8 (2.6%)
Dyspnea	7 (2.3%)
Abdominal pain	7 (2.3%)
Sepsis	7 (2.3%)
Confusional state	7 (2.3%)

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 47 below provides information on the 10 patients who permanently discontinued atezolizumab due to an adverse event. Three patients discontinued due to infection including sepsis, skin infection of the foot, and retroperitoneal hemorrhage. The skin infection was

actually cellulitis following the development of what was thought to be a drug-related rash in a patient with underlying diabetes. This patient had a history of osteomyelitis. The adverse event termed retroperitoneal hemorrhage was actually a mycobacterial vertebral osteomyelitis (suspected mycobacterium bovis) that led to retroperitoneal hemorrhage. The patient had not been on immunosuppressive agents prior to study entry, but did receive a BCG vaccine (does not seem to be intravesical BCG) for bladder cancer.

One patient was stated to have discontinued due to posterior reversible leukoencephalopathy syndrome (PRES). This patient experienced seizure and syncope and had MRI findings suspicious for a new brain metastasis. The patient had a concurrent urinary tract infection. It is unclear why this event was termed PRES.

Dose interruptions occurred in 83 (27%) patients in the AE dataset (note that, in the exposure dataset, 61 patients are listed as having dose modifications). These interruptions are discussed further in Section 8.5.

**Table 47: Adverse Events Resulting in Permanent Discontinuation**

	Cohort 2 IMVigor 210 N = 310
Any Adverse Event Leading to Permanent Discontinuation	10 (3.2%)
Gastrointestinal Disorders	
Retroperitoneal Hemorrhage	1
General Disorders	
Fatigue	1
Infections	
Sepsis	1
Foot Infection	1
Pulmonary sepsis	1
Injury, Poisoning, and Procedural Complications	
Opiate Toxicity	1
Nervous System Disorders	
PRES	1
Renal Disorders	
Acute and Chronic Renal Insufficiency	2
Skin Disorders	
Pruritus	1

Data Cutoff: May 5, 2015

#### 8.4.4. Significant Adverse Events

Adverse events of special interest (AESIs) were pre-defined as described in Section 8.5. In Cohort 2, 79 patients (25%) experienced an AESI. Thirteen of these patients (4.2%) experienced

a Grade 3-4 AESI. The most common AESIs were skin disorders (15%) and laboratory abnormalities (7%), the majority of which were liver function test abnormalities. See Section 8.4.5 for discussion of severe (Grade 3-4) adverse events and Section 8.5 for further discussion of adverse events by system.

#### **8.4.5. Treatment Emergent Adverse Events and Adverse Reactions**

The most common adverse events (>20% of patients) were fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation. The most common Grade 3-4 adverse events (>2% of patients) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia (Table 48).

Urinary tract infection, including severe urinary tract infection, occurred at a high rate in this study compared to published reports of other trials of chemotherapy agents in the platinum-treated urothelial cancer population. Based on the mechanism of atezolizumab, the Applicant was queried whether increased infection may have been related to an inflammatory reaction in the bladder (i.e. sterile pyuria) rather than infection. The Applicant stated that confirmatory data on urinalysis, urinary pathogens, or urine cultures were not systemically collected, especially for Grade 1-2 events. Among the 34 Grade 3 or 4 events, 14 events were reported to have a urine culture performed and results were available for ten of these urine cultures; nine events had a positive culture while one event had a negative culture result. No event of sterile pyuria was identified among the 34 Grade 3 or 4 events. A review of the randomized POPLAR trial confirms an increase in infection in patients receiving atezolizumab (42%) relative to docetaxel (33%) per the system organ classification term "Infections and Infestations." In POPLAR, pneumonia was the most common cause of Grade 3 or higher infection, occurring in 7.7% of patients treated with atezolizumab.

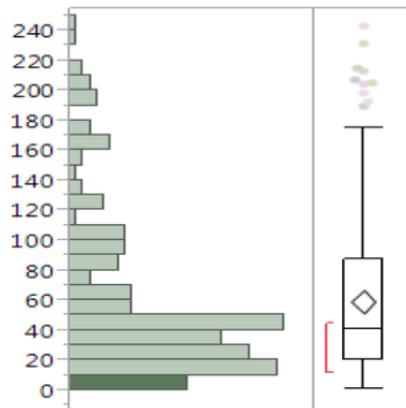
**Table 48: Grade 1-4 Adverse Reactions in  $\geq$  10% of Patients with Urothelial Carcinoma in Cohort 2**

Clinical and Statistical Reviews  
Drs. Ning, Zhang, and Suzman  
BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

	<b>Atezolizumab N = 310</b>	
<b>Adverse Reaction</b>	Grades 1-4 (%)	Grades 3 – 4 (%)
<b>All Adverse Reactions</b>	95	50
<b>Gastrointestinal Disorders</b>		
Diarrhea	18	1
Constipation	21	0
Nausea	25	0.3
Vomiting	17	1
Abdominal pain	18	4
<b>General Disorders and Administration</b>		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
<b>Infections and Infestations</b>		
Urinary tract infection	22	9
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	26	1
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back/Neck pain	15	2
Arthralgia	14	1
<b>Renal and urinary disorders</b>		
Hematuria	14	3
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Dyspnea	16	4
Cough	14	0.3
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	15	0.3
Pruritis	13	0.3

The time from start of treatment to Grade 3-5 AE is presented in Figure 4.

**Figure 4: Time to Grade 3-4 AE in Cohort 2**



Mean	60 days
Std Dev	55 days
Std Err Mean	4 days
Upper 95% Mean	67 days
Lower 95% Mean	52 days
N	201

#### 8.4.6. Laboratory Findings

Laboratory events in the alb.xpt databased were assessed per CTCAE v4.0 criteria. Abnormalities in hematology tests were primarily Grade 1 to 2 in severity. The most common Grade 3 and 4 hematologic abnormalities were lymphopenia (11%) and anemia (6%) (Table 49). Abnormalities in liver function tests were primarily Grade 1 to 2 in severity. The most common Grade 3-4 liver function test abnormalities were increased alkaline phosphatase (5%) and increased ALT and AST (2% each). There were three cases of Hy's Law identified through laboratory screening, however all three patients had alternative etiologies for their liver test abnormalities. Grade 3-4 increased creatinine occurred in 1% of patients. The most common Grade 3-4 electrolyte abnormalities were hyponatremia (10%) and hyperglycemia (5%).

**Table 49: Incidence of Grade 3-4 Laboratory Abnormalities (Data cut-off 5-7-15)**

Laboratory Test	Grades 3-4 (%)
Lymphopenia	11
Hyponatremia	10
Anemia	6
Increased Alkaline phosphatase	5
Hyperglycemia	5
Increased ALT	2
Increased AST	2
Hypoalbuminemia	2
Increased Creatinine	1

#### **8.4.7. Vital Signs**

Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in systolic blood pressure, diastolic blood pressure, heart rate, or temperature were observed during the course of treatment with atezolizumab.

#### **8.4.8. Electrocardiograms (ECGs)**

Safety ECGs and/or triplicate ECGs were not collected in IMVigor 210. Therefore, no QT prolongation effect can be assessed for patients in IMVigor 210. In study PCD4989g, digitized 12-lead ECGs were collected in triplicate for patients enrolled in the dose-expansion cohorts at screening, 30 minutes before and after end of infusion on Day 1 of Cycles 1 and 4, and at treatment discontinuation. There was no relationship between atezolizumab concentration and change in QTcF at atezolizumab concentrations up to the geometric mean C<sub>max</sub> following four doses of atezolizumab 20 mg/kg administered once every three weeks. After examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation, and tachycardia, no event was determined to be associated with an abnormal ECG finding and none were potentially related to an arrhythmia.

#### **8.4.9. QT**

Refer to Section 8.4.8 and Clinical Pharmacology Review for additional details.

#### **8.4.10. Immunogenicity**

Anti-therapeutic antibodies (ATAs) were assessed at multiple time-points in a subset of patients in IMVigor Cohorts 1 and 2 and PCD4989g. Of those sampled, 47 patients (43%) in Cohort 1, 114 patients (41%) in Cohort 2, and 43 patients (51%) in PCD4989g were considered ATA-positive. ATA positivity had only a minor impact on atezolizumab exposure, yielding a 13.6%

increased clearance in a population PK analysis. Incidence of adverse events in IMVigor 210 Cohorts 1 and 2 and PCD4989g by anti-therapeutic antibody (ATA) status is presented in Table 50.

**Table 50: Adverse Effect Incidence by Presence of Anti-therapeutic Antibodies**

	IMVigor 210 Cohort 1		IMVigor 210 Cohort 2		PCD4989g Urothelial Carcinoma Cohort	
	ATA positive N= 47 (%)	ATA negative N=62 (%)	ATA positive N= 114 (%)	ATA negative N= 161 (%)	ATA positive N= 43 (%)	ATA negative N= 41 (%)
<b>Any AE</b>	44 (94%)	56 (90%)	111 (97%)	155 (96%)	43 (100%)	40 (98%)
<b>Grade 1-2 AE</b>	22 (47%)	35 (57%)	52 (46%)	84 (52%)	22 (51%)	25 (61%)
<b>Grade 3-5 AE</b>	22 (47%)	21 (34%)	59 (52%)	71 (44%)	21 (49%)	15 (37%)
<b>AESI</b>	12 (26%)	13 (21%)	35 (31%)	42 (26%)	13 (30%)	13 (32%)

**Reviewer note:** No significant impact of anti-therapeutic antibodies on safety or efficacy were noted. Refer to the Clinical Pharmacology Review for additional details.

## 8.5. Analysis of Submission-Specific Safety Issues

Class effects associated with anti-PD-1/anti-PD-L1 drugs, including nivolumab and pembrolizumab, are primarily immune-related and include pneumonitis, colitis, hepatitis, hypophysitis, renal failure/nephritis, hyper/hypothyroidism. The Applicant thus identified adverse events of special interest (AESIs) in categories comprising endocrine, GI, hepatic, pulmonary, renal, and skin toxicities, as well as infection and hypersensitivity reactions. These included

1. Conditions suggestive of an autoimmune disorder
2. Grade 3 or greater acute infection
3. Grade 3 or greater events suggestive of hypersensitivity
4. Grade 3 or greater rash or pruritis
5. Grade 3 or greater diarrhea
6. Grade 2 or greater colitis
7. Grade 3 or greater LFT elevations
8. Grade 2 or greater LFT elevations with symptoms
9. Grade 2 or greater dyspnea not attributable to UBC
10. Grade 2 or greater hypoxia
11. Grade 2 or greater pleural effusion
12. Grade 2 or greater pericardial effusion
13. Cases of potential drug-induced liver injury as defined by Hy's Law
14. Suspected transmission of an infectious agent by the study drug

In Cohort 2, the Applicant identified 79 patients (25%) who experienced at least one AESI. The most common AESIs were rash (15%) and hepatic events (4% Grade 3-4 events). In Cohort 1 and PCD4989g, 22% and 36% of patients respectively experienced an AESI.

Additionally, the Applicant identified immune-mediated adverse events (imAEs) as those in which the date of systemic corticosteroid initiation was on or up to 30 days after the AE onset date, the date of corticosteroid initiation was prior to the AE resolution date, and no clear alternate etiology could be identified. The incidence of these events is shown in Table 51 below. Across the integrated safety database, including mUC patients and patients with other malignancies treated on the PCD4989g, BIRCH, FIR, and POPLAR trials, the most common imAEs were pneumonitis and rash, which each occurred in 1.2% of patients. Incidence of corticosteroid administration is discussed in more detail in section 8.5.16.

*Reviewer note: The incidence of immune-mediated adverse events appears consistent with those noted with other PD-1/PD-L1 inhibitors.*

**Table 51: Immune-mediated Adverse Events in Patients with Urothelial Carcinoma (including IMVigor 210 Cohorts 1 and 2 and PCD4989g)**

ImAEs	All mUC (n = 523)	All patients (n = 1189)
ALT increased	5 (1.0%)	10 (0.8%)
Pneumonitis	5 (1.0%)	14 (1.2%)
Rash	5 (1.0%)	14 (1.2%)
AST increased	4 (0.8%)	9 (0.8%)
Diarrhea	4 (0.8%)	11 (0.9%)
Bilirubin increased	3 (0.6%)	5 (0.4%)
Dyspnea	3 (0.6%)	5 (0.4%)
Hypoxia	0 (0%)	5 (0.4%)

### 8.5.1. Pneumonitis

#### IMVigor 210 Cohort 2

Six patients (1.9%) developed pneumonitis or interstitial lung disease of which 2 cases were Grade 3-4. The median day of onset for the first event for these six patients was day 81 (range: 14-127). Two of these events were ongoing and a date of resolution (and therefore duration) was not available for these patients. In the remaining 4 patients, the median duration of the first event was 11 days (range: 6-19). Five of these patients were treated with corticosteroids. In one patient (1087), pneumonitis was concomitant with multiple new bilateral pulmonary nodules consistent with metastases. He died from hypoxic respiratory failure 8 days after

development of pneumonitis despite treatment with corticosteroids and this was considered a Grade 5 toxicity.

Dyspnea or exertional dyspnea was reported in 49 patients of which 9 cases were Grade 3-4. Three of these patients were treated with corticosteroids, however there was no clear radiographic evidence of pneumonitis in these cases.

### IMVigor 210 Cohort 1

There were no reports of pneumonitis or interstitial lung disease. Dyspnea or exertional dyspnea was reported in 11 patients; all cases were Grade 1-2.

### PCD4989g

There were no reports of pneumonitis or interstitial lung disease. Dyspnea or exertional dyspnea was reported in 17 patients. One patient (101716) died due to acute respiratory failure. On review of this narrative, this appears to be disease progression.

**Reviewer note:** *In conclusion, the incidence of pneumonitis was 1.9% in Cohort 2 of IMVigor 210. The median date of onset was Day 81. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 6/523 (1.1%). There was one case of fatal pneumonitis that was initially reported as a Grade 4 event. Atezolizumab was permanently discontinued in 1/523 patients and interrupted in 3/523 patients. Steroids were used in 5 of the 6 patients, of whom one died and three recovered. Overall, the incidence of pneumonitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors. The incidence of pneumonitis was higher in the integrated safety database which contains a high proportion of patients with NSCLC treated with atezolizumab*

## 8.5.2. Hepatitis

### Safety Database

Table 52 below presents the incidence of Grade 3-4 liver function test abnormalities in the safety database, comprising 1848 patients with multiple tumor types in several studies. On-study labs were not available for all patients.

**Table 52: Liver Function Test Abnormalities in the Adverse Event Datasets**

	Grade 3-4 AST	Grade 3-4 ALT	Grade 3-4 bilirubin
Total N = 1848	40/1750 (2.3%)	43/1752 (2.5%)	28/1752 (1.6%)
IMvigor Cohort 2	7/284	6/284	4/284

N = 310			
IMVigor Cohort 1 N = 119	3/110	5/110	2/110
PCD4989g N = 481	18/461	18/462	17/462
FIR N = 137	4/129	5/129	2/129
POPLAR N = 142	3/134	3/134	0/134
BIRCH N = 659	5/632	6/633	3/633

### IMVigor 210 Cohort 2

Table 53 below provides information on the incidence of hepatic adverse events, including laboratory abnormalities that were reported as adverse events. Forty-nine (49) events occurred in 27 patients. 51 patients had an isolated elevation in alkaline phosphatase and are not included in the table. The median day of onset for the first event for the 27 patients was day 26 (range: 8-204). Many events were ongoing and a date of resolution (and therefore duration) was not available for 11 patients. The median duration of the first event was 14 days (range: 1-75) in the remaining 16 patients. 10 of these patients had liver metastases at baseline.

Three patients developed liver enzyme elevations that appeared to be immune-mediated. Patient 1141 developed flu-like symptoms on day 2 and Grade 1 AST/ALT increases on day 13 followed by delirium on day 15. AST/ALT worsened to Grade 2 and he developed Grade 1 hyperbilirubinemia. No liver biopsy was performed, however ultrasound demonstrated non-specific fatty liver. Atezolizumab was not withheld. He received prednisone for possible autoimmune hepatitis and his liver enzymes and encephalopathy resolved by days 42 and 47 respectively. Patient 1115 developed AST/ALT on day 8 which worsened to Grade 3 by day 16. Atezolizumab was temporarily interrupted. He received prednisone with resolution of liver enzyme elevation by day 51. Atezolizumab was restarted on day 37 without recrudescence. A third patient (1069) developed non-necrotizing granulomatous hepatitis on day 32. Liver biopsy did not demonstrate plasma cells, however no new concomitant medications had been started within four months of the event. He received steroids and hepatitis was considered resolved on day 71. Atezolizumab was restarted on day 86 without recrudescence.

**Table 53: Incidence of Hepatic Adverse Events in Cohort 2 (Data cut-off May 5, 2015)**

	IMVigor 210 Cohort 2 N = 310	
	Grade 1-4	Grade 3-4

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

All	49 (15.8%)	13 (4.2%)
AST Increased	13 (4.2)	2 (0.6)
ALT Increased	12 (3.9)	3 (1)
AKP Increased	10 (3.2)	4 (1.3)
Elevated Bilirubin/Hyperbilirubinemia	7 (2.3)	1 (0.3)
GGT Increased	1 (0.3)	0
Transaminases Increased	3 (1.0)	0
Hepatitis	1 (0.3)	1 (0.3)
Autoimmune hepatitis	1 (0.3)	1 (0.3)
Cholestasis	1 (0.3)	1 (0.3)

There were three cases in which patients had concurrent elevation in transaminases and bilirubin meeting the laboratory criteria for Hy's Law (bilirubin > 2xULN (grade 2) and ALT/AST > 3xULN (Grade 2) without concomitant elevated alkaline phosphatase) in Cohort 2. However, these cases were not considered as Hy's Law cases due to the presence of an alternative etiology rather than atezolizumab-related toxicity. Figure 5 below highlights these three cases. Figure 6 below depicts the time-course of liver function test elevation relative to discontinuation of treatment. Patient 1236 experienced Grade 3 increases in ALT, AST, and blood bilirubin on Day 164. He was treated with prednisone. Abdominal CT scan demonstrated a distended gallbladder with pericholecystic fluid concerning for acute cholecystitis as well as possible new liver metastases. MRCP demonstrated evidence of choledocholithiasis and he subsequently underwent ERCP with sphincterotomy and extraction of gallstones within the common bile duct. LFTs resolved by Study Day 165. Patient 1073 had liver metastases on screening and developed Grade 3 AST increase and Grade 2 bilirubin increase on day 22. MRCP showed worsening of his liver metastases. He received dexamethasone on day 32, however liver enzymes continued to worsen and were associated with encephalopathy. He was transitioned to hospice care. Patient 1197 had liver metastases on screening. She developed disease progression following her first dose of atezolizumab and died on day 17.

Figure 5: Hy's Law Cases in Cohort 2

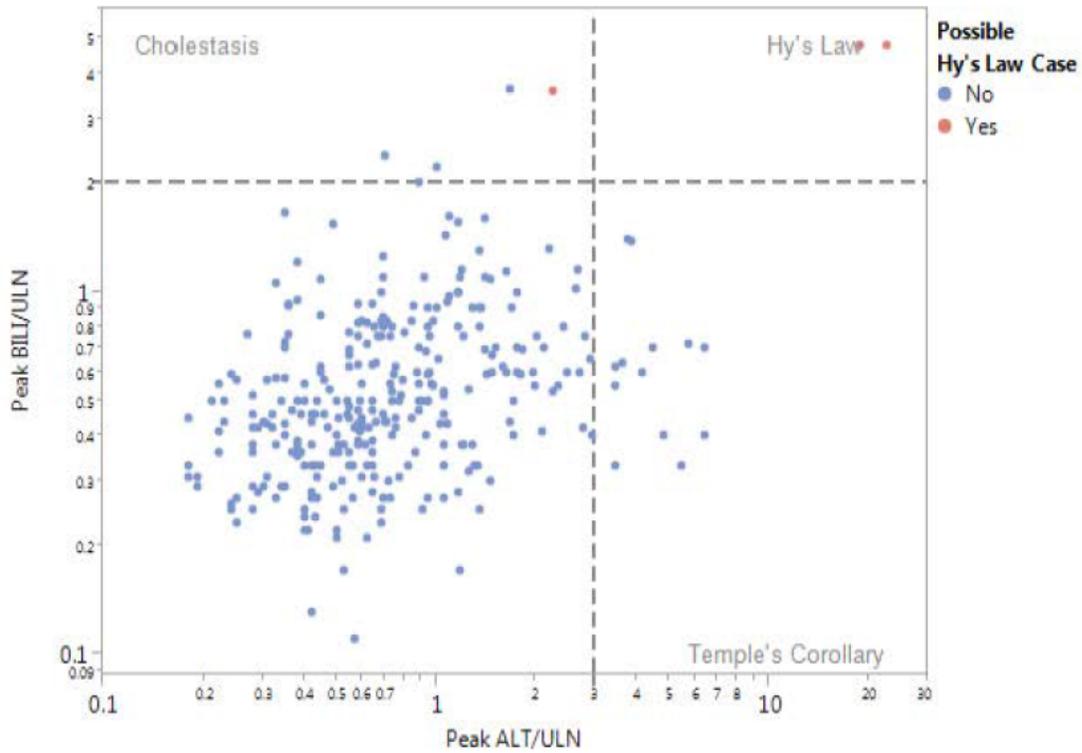
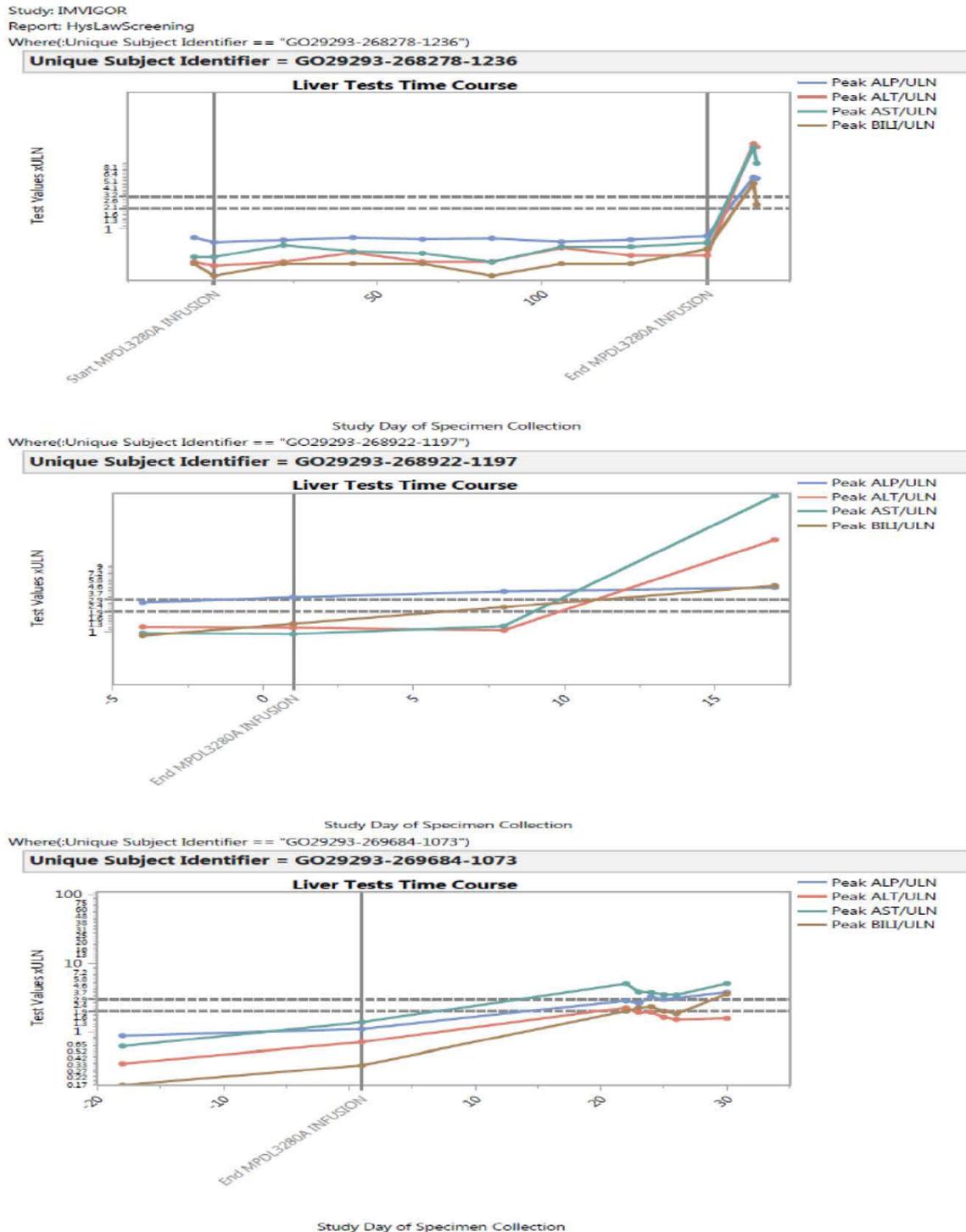


Figure 6: Time Course of Hy's Law Cases in Cohort 2

Hy's Law Time Course Plots



### **IMVigor 210 Cohort 1**

There was one case that met criteria for Hy's Law. Patient 4026 developed Grade 3 AST and ALT elevation and Grade 3 hyperbilirubinemia in the context of leukocytosis, fever, and confusion on day 13. The preferred term was Grade 3 liver disorder. He was treated with high-dose corticosteroids and antibiotics. An ultrasound demonstrated left portal vein thrombosis, but no evidence of obstruction. Liver function continued to worsen and the patient died on day 19.

**Reviewer note:** *In this case, portal vein thrombosis was non-obstructive on ultrasound and there was no clinical evidence of acute portal vein thrombosis (e.g. right upper quadrant pain and splenomegaly). Further, liver function test abnormalities are typically only mildly elevated in the setting of portal vein obstruction. Thus, it is likely that portal vein thrombosis was not the direct cause of this patient's liver failure. The most likely etiology is atezolizumab-induced immune-mediated hepatitis leading to liver failure and death.*

### **PCD4989g**

Table 54 below provides information on the incidence of hepatic adverse events, including laboratory abnormalities that were reported as adverse events. Four patients had an isolated elevation in alkaline phosphatase and are not included in the table. The median day of onset for the first event for the 15 patients was day 106 (range: 6-469). Many events were ongoing and a date of resolution (and therefore duration) was not available for 8 patients. The median duration of the first event was 26 days (range: 6-64) in the remaining 7 patients. The Applicant provided narratives in 14 patients.

Among the 14 patients with narratives, 7 had liver metastases at baseline and 7 did not. Patient 131016 did not have liver metastases and appeared to have an immune-mediated event. Here, atezolizumab was interrupted and the patient had a liver biopsy which showed a dense inflammatory infiltrate in the portal space, predominantly lymphocytic with some plasma cells and eosinophils. The patient's liver enzymes began to improve prior to initiation of low-dose steroids. The patient was able to resume atezolizumab on Day 421. However, on day 722, he again experienced an increase in liver enzymes and permanently discontinued on Day 743. The Applicant notes that the patient was also on atorvastatin, but the concomitant medication dataset reports the last dose on Day 260.

One additional case, patients 101715, is of concern. Patient 101715 developed an increase in liver enzymes after the last dose of atezolizumab. Atezolizumab was given on Day 85 and on Day 92, the patient had a CVA. A rash developed on Day 113, 28 days after the last dose of atezolizumab, and was treated with low dose steroids. The patient then developed, 42 days after the last dose of atezolizumab, an increase in ALT and bilirubin. Prednisone 20 mg daily was started on Day 127. There are no laboratories after Day 127. The patient died 7 days later.

Four patients received steroids for elevations in liver enzymes. This includes patients 101715 and 131016 (discussed above) as well as patients 101718 and 102015. Patient 101718 had a decrease in AST from grade 3 to grade 1 after administration of a Medrol dose pack. Patient 102015 received dexamethasone for back pain (per narrative) rather than for a Grade 1 increase in ALT and bilirubin.

**Table 54: Incidence of Hepatic Adverse Events in PCD4989g (Data cut-off August 7, 2015)**

	PCD4989g N = 94	
	Grade 1-4	Grade 3-4
All	15 (16%)	6 (6%)
AST Increased	10	3
ALT Increased	8	2
AKP Increased	5	2
Elevated Bilirubin/Hyperbilirubinemia	5	4
GGT Increased	3	1
Hepatic Function Abnormal	1	0
Hepatic Enzymes Increased	1	0
Transaminases Increased	1	0

Table 55 below provides information of laboratory abnormalities in the 92 patients included in the original study report. All of the patients with grade 3-4 AST or ALT and with grade 2-4 bilirubin have a liver abnormality reported as an adverse event.

Laboratories and adverse events were examined for concurrent reports of bilirubin > 2xULN (grade 2) and ALT/AST > 3xULN (grade 2). Thirteen patients had concurrent elevations, 11 with baseline liver metastases and 2 patients, 101306 and 101715, without liver metastases. Patient 101306 had biliary obstruction due to periportal nodes and developed a blocked stent during the treatment period. Patient 101715 is discussed above.

**Table 55: Hepatic Laboratory Abnormalities in PCD4989g**

	PCD4989g N = 92		PCD4989g N = 91	
	Baseline		On-Study	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
ALT	5	0	32	2
AST	9	0	46	3

Bilirubin	2	0	12	5
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Data Cutoff: 12-2-14

**Reviewer note:** In conclusion, hepatic adverse events occurred in 49 (15.8%) of patients in Cohort 2 of IMVigor 210, including 13/310 (4.2%) Grade 3-4 hepatic adverse events. The median day of onset for the first event was Day 26 and the event resolved in 16 patients with a median duration of 14 days. In all patients with bladder cancer treated with atezolizumab for whom on-study laboratory values were available (485 patients), the incidence of Grade 3-4 AST, ALT, and total bilirubin elevation were 2.7%, 2.7%, and 2.3% respectively. There was one case of fatal immune-mediated hepatitis in Cohort 1 and there was one case of biopsy-confirmed immune-mediated hepatitis in the bladder cohort of PCD4989g. Atezolizumab was permanently discontinued for hepatic events in 1/523 patients and interrupted in 14/523 patients. Steroids were used for hepatic events in 8/523 (1.5%) of patients, of whom one patient died, one patient had recurrence of hepatitis after restarting atezolizumab, and four patients experienced resolution of the event. Overall, the incidence of hepatitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors.

### 8.5.3. Diarrhea/Colitis

#### IMVigor 210 Cohort 2

Table 56 below provides information on the incidence of diarrhea.

**Table 56: Diarrhea/Colitis Adverse Events in Cohort 2**

	IMVigor 210 Cohort 2 N = 310	
	Grade 1-4	Grade 3-4
All	60 (19.3%)	5 (1.6%)
Diarrhea	56 (19)	3 (1.0)
Colitis	1 (0.3)	1 (0.3)
Frequent bowel movements	1 (0.3)	0
Colitis microscopic	1 (0.3)	0
Gastroenteritis	1 (0.3)	1 (0.3)

Data Cutoff:5-5-15

60 events of diarrhea occurred in 58 patients. The median day of first event onset was day 41 (range: 3-259). 7 events were unresolved. Among the 51 patients in whom the event had resolved and in whom data was available, the median duration was 2 days (range: 0-76). Drug was interrupted in 5 patients; no patient withdrew due to diarrhea. Among the 4 patients with Grade 3 diarrhea, two patients were hospitalized and the drug was interrupted in both patients. In one patient (1221), diarrhea was ongoing. Flexible sigmoidoscopy in this patient showed

diffuse congested, friable, erythematous mucosa from the rectum to sigmoid colon. He was treated with steroids. Atezolizumab was not restarted due to disease progression and he died from disease progression on day 212 with unresolved colitis.

Patient 1090 experienced Grade 2 microscopic colitis. Biopsies of the left and right colon showed questionable wall thickening. Atezolizumab was withheld and no other treatment was reported. Atezolizumab was resumed on day 163 and the colitis resolved by day 203.

### IMVigor 210 Cohort 1

Table 57 below provides information on the incidence of diarrhea.

**Table 57: Diarrhea/Colitis events in Cohort 1**

	IMVigor 210 Cohort 1 N = 119	
	Grade 1-4	Grade 3-4
All	23 (19.3%)	4 (3.4%)
Diarrhea	20 (17)	2 (1.7)
Colitis	2 (1.7)	2 (1.7)
Frequent bowel movements	1 (0.8)	0

Data Cutoff:5-5-15

23 events of diarrhea or colitis occurred in 22 patients. The median day of onset was day 36 (range: 2-190). Among the 13 patients in whom the event had resolved and in whom data was available, the median duration was 6 days (range: 1-47). Drug was interrupted due to diarrhea in two patients and was discontinued in two patients. One patient (8026) died one day after his diarrhea worsened from Grade 1 to Grade 3. He developed concomitant hypovolemic renal failure despite treatment with hydration and red blood cell transfusion. Atezolizumab was interrupted and he was treated with antibiotics. On day 25, he died due to renal failure and respiratory failure.

Patient 1316 experienced Grade 3 colitis on Day 38 of the study. A fecal culture was positive for *Clostridium difficile* and he received treatment with vancomycin. Atezolizumab was withdrawn, however the event was ongoing at the time of data cutoff.

Patient 1265 experienced Grade 3 colitis on day 36. She concurrently developed new large volume ascites and carcinomatosis. She was treated with prednisone without drug interruption. She experienced respiratory failure and died on day 44, at which time the colitis was ongoing.

Patient 1244 experienced Grade 3 diarrhea on day 177 in the context of possible citrobacter urinary tract infection. She received rehydration and diarrhea resolved after 6 days.

### PCD4989g

Table 58 below provides information on the incidence of diarrhea. Colitis was not reported. All events were grade 1-2. The day of onset was not reported in 4 patients. The median day of the first event onset in the remaining 14 patients was day 114 (range; 1-513). Two events were unresolved. Among the 12 patients in which the event had resolved and in whom data was available, the median duration was 2.5 days (range; 1-51). Seven patients experienced more than 1 event. Atezolizumab was interrupted in 1 patient (101224). In patient 101224, Grade 2 hypotension and gr 2 dehydration may have been associated with diarrhea. Narratives were not provided for patients with diarrhea.

There was 1 report of GI hypermotility and 1 report of gastroenteritis. Both were Grade 1 events.

**Table 58: Diarrhea/colitis Events in PCD4989g**

	PCD4989g N = 94
	Grade 1-4
All	20 (21%)
Diarrhea	18
GI Hypermotility	1
Gastroenteritis	1

Data Cutoff: 8-7-15

Surprisingly, stomatitis was reported in 3 pts and mucositis in 2 pts. All were Grade 1 events. None of these patients reported diarrhea.

**Reviewer note:** In conclusion, the incidence of diarrhea was 19% in Cohort 2 of IMVigor 210. The median date of onset was Day 41. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 103/523 (20%). The majority of these events were grade 1-2 and most were of short duration. One patient had a sigmoidoscopy suggestive of immune-mediated colitis (friable, erythematous mucosa). One patient developed renal failure following the onset of diarrhea and died due to renal and respiratory failure. Atezolizumab was permanently discontinued in 2/523 pts and interrupted in 8/523 patients. Steroids were used in only 2 patients.

### 8.5.4. Thyroid Disease

#### IMVigor 210 Cohort 2

Hypothyroidism or increased TSH was reported in seven patients. The median time of onset was 121 days (range: 45-176). Two cases were reported as resolved with a median duration of 25 days (range: 2-47). One patient (1016) developed Grade 3 hypothyroidism due to concurrent hospitalization for pyelonephritis. One patient (4009) had a PMH of hypothyroidism but normal TSH at entry and subsequently developed worsening of his hypothyroidism requiring an increase in his levothyroxine. Six of the patients were treated with levothyroxine.

Table 59 below provides information on thyroid function tests at baseline and on study for both Cohort 1 and Cohort 2, which were combined due to the relatively small number of patients with a follow-up TSH. On study includes the treatment period and the 30 day safety follow-up visit.

**Table 59: Thyroid Stimulating Hormone (TSH) Changes in Cohorts 1 and 2**

	Cohort 1/2 N = 424	Cohort 1/2 N = 97
	Baseline	On Study
TSH > ULN	33 (7.8%)	16 (16.5%)
TSH > 3x ULN	4 (0.9%)	3 (3.1%)
TSH > 10xULN	0	2 (2.1%)

Data Cutoff: 5-5-15

#### IMVigor 210 Cohort 1

Hypothyroidism or increased TSH was reported in one patient. The event was Grade 2 and occurred on day 163. The patient was treated with levothyroxine. The event was considered ongoing.

#### PCD4989g

Hypothyroidism was reported in 4 patients. One patient (101717) had a PMH of hypothyroidism, was on thyroid replacement, and had a normal TSH at entry. All events were grade 1-2. Given the small number of patients, the median day of onset was not calculated. All events were considered ongoing.

**Table 60: Thyroid Events in PCD4989g**

	PCD4989g N = 94

	Grade 1-4
Hypothyroidism	4 (4%)

Data Cutoff: 8-7-15

Table 61 below provides information on thyroid function tests at baseline and on study. On study includes the treatment period and the 30 day safety follow up visit.

**Table 61: Changes in TSH in PCD4989g**

	PCD4989g N = 92	PCD4989g N = 38
	Baseline	On Study
TSH > ULN	2 (2%)	6 (16%)
TSH > 3xULN	0	3
TSH > 10xULN	0	2
TSH < LLN	1	2

Data Cutoff: 12-2-14

Two patients had an elevated TSH at baseline. One of those patients had an elevated end-of-study value. One patient had a decreased TSH at baseline, but has no follow up values. Hypothyroidism or hyperthyroidism was not reported in these 3 patients. On study, 6 patients had an elevated TSH and 2 patients had a TSH below the LLN. Three patients with a laboratory elevation in TSH were reported to have the adverse event hypothyroidism.

**Reviewer note:** *In conclusion, the incidence of hypothyroidism 7/310 (2.3%) in Cohort 2 of IMVigor 210. The median date of onset was Day 121. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 13/523 (2.5%). TSH was elevated at least 10-fold over baseline in 4/135 (3.0%) patients with available follow-up laboratory values. Twelve patients were treated with replacement thyroid hormone (levothyroxine). Overall, while the incidence of hypothyroidism appears consistent or lower than other PD-1/PD-L1 agents, TSH was routinely evaluated only at baseline and end-of-study, thus this incidence likely underestimates the true incidence of hypothyroidism. The Applicant has agreed to a Post-Marketing Requirement (PMR) to assess TSH more frequently (every 6 weeks) in one large trial.*

### 8.5.5. Hyperglycemia/Diabetes Mellitus

No cases of likely immune-mediated diabetes mellitus (as identified by low C-peptide and/or auto-antibodies) were noted in the IMVigor 210 or PCD4989g datasets, nor in the FIR, POPLAR, or BIRCH datasets. In the IMVigor 210 database, there was one case of new-onset diabetes mellitus without an alternative etiology, as discussed below. The Applicant provided a drug safety update indicating seven cases of new onset diabetes mellitus suggestive of immune-mediated islet cell destruction. Two cases occurred in patients with non-small cell lung cancer,

one in a patient with renal cell carcinoma, one in a patient with breast cancer, three with an unspecified advanced solid tumor. In two cases, GAD65 auto-antibodies were positive. Two patients had low C-peptide. Three patients presented with ketoacidosis. Insulin was started in all cases and six of the seven patients resumed atezolizumab.

**IMVigor 210 Cohort 2**

Eleven patients reported the adverse events “hyperglycemia” or “worsening hyperglycemia” during the treatment period. The median time of onset was 42 days (range: 20-179). Six cases were reported as resolved with a median duration of 23 days (range: 6-168). Two patients experienced Grade 3-4 events. Patient 1097 experienced Grade 4 hyperglycemia in the setting of high-dose steroids administered for cytokine release syndrome and sepsis. Patient 1169 had a history of insulin-dependent diabetes mellitus and developed Grade 3 hyperglycemia on day 88 following discontinuation of atezolizumab for disease progression on day 66.

**Table 62: Glycemic Events in Cohort 2**

	IMVigor Cohort 2 N = 310			
	Baseline		On-Study	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hyperglycemia	166	0	293	24
Hypoglycemia	0	0	28	2

Data Cutoff: 5-5-15

**IMVigor 210 Cohort 1**

Eight patients reported the adverse events “diabetes mellitus,” “hyperglycemia,” or “worsening hyperglycemia.” In seven patients, these were Grade 1-2 events. One patient (1284) without a prior history of diabetes experienced a Grade 3 event on day 77 without an alternative etiology. He was treated with insulin, which was ongoing at the time of data cut-off.

**PCD4989g**

Three patients reported the adverse events hyperglycemia or worsening hyperglycemia during the treatment period. All were grade 1 events. The adverse event Grade 2 hypoglycemia was reported in 1 patient. Table 65 below provides information on the changes in laboratory measurement of serum glucose. All 3 patients with a Grade 3-4 elevation in glucose had a history of diabetes.

**Table 63: Glycemic Events in PCD4989g**

	PCD4989g

	N = 92			
	Baseline		On-Study	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hyperglycemia	35	0	77	3
Hypoglycemia	0	0	8	0

Data Cutoff: 12-2-14

**Reviewer note:** *In conclusion, there were no cases of likely immune-mediated diabetes mellitus that occurred in Cohort 2 of IMVigor 210. The incidence of hyperglycemia was 11/310 patients (3.5%). There was one patient in Cohort 1 with new-onset diabetes mellitus requiring insulin therapy without a clear alternative cause that may have been immune-mediated. In all patients treated with atezolizumab in the Applicant's database (N = 1978), there were two cases of confirmed immune-mediated diabetes mellitus. Overall, the incidence of diabetes mellitus is consistent with other PD-1/PD-L1 inhibitors.*

### 8.5.6. Adrenal Insufficiency

In addition to the cases discussed below, two patients in the BIRCH trial of non-small cell lung cancer developed adrenal insufficiency. Patient 313032 developed Grade 2 on day 158 treated with fludrocortisone and hydrocortisone. The event is ongoing. Patient 36007 developed Grade 1 adrenal insufficiency on day 2. He was treated with dexamethasone, however died on day 30 due to disease progression. The event was ongoing at that time. Neither patient had adrenal metastases at screening.

#### IMVigor 210 Cohort 2

No patients with bladder cancer reported new adrenal insufficiency. There were 32 cases of concomitant elevations in laboratory potassium and decreases in laboratory sodium noted and eosinophils were elevated in five of these patients. There were no concomitant reports of hypotension.

#### IMVigor 210 Cohort 1

No patient in Cohort 1 reported new adrenal insufficiency. No patients experienced concomitant events of hyperkalemia and hyponatremia or either hyperkalemia or hyponatremia and orthostatic hypotension.

#### PCD4989g

No patients with bladder cancer reported adrenal insufficiency. Patients were examined for reports of the adverse events hyponatremia and hyperkalemia. One patient, 111108, reported grade 1 hyponatremia on day 21 which was ongoing when grade 1 and 2 hyperkalemia were reported on days 28 and 29.

Fourteen (14) patients had an elevation in laboratory potassium and a decrease in laboratory sodium on the same day. All laboratory abnormalities were grade 1-2. However, 5 patients reported multiple episodes of concurrent hyponatremia and hyperkalemia. In these patients, there were no reports of hypotension. There were a number of reports of fatigue and diarrhea, but these could not be distinguished from concomitant conditions.

*Reviewer note: There were no cases of likely immune-mediated adrenal insufficiency in patients with bladder cancer treated with atezolizumab. Two patients with non-small cell lung cancer developed adrenal insufficiency as discussed above. Overall, the incidence of immune-mediated adrenal insufficiency appears similar to other PD-1/PD-L1 inhibitors.*

### **8.5.7. Hypophysitis**

No cases of hypophysitis or pituitary dysfunction were reported in IMVigor Cohorts 1 or 2 or in the NSCLC studies BIRCH, FIR, or POPLAR.

#### **PCD4989g**

Patient 121018 developed dizziness, lethargy, and confusion and was found to have a hypothalamic mass which was thought to be an inflammatory lesion. She was treated with high dose dexamethasone with reduction in the size of the lesion. Laboratory tests showed pituitary deficiency. It is unclear if hormone replacement was used, but there are no reports of hormone replacement in the concomitant medications. She permanently discontinued atezolizumab.

*Reviewer note: There were no cases of hypophysitis in IMVigor 210. There was one case of likely immune-mediated hypophysitis in the PCD4989g bladder cancer cohort as described above. Overall, the incidence of hypophysitis appears similar to other PD-1/PD-L1 inhibitors.*

### **8.5.8. Other Endocrinopathies**

#### **IMVigor 210 Cohort 2**

No other endocrinopathies were noted in Cohort 2.

#### **IMVigor 210 Cohort 1**

Grade 2 decreased blood testosterone was reported on day 22 in patient 1155 and is ongoing. Dosing was unchanged. Of note, this patient also developed Grade 2 hypothyroidism on day 163, treated with levothyroxine.

#### **PCD4989g**

Grade 1 hypogonadism was reported on day 703 in patient 102009 and is ongoing. Dosing was unchanged. This was not considered an AESI. The Applicant reports that no further details are available regarding this event.

### **8.5.9. Neurological Disorders**

Neurological disorders of concern are presented in the table below. This table does not include all neurological adverse events, but instead includes adverse events designed as AESIs by the Applicant or neurological events that have been seen with other PD-1/PD-L1 inhibitors.

Grade 2 optic neuritis was reported in a patient with NSCLC enrolled in the BIRCH study on day 89. Atezolizumab was discontinued for disease progression on day 85 and she received dexamethasone for brain metastasis-related edema on day 105. Optic neuritis remained unresolved at the time of death.

Grade 3 Guillain-Barre syndrome was reported in a patient with NSCLC enrolled in the FIR study on day 247. Atezolizumab was discontinued and she was treated intravenous immunoglobulin. The event resolved by day 282. Of note, she experienced concurrent hepatitis and hyperthyroidism.

#### **IMVigor Cohort 2**

One patient (6006) experienced Grade 3 paraplegia which was treated with steroids. He concurrently received radiotherapy to his thoracic, lumbar, and sacral vertebrae, suggesting cord compression as a cause of his paraplegia. Patient 6008 experienced Grade 3 diplegia, however MRI demonstrated epidural soft tissue metastases at C5 with high-grade stenosis of his cervical neuroforamina. He underwent vertebral surgery demonstrating metastases; diplegia remained unresolved at his death. Patient 1167 experienced Grade 3 diplegia associated with possible T12 cord compression.

Four patients experienced Grade 3 mental status changes. Patient 1061 experienced Grade 3 delirium associated with a urinary tract infection. Grade 3 encephalopathy in patient 1010 occurred on day 15 and was not associated with a concurrent event. No action was taken and the event resolved by day 18. Patient 1177 experienced Grade 3 hallucination on day 50, concurrent with Grade 2 dehydration. No action was taken and the event resolved by day 52. Patient 1009 experienced Grade 3 confusional state on day 167, concurrent with ongoing Grade 3 radiation gastroenteritis. The drug was interrupted and the event resolved by day 174.

One patient (7020) experienced fainting, seizures, and loss of consciousness and was diagnosed with Grade 3 posterior reversible encephalopathy syndrome (PRES) on day 15. MRI additionally demonstrated a small brain metastasis. Atezolizumab was discontinued, however no treatment with additional medications is reported. The patient was discharged from the

hospital on day 34, however PRES remained unresolved at the time of the patient's death due to disease progression on day 138.

### IMVigor Cohort 1

One patient (1283) developed Grade 3 herpetic meningoencephalitis on day 22. He discontinued therapy on day 36 due to disease progression and died on day 48. Meningoencephalitis was ongoing at the time of death.

### PCD4989g

A Grade 3 altered state of consciousness was reported in patient 102026 and Grade 3 encephalopathy was reported in patient 102209. Both patients experienced urinary infections at the time of these events and the events resolved concurrent with resolution of the infection.

Two patients had a CVA, 1 additional patient had a Grade 1 intracranial hemorrhage (102165), and one had Grade 1 aphasia (101032). The grading of these events is unusual, however the Applicant reported that no additional information on these non-serious adverse events was available.

Peripheral neuropathy, including hypoesthesia, neuralgia, diabetic neuropathy, and paresthesia, was reported in 13 patients. One patient with ongoing Grade 1 hypoesthesia did not have confounding factors for neuropathy.

**Table 64: Neurologic Events in PCD4989g and IMVigor Cohorts 1 and 2**

	PCD4989g N = 94		IMVigor Cohort 1 N = 119		IMVigor Cohort 2 N = 310	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Confusional state <sup>1</sup>	2	2	10	2	22	4
Herpetic meningoencephalitis			1	1		
Transient ischemic attack					1	
Brain mass <sup>2</sup>	1					
Neuropathy <sup>3</sup>	13	2	6		17	
Phantom pain					1	
Aphasia					1	
Cognitive disorder					1	
Deafness					1	
Paraplegia <sup>4</sup>					4	3

Posterior reversible encephalopathy					1	1
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1 Includes: altered state of consciousness, mental status changes, depressed level of consciousness, disturbance in attention, confusion state, encephalopathy, hallucination, delirium

2 Discussed under hypophysitis

3 Includes: hypoesthesia, neuralgia, diabetic neuropathy, paresthesia, peripheral sensory neuropathy, peripheral neuropathy

4 Includes: paraplegia, diplegia, hemiparesis

Data Cutoff: 8-7-15 (PCD4989g) and 5-5-15 (IMVigor 210)

**Reviewer note:** *In conclusion, the incidence of neurologic adverse events in Cohort 2 of IMVigor 210 was 39/310 (12.6%), of which 2.6% represented Grade 3-4 events. The majority of these events were confusional state/delirium that may have been related to infection or peripheral neuropathy that may have been related to prior platinum therapy. There was one case of Grade 3 posterior reversible encephalopathy (PRES) without concomitant hypertension that may have been related to underlying infection. In Cohort 1, there was one case of Grade 3 herpes simplex encephalitis. Steroids were used for one patient with spinal cord compression. There were two cases of immune-mediated neurologic disorders (optic neuritis and Guillain-Barre syndrome) in the BIRCH and FIR trials of patients with non-small cell lung cancer. Overall, the incidence of neurologic events appears consistent with other PD-1/PD-L1 inhibitors.*

### 8.5.10. Musculoskeletal Disorders

Grade 2 polymyalgia rheumatic was reported on day 176 in a patient with NSCLC on the FIR trial. The patient received prednisone and atezolizumab was continued. The event improved to Grade 1, but remained ongoing.

Grade 2 autoimmune arthritis was reported on day 112 in a patient with NSCLC on the POPLAR trial. Atezolizumab was discontinued and the patient was treated with prednisone. The arthritis improved to Grade 1 by day 176, but remained ongoing.

#### IMVigor Cohort 2

Patient 7001 experienced Grade 3 proximal arthralgia of the wrists, shoulders, and elbows on day 59. Atezolizumab was discontinued. Auto-immune workup including rheumatoid factor, anti-double strand DNA, and anti-nuclear antibody was negative. He was treated with ketorolac and steroids, however his pain increased and he was rendered completely immobilized. Arthralgia was reported as resolved on day 77.

Patient 1050 experienced Grade 3 arthralgia on day 90 and was reported by the Investigator to be due to an unspecified concomitant medication. Atezolizumab was not interrupted and no medication was administered. The event resolved by day 100.

#### IMVigor Cohort 1

There were no cases of arthritis. Arthralgia was reported in 10 patients; these were all Grade 1-2 events.

One patient (1004) developed Grade 2 myelopathy, however this occurred in the context of multiple spinal pathologies including a T4 compression fracture and worsening spinal stenosis.

#### **PCD4989g**

Patient 102138 reported arthralgia on day 94 and was treated with prednisone. On day 329 per the narrative and day 553 (12-4-14) per the dataset and CRF, approximately 6 months after discontinuation of prednisone, he developed eosinophilia, neutropenia, and cough. The Applicant was asked to provide further information and reported that no additional detail was available.

Terms used to report arthralgias, myalgias, and musculoskeletal weakness were reviewed. There were no terms which raised suspicion of an autoimmune event. One patient with a history of fibromyalgia (102007) was reported as receiving steroids during the treatment period. However, per the Investigator, the steroids were administered for “disorientation” rather than fibromyalgia symptoms.

### **8.5.11. Skin Disorders**

#### **IMVigor Cohort 2**

Grade 3 rash was reported in one patient (1172), beginning as Grade 1 on day 29 and worsening to Grade 3 by day 71. Atezolizumab was discontinued and the patient was treated with oral steroids from day 39-40 and again from day 85. Rash remained unresolved at the time of death due to disease progression.

All other skin events were Grade 1-2. Among the 44 patients with rash, the median day of onset of the first event was Day 71 (range: 1-253). Duration was available in 31 patients and the median duration of the first event was 34 days (range: 3-119). None of the Grade 1-2 events resulted in a change of dose. Three patients (1051, 1172, 8018) were treated with oral steroids. Patient 8018 developed Grade 2 rash on day 105, concurrent with ongoing steroid administration for Grade 2 pneumonitis that occurred on day 84; pneumonitis resolved on day 147, while rash remained ongoing.

#### **IMVigor Cohort 1**

All skin events were Grade 1-2. Seven patients developed rash. One patient developed Grade 1 palmar-plantar erythrodysesthesia. Atezolizumab was interrupted in one patient (1076). No

patients received systemic steroids. Five patients received steroid creams and one patient received an antifungal.

### PCD4989g

All skin events were Grade 1-2. Examining the 14 patients with rash, the median day of onset of the first event was Day 122.5 (range: 8-463). Duration was available in 11 patients and the median duration of the first event was 64 days (range: 11-262). None of the events resulted in a change in dose. One patient received oral steroids (methylprednisolone 4 mg/d) and 5 received a steroid cream. One patient was treated with an anti-fungal and another with an anti-viral (valacyclovir).

Patient 101907 was on steroid and retinal creams for psoriasis on study entry. He developed a Grade 1 worsening of psoriasis (slight increase in the amount of skin involvement) after 3 cycles of atezolizumab and discontinued atezolizumab due to disease progression.

**Table 65: Dermatitis Events in PCD4989g and IMVigor Cohorts 1 and 2**

	PCD4989g N = 94	IMVigor Cohort 1	IMVigor Cohort 2	
	Grade 1-4	Grade 1-4	Grade 1-4	Grade 3-4
Rash <sup>1</sup>	14	7	44	1
Dermatitis Acneiform <sup>2</sup>	2	1		
Eczema	2	0	1	
Lichen Planus	1	0	1	
Seborrheic Dermatitis	1	0		
Photosensitivity reaction	0	0	1	
Psoriasis	1	0	1	
Pruritus/Generalized Pruritus	13	18	35	
Erythema	1	0	1	
Other <sup>3</sup>	0	1	4	

<sup>1</sup>Including erythematous, maculo-papular, pustular, papular, and pruritic rash

<sup>2</sup>Including dermatitis psoriasiform

<sup>3</sup>Including skin toxicity, skin lesion, skin disorder

Data Cutoff: 8-7-15 (PCD4989g) and 5-5-15 (IMVigor 210)

**Reviewer note:** In conclusion, the incidence of skin disorders (including pruritis) was 88/310 (28.4%) in Cohort 2 of IMVigor 210. The median date of onset was Day 71. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 150/523 (28.7%). The majority of these events were grade 1-2 and most were of short duration. One patient developed Grade 3 rash that led

*to discontinuation of atezolizumab. Atezolizumab was permanently discontinued in 2/523 pts and interrupted in 3/523 patients. Systemic steroids were used in four patients with resolution in three patients. Overall, the incidence of skin disorders was consistent with other PD-1/PD-L1 inhibitors.*

### **8.5.12. Increased Amylase and Lipase**

The Applicant considered these to be AESIs.

#### **IMVigor 210 Cohorts 1 and 2**

There were no cases of increased amylase or lipase reported in IMVigor 210 in either Cohort 1 or Cohort 2.

#### **PCD4989g**

A grade 2 increase in amylase was reported in patient 111023. This was associated with dyspepsia, but not with abdominal pain, nausea, and vomiting. Lipase is unknown. The event resolved with no change in atezolizumab. A grade 3 increase in lipase and intestinal obstruction was reported in patient 111035. Amylase is unknown. The atezolizumab dose was not changed, but it was later discontinued for disease progression.

***Reviewer note:** There were no cases of pancreatitis or increased amylase/lipase in all patients with bladder cancer treated with atezolizumab. There were two patients with amylase or lipase elevations in PCD4989g. In the Applicant's database of all patients treated with atezolizumab (N = 1978), there were two cases of Grade 3 acute pancreatitis without plausible alternate explanations. Both patients were treated with steroids. One patient recovered, while the event was ongoing in the other. Atezolizumab was discontinued without rechallenge in both patients. Overall, the incidence of pancreatitis appears consistent with other PD-1/PD-L1 inhibitors.*

### **8.5.13. Renal Abnormalities**

#### **IMVigor Cohort 2**

Renal Failure/impairment and acute kidney injury were reported as 37 events in 28 patients. One case (7005) was considered an imAE. The median day of onset was day 64 (range: 9-231). Twenty-six of the events were considered resolved with a median duration of 11 days (range: 2-148).

Patient 7005 experienced Grade 3 acute kidney injury on day 91. Urine culture was positive. CT imaging did not reveal evidence of obstruction. He received antibiotics and corticosteroids. Atezolizumab was permanently discontinued. The kidney injury resolved by day 101.

## Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Patient 1140 experienced Grade 3 elevated creatinine of day 51. Ultrasound showed no evidence of obstruction, however, it did demonstrate increased renal arterial velocities without evidence of diastolic flow. She died on day 215 due to disease progression; the event remained unresolved at that time.

Among the other 8 patients with a Grade 3 renal event, five had concurrent documented or suspected urinary tract infection. One (1097) was additionally receiving concomitant vancomycin and ketorolac. One patient (1060) experienced worsening of pre-existing hydronephrosis and creatinine elevation resolved with placement of an indwelling foley catheter. Patient 1244 experienced Grade 3 elevated creatinine following loss of appetite and diarrhea; creatinine elevation resolved with receipt of intravenous fluids.

### **IMVigor Cohort 1**

Renal Failure/impairment and acute kidney injury was reported as 20 events in 16 patients. The median day of onset was day 51 (range: 4-182). Twelve of the events were considered resolved with a median duration of 8 days (range: 3-112). No patient was treated with steroids. Among the patients with Grade 3 or higher acute kidney injury, one patient (1269) had a concurrent UTI, two (1275, 1024) had urinary obstruction, and two (1244, 8026) developed renal injury secondary to Grade 3 diarrhea. One patient (1264) developed Grade 3 renal failure on day 125 without clear etiology. He had previously discontinued atezolizumab on day 113 due to disease progression. Renal failure remained ongoing at the time of death.

### **PCD4989g**

Renal Failure/impairment and acute kidney injury were reported as 12 events in 7 patients. None were considered AESIs or imAEs and no patients received steroids. The median day of the first event was Day 41 (range: 15-158). Only 4 first events were considered resolved and the median duration was not calculated, but ranged from 3-135 days.

Five patients of the 7 patients had an AE that resulted in a procedure. Among these 5 patients, patient 102026 had several additional reports of renal failure (not just the one that resulted in a procedure). The Applicant was asked to provide more information concerning this patient's renal failure and reported that the patient developed a confusional state and acute kidney injury in the setting of an indwelling Foley catheter and urinary tract infection. Of the remaining 2 patients, patient 101715 had Grade 2 acute kidney injury associated with a urinary infection and dehydration. However, this event was not considered resolved. The final patient, 111108, had Grade 3 renal failure and a Grade 3 decrease in GFR. This patient had liver metastases at baseline and at the time of the Grade 3 renal failure was experiencing Grade 3 elevations in bilirubin (conjugated) and a grade 1 elevation in ALT. The day prior to the report of Grade 3 renal failure, she had a normal creatinine associated with hyperkalemia and

hyponatremia in the face of Grade 2 diarrhea. She received high dose methylprednisolone. She is said to have died due to disease progression and hepatorenal syndrome.

The other Grade 3 event was a Grade 3 increase in creatinine. This patient, 102143, had a concomitant urinary tract obstruction.

**Table 66: Renal Events in PCD4989g and IMVigor 210 Cohorts 1 and 2**

	PCD4989g N = 94		IMVigor Cohort 1 N = 119		IMVigor Cohort 2 N = 310	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	28	5	20	6	45	9
Creatinine Increased	22	1	15	3	22	1
GFR Decreased	1	1	0	0	0	0
All Renal Failure/Impairment	7	3	5	3		8
Acute Kidney Injury	4	0	3	1	13	7
Renal Failure	4	3	2	2	1	1
Renal Impairment	1	0	0	0	1	0

Data Cutoff: 8-7-15 (PCD4989g) and 5-5-15 (IMVigor 210)

Table 67 below provides information on laboratory abnormalities at baseline and during the treatment period/30 day follow up. The one patient with a Grade 3 increase in laboratory creatinine, patient 121013, is described above. However, the Grade 3 increase in the laboratory creatinine and the adverse event report of Grade 3 increased creatinine occurred at markedly different time points. This patient had intermittent Grade 2 laboratory creatinine elevations throughout the treatment period.

**Table 67: Creatinine Changes in PCD4989g**

	PCD4989g N = 92		PCD4989g N = 91	
	Baseline		On Study	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Creatinine	36 <sup>1</sup>	0	80	1

<sup>1</sup>2 Grade 2 creatinine

Data Cutoff: 12-2-14

**Reviewer note:** In conclusion, the incidence of renal abnormalities was 45/310 (14.5%) in Cohort 2 of IMVigor 210. The median date of onset was Day 64. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence was 93/523 (17.8%). The majority of these events were grade

*1-2 and most were of short duration. Concomitant urinary tract infection was common. Atezolizumab was permanently discontinued in 2/523 pts and interrupted in 10/523 patients. One patient received steroids and antibiotics for a Grade 3 event in the context of a likely urinary tract infection; the event resolved. Overall, the incidence of renal abnormalities appears consistent with other PD-1/PD-L1 inhibitors.*

#### 8.5.14. Infusion Reactions

##### IMVigor Cohorts 1 and 2

The terms “infusional-related reaction” or “urticaria” that occurred on an infusion day were reported in nine patients. All events were Grade 1-2.

Grade 4 cytokine release syndrome was reported in Patient 1097, however on review of his narrative, the event occurred on day 13 and he had evidence of a pseudomonal urinary tract infection. Thus, the reported cytokine release syndrome was unlikely to be due to an infusion reaction. Grade 3 systemic inflammatory response was reported in Patient 2019, however the event occurred 12 days after the prior infusion. This event was deemed unlikely to be related to an infusion reaction.

##### PCD4989g

The terms infusion reaction, cytokine-release syndrome, or systemic inflammatory response syndrome were not reported. The Applicant flagged the events listed in the table below as infusion-related reactions. All were Grade 1-2. Among these 16 events in 11 patients, 7 were thought to be related and 12 occurred on the day of dosing. For the remaining 4 events, the day of occurrence is not recorded. The dose of atezolizumab was not changed in these pts.

Patient 102151 underwent a procedure for tachycardia on Day 164. This was flagged as an infusion-related event, but the procedure was not recorded in the datasets or provided in the patient narrative. This patient had culture negative fever during the treatment period and received methylprednisolone. Patient 121020 received an unknown concomitant medication to treat fever (flagged as an infusion-related event) on Day 1.

**Table 68: Infusion Reactions in PCD4989g and IMVigor 210 Cohorts 1 and 2**

	PCD4989g N = 94	Cohorts 1 and 2 N = 429
	Grade 1-4	Grade 1-4
Any	11	18
Chills	3	2
Pyrexia	5	5
Tachycardia	1	0

Dyspnea	4	0
Wheezing	1	0
Urticaria	1	2
Infusion-related reaction	0	7
Cytokine-release syndrome	0	1
Systemic inflammatory response	0	1

Data Cutoff: 8-7-15

Data Cutoff: 5-5-15

An examination of events reported on the day of administration found 385 events in 69 patients.

- Thirteen (13) Grade 3-4 events occurred in 10 patients. Non-laboratory AEs included hypertension, renal failure, and bladder hemorrhage.
- Dosing was interrupted in 1 patient for hypertension (Grade 3).

**Reviewer note:** *In conclusion, the incidence of infusion reactions (as defined by the terms “infusion-related reaction” or “urticarial” occurring on the date of infusion) was 10/523 (1.9%) in all patients with bladder cancer treated with atezolizumab. There were no Grade 3-4 events. No patients required discontinuation or steroids for infusion reaction. Atezolizumab was interrupted in seven patients. Overall, the incidence of infusion-related reaction appears consistent with other PD-1/PD-L1 inhibitors.*

### 8.5.15. Corticosteroid Use

#### IMVigor 210 Cohort 2

Fifty-seven patients (18.3%) received systemic corticosteroids within 30 days of an AE. Of these, 18 patients (5.8%) experienced Grade 1 or 2 AEs and 38 (12.2%) of patients experienced Grade 3 or 4 AEs. Twenty of these patients (6.4%) were considered to have experienced an imAE. Of these, seven patients (2.3%) experienced a Grade 1-2 AE and 13 patients (4.2%) experienced a Grade 3-4 AE. One patient (0.3%) died from sub-ileus, which was considered an imAE. Of the thirty-seven patients who received systemic corticosteroids who were not considered to have an imAE, the most common associated AEs were decreased appetite (9 patients), urinary tract infection (8 patients), fatigue (7 patients), back pain (7 patients), peripheral edema (7 patients), and pyrexia (6 patients). Five patients received corticosteroids without a corresponding AE:

268261-1104: Hydrocortisone 10mg for skin irritation

268261-1118: Dexamethasone 2mg for nausea and vomiting

268833-1082: Hydrocortisone 20mg for adrenal insufficiency and 10mg for rosacea

269137-7001: Dexamethasone 8mg for “worsening condition”

269145-1106: Cortisone 10mg for sciatic nerve pain

The indication for steroid use in the concomitant medication data is listed in these 5 pts (e.g., skin irritation), but there was no corresponding AE from the AE dataset that could be considered immune-mediated.

No patients were identified who received a non-corticosteroid immunomodulatory agent including tumor necrosis factor-alpha antagonists (e.g. adalimumab, infliximab, etanercept), interleukin-2 receptor antagonists, anti-interleukin-6 receptor antibody (e.g. tocilizumab), or mycophenelate.

### **IMVigor 210 Cohort 1**

Eighteen patients (15.3%) received corticosteroids within 30 days of an AE. Of these, 10 patients (8.5%) experienced Grade 1-2 events and 8 patients (6.8%) experienced Grade 3-4 events. Six of these patients (5.1%) were considered to have experienced an imAE. Of these, four patients (3.4%) experienced a Grade 1-2 event and two patients (1.7%) experienced a Grade 3-4 event. Of the twelve patients who received systemic corticosteroids who were not considered to have an imAE, the most common associated AEs were fatigue (10 patients), decreased appetite (3 patients), anxiety (3 patients), and back pain (3 patients).

No patients were identified who received a non-corticosteroid immunomodulatory agent.

### **PCD4989g**

Eighteen (18) patients received corticosteroids during the treatment period, 8 for AESIs (including fever) and 10 for other indications such as COPD and clinical deterioration. All of the patients who received corticosteroids for AESIs are discussed above.

***Reviewer note:** In conclusion, the incidence of corticosteroid use was 18.3% in Cohort 2 of IMVigor 210, of which 20 patients (6%) of patients received steroids for an adverse event considered possibly immune-mediated. Patients with bladder cancer from Cohort 1 of IMVigor 210 and the Phase 1 study are discussed in this section. In all patients with bladder cancer, the incidence of corticosteroid use was 93/523 (17.8%), of whom 34 (6.5%) patients received steroids for a possibly immune-mediated event. No systemic non-corticosteroid immunomodulatory drugs were administered. Overall, the incidence of systemic corticosteroid use was somewhat lower than in trials of other PD-1/PD-L1 inhibitors. This may have led to an incidence of adverse events termed IMAEs that underestimates the true incidence of immune-mediated events.*

## **8.6. Specific Safety Studies/Clinical Trials**

Subgroup analysis based on race were not performed as the study population was almost entirely Caucasian. Subgroup analyses based on age and gender in Cohort 2 are shown below. All common AEs appear to be similar across ages <65 years and ≥65 years. There were

relatively few female patients; however no adverse events appeared to be significantly disproportionate across male and female patients.

**Table 69: Grade 1-4 Adverse Events in >15% of Patients by Age (Cohort 2)**

	< 65 years N = 127		≥ 65 years N = 183	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	122 (96%)	64 (50%)	174 (95%)	91 (50%)
Fatigue	64 (50%)	9 (7%)	96 (52%)	10 (5%)
Decreased Appetite	34 (27%)	2 (2%)	51 (28%)	2 (1%)
Nausea	30 (24%)	4 (3%)	45 (25%)	2 (1%)
Urinary Tract Infection	28 (22%)	13 (10%)	41 (22%)	15 (8%)
Pyrexia	26 (20%)	1 (0.8%)	39 (21%)	3 (2%)
Constipation	20 (16%)	0	44 (24%)	1 (0.5%)
Diarrhea	22 (17%)	0	36 (20%)	4 (2%)
Peripheral Edema	21 (17%)	1 (0.8%)	34 (19%)	2 (1%)
Abdominal Pain	25 (20%)	7 (6%)	30 (16%)	5 (3%)
Back Pain	21 (17%)	5 (4%)	27 (15%)	2 (1%)
Vomiting	21 (17%)	1 (0.8%)	31 (17%)	1 (0.5%)
Dyspnea	17 (13%)	5 (4%)	33 (18%)	6 (3%)

Data Cutoff: 5-5-2015

**Table 70: Grade 1-4 Adverse Events in > 15% of Patients by Sex (Cohort 2)**

Grade 1-4 Adverse Events in > 15% of Patients by Sex				
	Male N = 241		≥ 65 years N = 69	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All				
Fatigue	178 (74%)	18 (7%)	45 (65%)	4 (6%)
Decreased Appetite	73 (30%)	2 (0.8%)	24 (35%)	0
Nausea	68 (28%)	5 (2%)	25 (36%)	2 (3%)
Urinary Tract Infection	61 (25%)	23 (10%)	18 (26%)	6 (9%)
Pyrexia	69 (29%)	3 (1%)	10 (14%)	1 (1%)
Constipation	61 (25%)	0	10 (14%)	0
Diarrhea	58 (24%)	3 (1%)	14 (20%)	2 (3%)
Peripheral Edema	50 (21%)	4 (2%)	15 (22%)	0
Abdominal Pain	54 (22%)	9 (4%)	17 (25%)	4 (6%)
Back Pain	46 (19%)	3 (1%)	13 (19%)	5 (7%)
Vomiting	52 (22%)	3 (1%)	16 (23%)	0

Dyspnea	46 (19%)	8 (3%)	15 (22%)	3 (4%)
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Data Cutoff: 5-5-2015

## **8.7. Specific Safety Studies/Clinical Trials**

No studies were performed to address specific safety concerns.

## **8.8. Additional Safety Explorations**

### **8.8.1. Human Carcinogenicity or Tumor Development**

The Applicant did not conduct carcinogenicity studies.

### **8.8.2. Human Reproduction and Pregnancy**

Based on its mechanism of action, atezolizumab can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. Females of reproductive potential are advised to use effective contraception during treatment with atezolizumab and for at least five months after the last dose.

### **8.8.3. Pediatrics and Assessment of Effects on Growth**

Atezolizumab has not been studied in a pediatric population. The Applicant has been granted a waiver of pediatric studies based on the low incidence of bladder cancer in the pediatric population.

### **8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

In the PCD4989g Phase I study, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The maximum dose evaluated was 20 mg/kg, therefore doses greater than 20 mg/kg of atezolizumab should be considered overdose. There was no evidence that suggests a risk for dependence of atezolizumab. No cases of withdrawal symptoms were reported during human clinical trials.

## **8.9. Safety in the Postmarket Setting**

### **8.9.1. Safety Concerns Identified Through Postmarket Experience**

Atezolizumab has not yet been approved in any market.

### **8.9.2. Expectations on Safety in the Postmarket Setting**

Patients with autoimmune disorders, except those with Type 1 diabetes mellitus or hypothyroidism on stable hormone replacement, were excluded from trials evaluating atezolizumab. Thus, off-label use in these patients would constitute a safety concern regarding immune-mediated adverse events.

The true incidence of hypothyroidism may be higher than that reported in the trials reviewed here. The Applicant will perform TSH evaluation every 6 weeks in one planned trial to better estimate the incidence of hypothyroidism as a post-marketing requirement.

### **8.10. Additional Safety Issues From Other Disciplines**

No additional safety issues from other disciplines were raised during the review. Refer to the pharmacometrics review for additional discussion of anti-drug antibodies and exposure-toxicity relationship.

### **8.11. Integrated Assessment of Safety**

The safety profile of atezolizumab in patients with urothelial carcinoma who have progressed following treatment with a platinum-based regimen is acceptable. The size of the safety database and duration of atezolizumab exposure were sufficient to characterize the safety of atezolizumab for treatment of a serious and life-threatening condition with the exception of updated safety data from the ongoing Phase 3 trial as well as additional data regarding the incidence of thyroid toxicity, which will be obtained via a PMR. Notable toxicities included a high incidence of infections, including severe urinary tract infections and sepsis that was confirmed in the randomized POPLAR trial of atezolizumab versus docetaxel in patients with non-small cell lung cancer. Incidences of immune-mediated adverse events, including pneumonitis, hepatitis, and diarrhea/colitis, were similar to or lower than other checkpoint inhibitors such as nivolumab and pembrolizumab. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of atezolizumab and the experience of the medical community in managing immune-mediated adverse reactions, based on use of other FDA-approved immune-modulating agents, such as nivolumab and pembrolizumab. Recommendations for safe and effective use of atezolizumab, including monitoring for immune-mediated adverse events, will be made in labeling, including a patient medication guide.

## **9 Advisory Committee Meeting and Other External Consultations**

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There were no safety or efficacy issues identified for the proposed indication and the product itself. The safety profile of atezolizumab is similar to that of two similar products currently marketed in the USA. The demonstrated benefit-risk profile for atezolizumab is favorable in the

intended patient population. Therefore, this application was not referred to the Oncologic Drugs Advisory Committee.

## 10 Labeling Recommendations

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### 10.1. Prescribing Information

Based on our review findings and the Applicant's submitted initial and revised labels during the review, the clinical and statistical reviewers recommended the following for the final label of atezolizumab for this BLA.

- a) Section 1:  
Emphasized the requirement of "disease progression" for use of atezolizumab and simplified the proposed indication to make it consistent with clinical descriptions of the disease conditions
- b) Section 2:  
Modified the statement [REDACTED] (b) (4) to "Do not administer TECENTRIQ as an intravenous push or bolus"
- c) Section 5:
  - *Pneumonitis*
    - [REDACTED] (b) (4)
    - Provided additional details on management and outcome of all cases
  - *Hepatitis*
    - Added one case of fatal immune-mediated hepatitis from Cohort 1 of IMVigor 210
    - Provided additional details on management and outcome of all cases
  - *Colitis*
    - Included diarrhea in addition to colitis given that some cases of diarrhea may have been immune-mediated despite lack of steroid administration.
    - Added one fatal case of colitis from Cohort 1 of IMVigor 210
    - Provided additional details on management and outcome of all cases
  - *Thyroid Disorders*
    - Included statement that thyroid function as assessed routinely only at baseline and the end of study.
    - Included data from safety database regarding incidence.
    - Included data on patients with elevated or decreased TSH regardless of whether they experienced an AE
  - *Adrenal Insufficiency*

- Included data from the safety database regarding incidence
- *Diabetes Mellitus*
  - Included data from the safety database regarding incidence.
  - Removed [REDACTED] (b) (4)
- *Other Immune-Related Adverse Reactions*
  - Included data from the safety database regarding incidence of symptomatic acute pancreatitis without an alternate etiology
- *Infection*
  - Included a new Warning since a high incidence of infection has not been well-documented in prior trials of bladder cancer, may be immune-mediated, and is an unusual and potentially serious event of which treating physicians should be aware. Although the incidence of infection is partially described in Section 6, a more detailed description in Section 5 is warranted.
  - Included a reference to cases of herpes [REDACTED] (b) (4) *mycobacterium* [REDACTED] (b) (4) leading to retroperitoneal hemorrhage
- *Infusion-Related Reactions*
  - Included a new section for consistency with other monoclonal antibody USPIs

d) Section 6:

- Additional data regarding the conduct of the trial and the extent of exposure based on the May 2015 database cut-off date are provided.
- Adverse reactions with incidence of 20% or greater are listed in decreasing order of frequency.
- Deaths associated with atezolizumab were updated to include a case of fatal pneumonitis.
- Adverse events, including serious adverse events, were updated to reflect pooled terms.
- A table was added to include Grade 3-4 laboratory abnormalities.

e) Section 8:

Revised the number of patients in “Geriatric Use” based on the number of patients enrolled in the key study supporting this BLA

f) Section 12:

Added information about the effects of hepatic and renal impairment on the pharmacokinetics of atezolizumab, and specified that key baseline characteristics such as body weight, race, and performance status had no clinically significant effect on the systemic exposure of atezolizumab. (See Clinical Pharmacology Review for details)

g) Section 14:

- Deleted (b) (4)
- Clarified the statement regarding continuation of atezolizumab (b) (4) “until unacceptable toxicity or either radiographic or clinical progression”.
- In the baseline characteristics of study patient, added the percentage of patients with non-bladder urothelial carcinoma and percentage of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.
- Specified that PD-L1 expression in tumor specimens was prospectively assessed at a central laboratory and clarified the definition of PD-L1 expression in ICs by using the 5% cutoff point to classify the two PD-L1 subgroups
- Rearranged the efficacy table and listed the efficacy results from all patients first (b) (4) Also inserted the number of patients who responded in the study.
- Specified the median duration of follow-up for the study cohort was 14.4 months. (b) (4)
- Deleted (b) (4)

h) Patient Counseling Information:

- Highlighted immune-related adverse reactions and insert subtitles concerning Embryo-Fetal Toxicity and Lactation
- Included the risk of Infection in the section
- Revised the Medication Guide” as recommended by Division of Medical Policy Programs

## 10.2. Patient Labeling

Medication Guide was proposed by the Applicant. This guide was revised with the recommendations from Division of Medical Policy Programs. The review conclusion was that the revised Medication Guide is acceptable.

## 10.3. Nonprescription Labeling

Not Applicable

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

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No REMS is indicated for the proposed indication.

## **12 Postmarketing Requirements and Commitments**

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The FDA review team for this BLA identified the following postmarketing clinical trials or studies for the recommended approval. These requirements and commitments have been agreed by the Applicant.

### **PMRs:**

- 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: Q3 2017  
Final Study Report Submission Date: Q4 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 2016  
Study/Clinical Trial Completion Date: August 2020  
Final Report Submission Date: February 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: Q2 2018

### **PMCs:**

- Submit the median duration of response for all patients, IC 2/3, and IC 0/1 patients, who responded to atezolizumab on IMvigor 210. Submit datasets and revised labeling

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

concerning the median duration of response.

Final protocol Submission Date: N/A

Study/Clinical Trial Completion Date: Q3 2016

Final Report Submission Date: Q4 2016

- Perform supplemental characterization of the MCB to provide additional assurance that the cell bank was (b) (4). These data should include the evaluation (b) (4) and 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: Q2 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 PDL1 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 2016

Study/Clinical Trial Completion Date: July 2017

Final Report Submission Date: January 2018

## 13 Appendices

### 13.1. References

See footnotes on pages where the references were inserted.

### 13.2. Financial Disclosure

The covered study for this BLA is Cohort 2 of the Phase 2 Study GO29293. Since this study relied on independent-review determined objective responses, financial issues are less likely to affect the analyses of the effectiveness of atezolizumab in the intended patient population.

**Covered Clinical Study (Name and/or Number): Study GO 29293-Cohort 2**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>62</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>6</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>6</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		

Clinical and Statistical Reviews

Drs. Ning, Zhang, and Suzman

BLA 761034 for Atezolizumab for Second-Line Use in Advanced Urothelial Carcinoma

Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)
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/s/  
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