APPLICATION NUMBER:

761069Orig1s000

MEDICAL / STATISTICAL REVIEW(S)
**CLINICAL and STATISTICAL REVIEWS**

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<tr>
<td>Priority or Standard</td>
<td>Priority Review</td>
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<tr>
<td>Submit Date(s)</td>
<td>October 13, 2016</td>
</tr>
<tr>
<td>Received Date(s)</td>
<td>November 1, 2016</td>
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<tr>
<td>PDUFA Goal Date</td>
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| Reviewer Name(s) | Efficacy and Safety Review: Daniel Suzman, MD  
Statistical Review: Laura Fernandes, PhD |
| Review Completion Date | March 6, 2017 |
| Established Name | Durvalumab |
| (Proposed) Trade Name | IMFINZI |
| Applicant | AstraZeneca UK Limited |
| Formulation(s) | Injection/500 mg per 10 mL vial and 120 mg per 2.4 mL vial |
| Dosing Regimen | 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks |
| Applicant Proposed Indication(s)/Population(s) | Imfinzi is a humanized programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:  
- locally advanced or metastatic urothelial carcinoma |
| Recommendation on Regulatory Action | Accelerated Approval |
| Recommended Indication(s)/Population(s) (if applicable) | IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:  
- Locally advanced or metastatic urothelial carcinoma who:  
  - have disease progression during or following platinum-containing chemotherapy.  
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. |

**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 durvalumab. 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 Office of FDA.
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Common Abbreviations Used in the Review

AC  advisory committee
AE  adverse event
ATA  anti-therapeutic antibody
BLA  biologics license application
BICR  Blinded Independent Central Review
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
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
PI  prescribing information
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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
1 Executive Summary

1.1. Product Introduction

Durvalumab (IMFINZI) 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 is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

- The proposed indication for this BLA is for use of durvalumab in patients with locally advanced or metastatic urothelial carcinoma.

The recommended dose for durvalumab is 10 mg/kg, administered as an intravenous infusion over 60 minutes every 2 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 durvalumab for the proposed indication under Subpart E of the Biological Licensing Regulations.

Our review found that this BLA provides substantial evidence to support second-line use of durvalumab in patients with locally advanced or metastatic urothelial carcinoma. In the United States, this represents the third approval of a second-line treatment in this disease setting following the approvals of atezolizumab and nivolumab under the Accelerated Approval pathway.

As summarized in the following Benefit Risk Assessment, evidence supporting this BLA came from one single-arm study. Treatment with durvalumab in the intended patient population elicited confirmed objective antitumor responses in 17.0% 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 ≥6 months and some for ≥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).

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 durvalumab in the intended patient population. Combined with the demonstrated safety profile, the evidence contained in this BLA is considered sufficient for accelerated approval of durvalumab for the proposed indication. An ongoing randomized, active controlled trial of durvalumab versus durvalumab in combination with tremelimumab vs the Investigator’s choice of a platinum-

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1 21 Code of Federal Regulations, Part 601.41
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BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma containing chemotherapeutic (NCT02516241) may provide confirmatory evidence to verify the clinical benefit in the same patient population.

Use of the PD-L1 (SP263) IHC assay, as proposed for this BLA, may identify patients who may have a modestly higher chance to respond to durvalumab. Nevertheless, the observed durable responses in patients with low or no PD-L1 expression (as defined by <25% staining of both tumor and immune cells) in their tumor specimens 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 durvalumab clinically available to all patients who may benefit from this second-line treatment.

1.3. Benefit-Risk Assessment
Durvalumab, 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. In the USA, there is no second-line therapy for this indication with full FDA approval. Atezolizumab, another anti-PD-L1 antibody, and nivolumab, an anti-PD-1 antibody, are approved under the Accelerated Approval pathway for second-line urothelial cancer. Standard of care for patients with advanced urothelial carcinoma, prior to the approvals of atezolizumab and nivolumab, has been platinum-containing chemotherapy. However, off-label use of chemotherapeutics in this disease setting is associated with low response rates and short response durations along with considerable toxicities. Further, almost all patients experience disease progression during or after platinum-containing chemotherapy. Patients with progressive disease may have a limited survival time of 5-10 months.

The effectiveness of durvalumab is demonstrated in 182 patients with locally advanced or metastatic urothelial carcinoma who had disease progression after prior platinum-containing chemotherapy. Durvalumab was administered intravenously at a dose of 10 mg/kg every 2 weeks. Confirmed ORR, as assessed by blinded independent central review (BICR) per RECIST v1.1, was 17.0% (95% CI: 11.9, 23.3). At the data cutoff time for the ORR analysis, median DOR in responders was not reached (range: 0.9 to 19.9 months). Of the 31 responders, 14 patients had ongoing responses of ≥6 months and 5 had ongoing responses of ≥12 months. ORR was also analyzed as pre-specified by PD-L1 expression status, which was prospectively assayed in tumor specimens at a central laboratory. In the 128 patients who were enrolled without regard to PD-L1 status and after the assay was finalized, the confirmed ORR was 19.0% (95% CI: 9.9, 31.4) in 58 patients with a high PD-L1 score and 3.6% (95% CI: 0.4, 12.3) in 56 patients with a low or negative PD-L1 score. Response durations in the PD-L1 subgroups were similar to those in the overall population. No patients out of 17 patients with a Bellmunt risk score (which includes hemoglobin, ECOG performance status, and the presence of liver metastases) of 3 responded. Additionally, these patients had an increased risk for progression or death prior to the first tumor assessment. Consideration of alternative therapies such as cytotoxic chemotherapy or best supportive care should be given to these patients, as they appear less likely to benefit from treatment with durvalumab.

The most common adverse reactions of durvalumab in at least 20% of patients were fatigue, musculoskeletal pain, constipation, decreased appetite, vomiting, peripheral edema, and nausea. Grade 3-4 adverse events were seen in 46% of patients. Infection and immune-related adverse events such as pneumonitis, hepatitis, colitis, thyroid disease, adrenal insufficiency, and diabetes were also seen with durvalumab.

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

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

<table>
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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| **Analysis of Condition**          | - Progressive advanced urothelial carcinoma following platinum-based first line therapy has a poor prognosis, with a median survival of 6-10 months.  
                                        - Approximately 15,000 deaths from advanced urothelial carcinoma each year.            | This disease is serious and life-threatening. There is a significant unmet medical need for patients with the disease. |
| **Current Treatment Options**      | - There are no products in the USA with full FDA approval for second-line therapy for the disease.  
                                        - Atezolizumab and nivolumab have been granted Accelerated Approval. Off-label, taxanes (docetaxel, paclitaxel, nab-paclitaxel) or a combination of paclitaxel with gemcitabine are used. Vinflunine is available outside the USA. | All the products are palliative and have significant adverse reactions and/or intolerance. Patients receiving conventional chemotherapy generally have a short response duration. Atezolizumab and nivolumab may have an improved duration of response compared to historical chemotherapy. Vinflunine is associated with a survival trend compared to best supportive care. |
| **Benefit**                        | - Of the population of 182 patients, 17.0% had confirmed responses. Among the 128 patients who were not pre-enriched for PD-L1 status and who were enrolled after finalization of the assay, the ORR was 19.0% in the PD-L1 high group and 3.6% in the PD-L1 low group.  
                                        - Median response duration was not reached (range 0.9+, 19.9+ months). Of the responders, 45.2% (14/31) had | Substantial evidence of effectiveness for second-line use of durvalumab monotherapy in advanced urothelial carcinoma, as supported by similar ORRs and durable responses, was found. The results are consistent with the benefits seen with other PD-1/PD-L1 agents in |
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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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</thead>
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<tr>
<td>Risk</td>
<td>- Tolerated in most study patients</td>
<td>The profile of adverse reactions associated with durvalumab is similar to that observed in other PD-1 targeted products.</td>
</tr>
<tr>
<td></td>
<td>- Important risks include hepatitis, pneumonitis, endocrine disorders, colitis, infection, and neurological disorders</td>
<td></td>
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<tr>
<td>Risk Management</td>
<td>- Non-endocrine immune-mediated adverse events were largely reversible with the use of corticosteroids.</td>
<td>The safe use of durvalumab can be managed through accurate labeling and routine pharmacovigilance. No REMS is indicated.</td>
</tr>
<tr>
<td></td>
<td>- A medication guide for durvalumab describing the risks of immune-mediated adverse events will be required to better allow early recognition and initiation of treatment of these events.</td>
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<tr>
<td></td>
<td>ongoing responses of ≥6 months and 16% (5/31) had ongoing responses of ≥12 months.</td>
<td>this disease setting. Patients positive for PD-L1 expression appear to have a higher response rate relative to patients negative for PD-L1 expression. Durable responses are observed in both PD-L1 high and low responders, although the number of responses in the PD-L1 low/negative group is very low. Given the low response rate seen in patients with a high Bellmunt risk score, providers should consider offering alternative therapies or best supportive care in these patients.</td>
</tr>
<tr>
<td></td>
<td>- No patients with Bellmunt risk score of 3 had a response (0/17).</td>
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2 Therapeutic Context

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\textsuperscript{2,3}. 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\textsuperscript{4}. In addition, approximately 10\% of patients have regionally advanced or metastatic disease at diagnosis\textsuperscript{2}.

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. Atezolizumab, a PD-L1 antibody, was approved for the second-line treatment of bladder cancer on June 7, 2016 on the basis of increased response rate and duration of response compared to available therapy. Subsequently, nivolumab, a PD-1 antibody, was approved for the same indication on February 2, 2017. However, as atezolizumab and nivolumab were approved under the Accelerated Approval pathway, they do not constitute available therapy with regards to the current application. There is no efficacious or standard second-line available 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, atezolizumab and nivolumab are the only FDA-approved second-line therapies 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 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

\textsuperscript{3} NCCN Guidelines v1 2016: Bladder Cancer
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BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma 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.

In general, no standard of care exists in the second-line setting. Aside from atezolizumab and nivolumab, taxane, gemcitabine, or pemetrexed monotherapy may be preferred off-label treatments of advanced urothelial carcinoma after platinum-containing chemotherapy. Given the modest activity of a taxane or other optional chemotherapeutics in the disease setting and the preliminary nature of the data for the activity of atezolizumab and nivolumab, participation in clinical trials is recommended.

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

<table>
<thead>
<tr>
<th></th>
<th>Vinflunine + BSC</th>
<th>Gemcitabine + Paclitaxel</th>
<th>Docetaxel</th>
<th>Nab-paclitaxel</th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
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</thead>
<tbody>
<tr>
<td><strong>Trial Phase</strong></td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>II</td>
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<tr>
<td><strong>Patient Population</strong></td>
<td></td>
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<tr>
<td>Regarding Prior Platinum Use Requirement</td>
<td>After first-line platinum-containing chemotherapy; no time interval specified</td>
<td>During or after cisplatin-based first-line chemotherapy; no time interval specified</td>
<td>After platinum-containing chemotherapy; no time interval specified</td>
<td>Progression on or within 12 months of treatment with one prior platinum-containing regimen</td>
<td>Progression on or within 12 months of treatment with one prior platinum-containing regimen</td>
<td>Progression on or within 12 months of treatment with one prior platinum-containing regimen</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Objective Response (#/Evaluable Patients)</th>
<th>Vinflunine* +BSC</th>
<th>Gemcitabine + Paclitaxelb</th>
<th>Docetaxelc</th>
<th>Nab-paclitaxelda</th>
<th>Atezolizumabf</th>
<th>Nivolumabf</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 185</td>
<td>N = 40</td>
<td>N = 70</td>
<td>N = 47</td>
<td>N = 310</td>
<td>N = 270</td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>16 (9%)</td>
<td>15 (38%)</td>
<td>5 (11%)</td>
<td>13 (28%)</td>
<td>46 (15%)</td>
<td>53 (20%)</td>
</tr>
<tr>
<td>Response Duration (mos), median</td>
<td>7.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10.3</td>
</tr>
<tr>
<td>Overall Survival*, median</td>
<td>6.9 months (vs 4.6 mos with BSC, HR 0.88 p=0.287)</td>
<td>7.8 months</td>
<td>7.0 months</td>
<td>10.8 months</td>
<td>7.9 months</td>
<td>8.6 months</td>
</tr>
</tbody>
</table>

**Key Safety Issues (Grade 3 or 4 Toxicity)**

<table>
<thead>
<tr>
<th></th>
<th>Vinflunine* +BSC</th>
<th>Gemcitabine + Paclitaxelb</th>
<th>Docetaxelc</th>
<th>Nab-paclitaxelda</th>
<th>Atezolizumabf</th>
<th>Nivolumabf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (50%);</td>
<td>Neutropenia (14%);</td>
<td>Neutropenia (1%);</td>
<td>Neutropenia (10%);</td>
<td>Urinary tract infection (9%);</td>
<td>Fatigue (7%);</td>
<td>Urinary tract infection (7%);</td>
</tr>
<tr>
<td>Febrile neutropenia (6%);</td>
<td>Anemia (1%);</td>
<td>Fatigue (6%);</td>
<td>Weakness (8);</td>
<td>Fatigue (6%);</td>
<td>Abdominal pain (4%);</td>
<td>Dyspnea (3.3%);</td>
</tr>
<tr>
<td>Anemia (19%);</td>
<td>Infection (6%);</td>
<td>Fatigue (6%);</td>
<td>Neuropathy (6%);</td>
<td>Dyspnea (4%);</td>
<td>Dyspnea (4%);</td>
<td>Diarrhea (2.6%);</td>
</tr>
<tr>
<td>Fatigue (19%);</td>
<td>Electrolyte abnormalities (6%);</td>
<td>Infection (6%);</td>
<td>Hypertension (6%);</td>
<td>Hematuria (3%);</td>
<td>Hematuria (3%);</td>
<td>Musculoskeletal pain (2.6%);</td>
</tr>
<tr>
<td>Constipation (16%);</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: not reported;

*In the relevant treatment arm or study of the enrolled patients.

**As reported from each study, which may not represent the comprehensive safety profile of each treatment based on the approved product label.

- a) Bellmunt J., et al. (2009) J Clin Oncol 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.
- b) Albers P, et al. (2011) Annals of Oncology 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.
- c) Choueiri TK et al (2011) J Clin Oncol 30:507-512. The results as shown were from the docetaxel + placebo arm alone.
- d) Ko YJ et al (2013) Lancet Oncol 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.
- e) Per FDA review of BLA 761034
- f) Per FDA review of BLA 125554, Supplement 24

Reference ID: 4068251
3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Durvalumab 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 Pre-submission/Submission Regulatory Activity

Major regulatory activities with FDA are summarized in Table 3. This summary focuses on activities relevant to the development program for durvalumab in urinary tract malignancies, which was initiated in June 2012. The initial IND (112249) for the same product was submitted in 2012.

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2012</td>
<td>IND 112249 was submitted for studies of durvalumab in advanced solid tumors.</td>
</tr>
<tr>
<td>May 2014</td>
<td>Amendment 5 was submitted for Study 1108 allowing recruitment of an additional expansion cohort of 40 patients with urothelial bladder cancer (UBC) with PD-L1 expression of ≥5% of tumor cells.</td>
</tr>
<tr>
<td>Dec. 2014</td>
<td>IND was submitted for studies of durvalumab and tremelimumab in UBC.</td>
</tr>
<tr>
<td>Nov. 2015</td>
<td>Amendment 8 was submitted for Study 1108 allowing recruitment of an additional 120 UBC patients that would not be selected for PD-L1 status.</td>
</tr>
<tr>
<td>February 2016</td>
<td>The applicant requested Breakthrough Therapy designation of durvalumab for the treatment of patients with locally advanced or metastatic urothelial bladder cancer (UBC) that is PD-L1 positive, as determined by an FDA-approved test, after progression on or intolerance to a platinum-containing chemotherapy regimen.</td>
</tr>
<tr>
<td></td>
<td>This request was granted based on preliminary evidence from 27 patients with locally advanced or metastatic UBC with a PD-L1 IHC tumor cell score of ≥25% or an immune cell score of &gt;0% (as determined by the prototype PD-L1 assay). Confirmed objective response (per RECIST v1.1) rate was 48%. The median response duration was not reached at the data cutoff.</td>
</tr>
</tbody>
</table>
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July 2016

- A Post-Breakthrough Therapy Designation Type B meeting was held to discuss the development plans and regulatory approval pathways. The single-arm study 1108 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 determination. A data cut-off of July 24, 2016 was agreed to for submission of Study 1108 for Accelerated Approval on the basis of the Applicant’s estimate that 103 patients with urothelial bladder cancer would have been undergone at least 2 tumor assessments following treatment with durvalumab. The Sponsor proposed to provide an efficacy update for these patients as part of the Day 90 safety update.
- The *in vitro* diagnostic for the proposed PD-L1 assay was evaluated with CDRH and the sponsor planned to conduct analytical validation studies of the assay based on data from additional patients.

Sept. 2016

- Pre-BLA submission written response was provided.
- Agreements reached on the contents, format, and analyses for a BLA submission based on results from the urothelial cancer cohort of the Phase 1 Study 1108 with supportive safety evidence from the ATLANTIC (D4191C00003) trial in non-small cell lung cancer


- Rolling submission of the BLA initiated, with the clinical datasets and study reports submitted on.
- The BLA was designated for priority review at the filing meeting.

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**

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

Three sites as well as the Applicant were selected for review in collaboration with OSI. See section 6.1.2 for discussion of results.
4.2. Product Quality

No significant issues were identified regarding the CMC part of the application.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There are no data available on the use of durvalumab in pregnant women. Based on animal data and literature review, the non-clinical toxicology reviewer noted that the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus and that disruption of this pathway results in increased fetal loss. In cynomolgus monkeys, administration of durvalumab resulted in premature delivery, fetal loss, and increase in neonatal deaths. Durvalumab was also detected in infant serum on post-partum Day 1, indicating that placental transfer can occur and potentially increasing the risk for the development of immune-mediated disorders in the infant.

4.5. Clinical Pharmacology

There were no significant clinically related issues identified in the clinical pharmacology review. Per population PK analysis, a fixed dose of 750mg was considered comparable to the 10 mg/kg weight-based dosing that was evaluated in Study 1108, however given the available vial sizes, the Applicant opted to pursue weight based dosing during this application and plans to continue to evaluate 1500mg Q4W as flat dosing for a future supplement.

4.5.1. Mechanism of Action

Durvalumab 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 durvalumab increased dose proportionally over the dose range of 3 mg/kg to 20 mg/kg. At 10 mg/kg steady state is achieved at approximately Week 16 and the half-life is approximately 21 days. More than 95% target saturation is expected at a dose of 10 mg/kg and approximately 97% of patients demonstrated serum PD-L1 suppression throughout the dosing interval at 10 mg/kg. The median minimum concentration at steady state was 145 µg/mL.
4.6. Devices and Companion Diagnostic Issues

The PD-L1 (SP263) IHC assay was submitted to CDRH for evaluation along with this BLA submission to CDER. This assay is intended for the qualitative immunohistochemical assessment of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial cancer tissue stained with an OptiView DAB IHC Detection Kit on a Ventana BenchMark ULTRA instrument. The scoring criteria rely on the percentage of both PD-L1 stained tumor cells (TCs) and immune cells (ICs) within the tumor area.

The Applicant states that the PD-L1 expression cut-offs were defined following analysis of the first 20 urothelial cancer patients enrolled on Study 1108. The current definition of high and low PD-L1 staining was applied after Amendment 8.

4.7. Consumer Study Reviews

Not applicable.
5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 5 summarizes key information of the two studies [Study CD-ON-MED14736-1108 (or Study 1108) and Study D4191C0003 (or ATLANTIC)] that supported this BLA submission. In October of 2016, the Applicant submitted datasets for both studies. These datasets constitute the basis for our analyses as described in this combined review. The data cutoff time for each study is listed in Section 6.
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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 182 2nd-line post-platinum UC patients treated with durvalumab in Study 1108 with additional analyses of adverse events of special interest (AESIs) including immune-mediated adverse events. This analysis 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 July 24, 2016. Adverse events that occurred within 90 days following discontinuation of durvalumab were included.

The clinical review of safety was supplemented with an evaluation of AESIs in an additional 788 patients with various tumor types in Study 1108 and 444 patients with NSCLC in ATLANTIC. Thus, the total integrated safety dataset comprised 1414 patients. ATLANTIC additionally provided limited ECG/QT data. The data cut-off for ATLANTIC was June 3, 2016. The data cut-off for the non-UC patients in Study 1108 was April 29, 2016.

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

6.1. Studies Supporting the BLA

6.1.1. Study Design

Overview and Objective

This BLA is primarily based on findings from the 2nd-line post-platinum UC patients from the Phase 2 study as listed in Table 5, with supportive safety evidence from the additional patients in Study 1108 and ATLANTIC.

Trial Design for Study 1108
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Study 1108 was a multicenter, open-label, dose-escalation/exploration and dose-expansion study of durvalumab in patients with selected advanced solid tumors. The key objectives for the dose-escalation phase were to determine the MTD or optimal biologic dose and the safety profile of durvalumab in patients with advanced melanoma, renal cell carcinoma, non-small cell lung cancer, and colorectal cancer for whom there was no standard therapy indicated. The key objectives for the dose-exploration phase were to determine the safety profile of durvalumab using a Q4W dosing schedule in patients with advanced melanoma, hepatocellular carcinoma (HCC), squamous cell carcinoma of the head and neck (SCCHN), NSCLC, gastroesophageal cancer, triple-negative breast cancer (TNBC), and pancreatic adenocarcinoma. The key objectives for the dose-escalation phase were to determine the safety profile of durvalumab in patients with advanced melanoma, HCC, SCCHN, NSCLC, glioblastoma multiforme, ovarian cancer, soft-tissue sarcoma, small-cell lung cancer, microsatellite instability-high cancers, human papilloma virus-positive cancer, or nasopharyngeal carcinoma and to evaluate the safety and anti-tumor efficacy of durvalumab in patients with NSCLC and PD-L1-high UC, as assessed by independent review per RECIST v1.1.

Figure 1 Trial Design for Study 1108

| Durvalumab Dose-escalation Phase, Q2W Dosing $^a$  
| (Melanoma, RCC, NSCLC, or CRC) |
|-----------------|-----------------|
| Cohort 1 Q2W    | 0.1 mg/kg       |
| (n = 3 - 6)     |                 |
| Cohort 2 Q2W    | 0.3 mg/kg       |
| (n = 3 - 6)     |                 |
| Cohort 3 Q2W    | 1.0 mg/kg       |
| (n = 3 - 6)     |                 |
| Cohort 4 Q2W    | 3.0 mg/kg       |
| (n = 3 - 6)     |                 |
| Cohort 5 Q2W    | 10 mg/kg        |
| (n = 3 - 6)     |                 |

| Durvalumab Dose-escalation Cohort, Q3W Dosing $^b$  
| (Melanoma, RCC, NSCLC, or CRC) |
|-----------------|-----------------|
| Durvalumab 15 mg/kg Q3W  |
| (n = 3 - 6)     |                 |

Durvalumab Dose-expansion Phase, Q2W Dosing

See Table 9.1-1 for tumor type details

Adapted from the CSR dated 10/8/2016
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In the UC cohort, which enrolled beginning with Protocol Amendment 5, patients were required to have inoperable or metastatic transitional cell carcinoma of the urothelium. Mixed transitional cell/non-transitional cell histologies were allowed. The first 20 patients were enrolled regardless of PD-L1 expression, while the next 43 patients were required to have tumor specimens in which at least ≥5% were positive for PD-L1 expression. Prior to Amendment 8, patients were eligible to enroll if they had progressed on, were intolerant to, or were eligible for standard first-line therapy. As of Amendment 8, patients must have received and progressed on at 1 or 2 lines of systemic therapy, including a platinum-based regimen for metastatic disease. If patients received prior chemotherapy for locally-advanced disease, this must have occurred at least 12 months prior to enrollment. As of Amendment 8, patients were required to provide an archived tumor specimen from within 6 months prior to enrollment or a fresh biopsy for PD-L1 IHC analysis and patients were enrolled regardless of tumoral PD-L1 expression. Patients were additionally required to have an ECOG performance score of 0 or 1 and measurable disease per RECIST v1.1.

The study excluded patients with a history of autoimmune disease (except for Grave’s disease, Hashimoto’s disease, vitiligo, or psoriasis not requiring systemic treatment within the past 2 years), HIV, active HBV/HCV, and tuberculosis, active or corticosteroid-dependent brain metastases, or had received a live, attenuated vaccine within 30 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 (equivalent to 10mg/day of prednisone or less).

Patients received an intravenous infusion of 10 mg/kg of durvalumab on Day 1 of a 2 week cycle until unacceptable toxicity, disease progression, or symptomatic progression. For patients who met RECIST v1.1 criteria for disease progression, continued treatment with durvalumab was allowed at the discretion of the Investigator if they met all of the following: 1) Absence of rapid clinical deterioration and 2) 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 at Week 6, Week 12, Week 16, and every 8 weeks thereafter. The Blinded Independent Central Review (BICR) was performed by BICR-determined measurable disease was a requirement for enrollment following January 2016. Each scan was assessed by two radiologists and, if there was a discrepant read between the two radiologists, a third radiologist adjudicated.

Study Endpoints of Study 1108 (UC cohort)

The primary study endpoints included Blinded Independent Central Review (BICR) confirmed

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ORR using RECIST v1.1. The primary analysis was planned to be performed in the 2\textsuperscript{nd} and 3\textsuperscript{rd}-line PD-L1-positive UC patients.

**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.

Key secondary efficacy endpoints of this study included disease-control rate (DCR), duration of response (DOR), PFS, and OS. All analyses were performed both on BICR assessment if available and investigator assessment.

- DOR was defined as the time from the initially documented CR or PR until evidence of disease progression or death due to any cause, whichever occurred first.
- DCR was defined as the proportion of patients with CR, PR, or SD (if SD for at least 12 weeks)
- PFS was defined as the time from the first dose of durvalumab to disease progression 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 durvalumab 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**

Patients enrolled in the dose-expansion phase of Study 1108 were to receive durvalumab 10 mg/kg Q2W. The sample size justification for the total of 192 patients planned for the UC cohort was based on the expected ORR in the PD-L1-high status group with a goal of excluding the historical ORR of 10%. With approximately 100 patients with a PD-L1-high status would provide an expected ORR in the range of 17\%-33\%. With a total of 70 PD-L1-high UC subjects, there is an 85\% chance of observing at least 13 responses (an ORR of 18.6\% with the lower-limit of the exact 95\% CI excluding a historical response rate of 10\%) if the true ORR is 23\%. With a total of 100 PD-L1-high UC subjects, there is a 94\% chance of observing at least 17 responses (an ORR of 17\% with the lower-limit of the exact 95\% CI excluding a historical response rate of 10\%) if the true ORR is 23\%.

The prevalence of PD-L1 status for UC subjects will be monitored through the study. After a total of approximately 132 subjects are enrolled under Amendment 8 and beyond, the enrollment of only PD-L1-high subjects may continue to ensure a minimum total of 70 PDL1-high subjects are enrolled.

With 70 PD-L1-high and 50 PD-L1-low/no expression UC subjects enrolled under Amendment 8 and beyond to validate the potential of PD-L1 expression to predict response
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to MEDI4736 treatment, the study has 80% power to detect a 20% difference in ORR
between the PD-L1-high group and the PD-L1-low/negative group at a 1-sided 5% of alpha level.

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.
Since this is not a randomized study, the difference in ORR analyses between the subgroups is
considered exploratory in nature.
The SAP did not provide details on which patients would be used to validate the diagnostic
device that determined PD-L1 status. All patients enrolled following protocol amendment 8
were unselected for PD-L1 status and were not used in validating the diagnostic test.

The study SAP outlined the following key analysis populations:

- As-treated Population is defined as all subjects who receive any dose of MEDI4736.
- Full analysis set (FAS) Population is defined as all subjects from the As-treated
  Population who had measurable disease at baseline per blinded central review (BICR)
  and had an opportunity to be followed for at least 24 weeks by the DCO date (i.e.,
  received the first dose of MEDI4736 at least 24 weeks prior to the DCO date).
- DLT Evaluable Population is defined as all subjects enrolled in the dose-escalation phase
  who receive at least two doses of MEDI4736 and complete the safety follow-up through
  the DLT evaluation period (defined as the time period until the administration of the
  third dose of MEDI4736) or experience any DLT.
- Re-treated Population is defined as all subjects who have entered follow-up and have
  been retreated with MEDI4736 after the initial 12 months treatment period.

The primary analysis of ORR based on RECIST v1.1 by BICR will be performed for all 2L+
PD-L1 high UC subjects in the FAS enrolled in the entire study. The primary endpoint for
UC cohort in PD-L1-high subgroup is considered to be met if the lower-limit of the exact 2-
sided 95% CI for ORR excludes a historical response rate of 10%. An analysis of ORR for all 2L+
PD-L1 high UC subjects in the FAS enrolled under Amendment 8 and beyond will be conducted
as a supportive analysis. The primary analysis for UC cohort will occur at least 24 weeks after
the last PD-L1-high UC subject’s first dose of study treatment.

If the primary endpoint for the PD-L1-high subgroup of the UC cohort is met, the ORR based
on RECIST v1.1 by BICR along with its 95% CI will be also provided for all 2L+ UC
subjects in the FAS (regardless of PD-L1 status) enrolled in the entire study. The primary
endpoint for UC cohort in all-comers is considered to be met if the lower-limit of the exact 2-
sided 95% CI for ORR excludes a historical response rate of 10%.

The secondary efficacy endpoints include objective response (except for subgroups of
NSCLC and UC cohorts where OR is considered the primary endpoint), duration of response
(DoR), disease control (DC), time to response (TTR), duration of stable disease (DSD),
progression-free survival (PFS), overall survival (OS), and change in target lesion size. All
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endpoints except Overall Survival (OS) are based on RECIST 1.1 as assessed by the BICR (if available) and investigator. The site investigator disease response assessment will be a programmatically-derived from the investigator’s recorded measurements and assessments for target, non-target, and new lesions according to RECIST v1.1.

Interim Analyses: Following review of PD-L1 expression and response data (assessed by investigator per RECIST v1.1) in the initial 20 UC subjects enrolled and followed for a minimum of 12 weeks, a cutoff of 25% for either IC or TC in a baseline sample was chosen for response analysis because the presence of PD-L1 in ≥ 25% of immune cells or ≥ 25% of tumor cells both appeared to enrich for response. In addition to TC- or IC-independent definitions, a combined TC/IC algorithm was developed and then subsequently applied to Study D419BC00001 [DANUBE]), where PD-L1 status is one of the stratification factors at randomization.

An interim analysis of efficacy was planned to be conducted after approximately 103 UC subjects treated with MEDI4736 had an opportunity to be followed for at least 13 weeks (at least two RECIST follow-up scans plus 1 week visit window).

An updated efficacy analysis would be conducted on the primary efficacy population from the first planned interim analysis (i.e., approximately 103 subjects, as described above). This analysis would be done based on a data cut-off date, which will be approximately 90 days after the DCO date for the first interim analysis. Key efficacy information, including ORR and duration of response would be updated at this time. There were no plans to stop the trial based on either of these analyses and no formal statistical adjustments were planned.

Review Comments: The review team considered the 2L+ UC subjects in Study 1108 (regardless of PD-L1 status) 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. 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.

The Agency was provided data from the 103 UC patients in the initial submission in October 2016 and an update on all the 182 patients in January 2017 which is used as the primary efficacy population.

Protocol Amendments
The study protocol was proposed in April 2012. Before its initiation and during the study, the protocol was amended with feedback from the Agency. There were 4 major amendments.
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relevant to the UC cohort, which are summarized in Table 5. Overall, the amendments did not affect the integrity of the study but rather helped improve interpretation of the results.

Table 5: Protocol Milestones and Amendments of Study 1108 Relevant to the UC Cohort

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
<th>Major Changes or Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Protocol</td>
<td>4/4/2012</td>
<td></td>
</tr>
</tbody>
</table>
| Amendment 5         | 5/21/2014 | * UC expansion cohort added  
|                     |        | * Pneumonitis was added as a potential imAE                                                  |
| Amendment 7         | 6/18/2014 | * Tumoral PD-L1 requirements were changed  
|                     |        | * Clarification that subjects with untreated CNS metastases were excluded but previously-treated CNS metastases were allowed |
| Amendment 8         |        | * The UC cohort was expanded                                                              |
| Amendment 9         | 2/4/2016 | * The renal function enrollment parameters were relaxed for UC patients  
|                     |        | * UC patients with incidental prostate cancer on surgical specimens were allowed to enroll as long as they were not receiving treatment for prostate cancer  
|                     |        | * UC patients with non-evaluable tumor samples were allowed to enroll                       |
| Enrollment Completion | N/A  | * This study continued to enroll as of the DCO                                           |
| Study Report        | 10/8/2016 | * Generated with a data cutoff date of 7/24/2016                                         |

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.

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. One site (Site 2000112), which enrolled eight 2nd-line post-platinum patients, had significant issues upon OSI inspection including many AEs found in the health record that were not included on CRFs and reported to the Applicant. Additionally, several patients were documented as “withdrew consent” rather than followed per protocol. OSI has indicated that there is Voluntary Action Indicated for this site. There were no significant inspectional findings at the other two sites or the Applicant based on the clinical inspection summary and there were no indications of a systemic issue.

Two patients (25%) out of the eight enrolled at Site 2000112 were responders, similar to the overall ORR. Four patients (50%) experienced Grade 3-4 AEs, which was also similar to the incidence of Grade 3-4 AEs in the overall 2nd-line post-platinum population (46%).

Review Comments: It is likely that the available data slightly underestimate the true incidence of adverse events, although Site 2000112 represented a relatively small proportion of the total number of UC patients enrolled.

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 Howard Hutchinson, Vice President of U.S. 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 durvalumab.

Results from UC cohort of Study 1108

Patient Disposition
A total of 191 patients enrolled in the UC cohort of Study 1108. Of these, 182 patients were considered to be 2nd-line post-platinum patients followed for at least 13 weeks on study with at least 2 RECIST follow-up scans. These patients constituted both the primary efficacy and primary safety populations. With the data cutoff date of 10/24/2016, 32% of patients were still on study treatment and 68% of patients had discontinued study treatment. An additional 8% of patients had completed the initial 12 month treatment period. As listed in Table 6, most patients discontinued due to disease progression.

Table 6: Patient Disposition in the 2nd-line Post-platinum UC Cohort of Study 1108

<table>
<thead>
<tr>
<th>2nd Line Urothelial N = 182 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Completed 12 Months of Treatment</td>
</tr>
<tr>
<td>Ongoing</td>
</tr>
<tr>
<td>Discontinued</td>
</tr>
<tr>
<td>Disease Progression</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>Patient Request/Investigator Decision</td>
</tr>
</tbody>
</table>

Source: ADSL datasets;  
Data Cutoff: October 24, 2016

Reviewer comments:

- Radiographic progression was documented by the BICR in 73/93 pts who discontinued due to disease progression.
- Among the 8 patients who withdrew consent, five had progressive disease (3 by scan). Four patients had recurrent, often complicated urinary infections with possible decreases in performance status.
- Among the patients who died while on study drug, one death was due to pneumonitis. Three additional deaths are of concern; one with increased AST and no known liver metastases and two with possible adrenal insufficiency. However, adrenal insufficiency was not documented and in 1 case could have been related to prior steroid use. One additional patient had multi-organ failure and a second had sepsis prior to his death which was stated to be due to disease progression.

Among the nine patients who discontinued due to an adverse event, three of the adverse events were drug-related. This includes elevations in ALT/AST (2 pts) and acute kidney...
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Injury (1). The disposition dataset includes 8/182 pts who discontinued due to an adverse event. The adverse event dataset includes 10/182 patients who discontinued due to an adverse event. The two additional patients in the AE dataset both received prior platinum-based therapy and discontinued due to bladder cancer and back pain.

- Among the 4 patients who discontinued due to patient request/investigator decision, three appear to have been due to progressive disease. One patient from South Korea developed pulmonary tuberculosis approximately 1 month prior to discontinuation and had a grade 3 ALT and the end of study visit. The patient had not received steroids and had no liver metastases.

Protocol Violations/Deviations

Table 7: Major Protocol Violations/Deviations

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>182</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>66 (36)</td>
</tr>
<tr>
<td>Eligibility Criteria Unmet</td>
<td>13¹ (7)</td>
</tr>
<tr>
<td>Study Drug Administration or Timing</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Procedural Deviations Affecting Safety</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Missing Scheduled Assessments</td>
<td>18² (10)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (6)</td>
</tr>
</tbody>
</table>

Note that some patients had >1 violations and/or deviations. This table is based on the ADDV dataset submitted with the 90 day safety update.

¹ Includes 5 patients with missing or ineligible screening lab values, five patients with no measurable disease by BICR at baseline, one patient with enrollment before confirmed measurable disease by BICR, one patient with a biopsy outside of the window, and one patient with three prior lines of systemic therapy documented as having received only two.

² Includes one patient (20001121221) with multiple missing assessment dates, one patient with confirmatory CT for PR assessed <4 weeks from the initial CT, and one patient in which the site of biopsy was also used as a target lesion for disease assessment.

Source: ADSL and ADDV datasets

Based on the review of the reported violation types, key protocol violations that may affect
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overall efficacy assessments were identified in ten patients. These violations include no
measureable disease at baseline by BICR, enrollment prior to BICR disease assessment, biopsy
outside of the screening window, multiple missing assessments, site of biopsy used as a target
lesion, and too short time for a confirmatory CT scan.

Table of Demographic Characteristics

Key baseline demographics and disease characteristics of the 2nd-line post-platinum cohort are
summarized in Table 8 and
Table 9. The median age of the patients was 66 years, 72% were male, 64% patients were
Caucasian. Thirty-four percent had non-bladder urothelial carcinoma and 66% of patients had
visceral metastases, including 34% with metastases to the liver, which portends a worse
prognosis. Nineteen percent of patients had disease progression following prior platinum-
containing neoadjuvant or adjuvant chemotherapy. Thirty-five percent of patients had received
≥ 2 prior systemic regimens in the metastatic setting. Seventy percent of patients received
prior cisplatin and 30% had prior carboplatin. One patient was previously treated with
oxaliplatin.

Demographics are also provided for the Bellmunt and MSKCC risk group scores based on BICR
evaluation, which were validated in the era of cytotoxic chemotherapy. The Bellmunt risk score
allocates one point each for hemoglobin at study entry of ≤10 g/dL, ECOG performance status
>0, and the presence of liver metastases. The MSKCC risk score allocates one point each for the
presence of visceral metastases and ECOG performance status >1. As no patients with ECOG
performance status of >1 were enrolled on Study 1108, the majority of patients had MSKCC risk
score of 1.

Table 8: Baseline Demographics of 2nd-line Post-platinum cohort of Study 1108

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patient Subgroups by PD-L1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(all PD-L1 scores)</td>
<td>High</td>
</tr>
<tr>
<td>N</td>
<td>182</td>
<td>95</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mos)</td>
<td>66 (34, 88)</td>
<td>66 (34, 88)</td>
</tr>
<tr>
<td>(Range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male n (%)</td>
<td>131 (72)</td>
<td>26 (27)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>51 (28)</td>
<td>69 (73)</td>
</tr>
<tr>
<td>Race</td>
<td>Overall (n=182)</td>
<td>Patient Subgroups by PD-L1 Score</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>High (N = 95)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>117 (64)</td>
<td>63 (66)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (3)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Asian</td>
<td>36 (20)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (3)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Missing</td>
<td>17 (9)</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG Score</th>
<th>Overall (n=180)</th>
<th>Patient Subgroups by PD-L1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>High (N = 95)</td>
</tr>
<tr>
<td>0</td>
<td>61 (34)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>1</td>
<td>121 (66)</td>
<td>54 (74)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bellmunt Risk Score (n=180)</th>
<th>Overall (n=182)</th>
<th>Patient Subgroups by PD-L1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>High (N = 95)</td>
</tr>
<tr>
<td>0</td>
<td>42 (23)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>1</td>
<td>69 (38)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>2</td>
<td>52 (29)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>3</td>
<td>17 (9)</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MSKCC Risk Score (n=182)</th>
<th>Overall (n=182)</th>
<th>Patient Subgroups by PD-L1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>High (N = 95)</td>
</tr>
<tr>
<td>0</td>
<td>62 (34)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>1</td>
<td>120 (66)</td>
<td>54 (74)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Size at Baseline per BICR (mm)</th>
<th>Overall (n=182)</th>
<th>Patient Subgroups by PD-L1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>High (N = 95)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>72.4 (49.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL, TU datasets;

1 Hemoglobin was not available at study entry in two patients
2 PD-L1 could not be assayed in 13 patients and was not yet available at the time of DCO in one patient

Table 9: Disease Characteristics of 2nd-line Post-platinum Cohort of Study 1108
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<table>
<thead>
<tr>
<th>Missing</th>
<th>Ureteric Orifice</th>
<th>Bladder Neck</th>
<th>TCC with Squamous Differentiation</th>
<th>TCC with Variant Histology</th>
<th>TCC with Glandular Differentiation</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (3)</td>
<td>3 (2)</td>
<td>1 (0.5)</td>
<td>15 (8)</td>
<td>4 (2)</td>
<td>1 (0.5)</td>
<td>4 (2)</td>
</tr>
<tr>
<td></td>
<td>3 (3)</td>
<td>0</td>
<td>6 (6)</td>
<td>3 (3%)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (1)</td>
<td>8 (11)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell Type n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional Cell Carcinoma (TCC) Only</td>
</tr>
<tr>
<td>TCC with Squamous Differentiation</td>
</tr>
<tr>
<td>TCC with Variant Histology</td>
</tr>
<tr>
<td>TCC with Glandular Differentiation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage at Study Entry per Investigator, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Disease</td>
</tr>
<tr>
<td>173 (95)</td>
</tr>
<tr>
<td>89 (94)</td>
</tr>
<tr>
<td>72 (99)</td>
</tr>
<tr>
<td>12 (86)</td>
</tr>
<tr>
<td>Locally Advanced</td>
</tr>
<tr>
<td>9 (5%)</td>
</tr>
<tr>
<td>6 (6)</td>
</tr>
<tr>
<td>1 (1)</td>
</tr>
<tr>
<td>2 (14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis Site n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph Node only</td>
</tr>
<tr>
<td>23 (13)</td>
</tr>
<tr>
<td>12 (13)</td>
</tr>
<tr>
<td>6 (8)</td>
</tr>
<tr>
<td>5 (36)</td>
</tr>
<tr>
<td>Visceral Disease³</td>
</tr>
<tr>
<td>120 (66)</td>
</tr>
<tr>
<td>59 (62)</td>
</tr>
<tr>
<td>54 (74)</td>
</tr>
<tr>
<td>7 (50)</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>79 (43)</td>
</tr>
<tr>
<td>35 (37)</td>
</tr>
<tr>
<td>39 (53)</td>
</tr>
<tr>
<td>5 (36)</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>62 (34)</td>
</tr>
<tr>
<td>37 (39)</td>
</tr>
<tr>
<td>24 (33)</td>
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<tr>
<td>1 (7)</td>
</tr>
<tr>
<td>Bone</td>
</tr>
<tr>
<td>35 (19)</td>
</tr>
<tr>
<td>17 (18)</td>
</tr>
<tr>
<td>15 (21)</td>
</tr>
<tr>
<td>2 (14)</td>
</tr>
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<table>
<thead>
<tr>
<th>Line of Therapy n (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>118 (65)</td>
</tr>
<tr>
<td>61 (64)</td>
</tr>
<tr>
<td>46 (63)</td>
</tr>
<tr>
<td>11 (79)</td>
</tr>
<tr>
<td>2+</td>
</tr>
<tr>
<td>64 (35)</td>
</tr>
<tr>
<td>34 (36)</td>
</tr>
<tr>
<td>27 (37)</td>
</tr>
<tr>
<td>3 (21)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Prior Platinum n (%)⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>139 (76)</td>
</tr>
<tr>
<td>76 (80)</td>
</tr>
<tr>
<td>54 (74)</td>
</tr>
<tr>
<td>9 (64)</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
<tr>
<td>71 (39)</td>
</tr>
<tr>
<td>36 (38)</td>
</tr>
<tr>
<td>31 (42)</td>
</tr>
<tr>
<td>4 (29)</td>
</tr>
<tr>
<td>Other/Unspecified</td>
</tr>
<tr>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>1 (1)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Adjuvant or Neoadjuvant Therapy as Only Prior Treatment (i.e. Prior Line of therapy = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
<tr>
<td>37 (20)</td>
</tr>
<tr>
<td>16 (17)</td>
</tr>
<tr>
<td>16 (22)</td>
</tr>
<tr>
<td>5 (36)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>145 (80)</td>
</tr>
<tr>
<td>79 (83)</td>
</tr>
<tr>
<td>57 (78)</td>
</tr>
<tr>
<td>9 (64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior cysctectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
<tr>
<td>143 (78)</td>
</tr>
<tr>
<td>76 (80)</td>
</tr>
<tr>
<td>57 (78)</td>
</tr>
<tr>
<td>10 (71)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>39 (22)</td>
</tr>
<tr>
<td>19 (20)</td>
</tr>
<tr>
<td>16 (22)</td>
</tr>
<tr>
<td>4 (29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
<tr>
<td>38 (21)</td>
</tr>
<tr>
<td>17 (18)</td>
</tr>
<tr>
<td>18 (25)</td>
</tr>
<tr>
<td>3 (21)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>144 (79)</td>
</tr>
<tr>
<td>78 (82)</td>
</tr>
<tr>
<td>55 (75)</td>
</tr>
<tr>
<td>11 (79)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior intravesical BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
<tr>
<td>29 (16)</td>
</tr>
<tr>
<td>14 (15)</td>
</tr>
<tr>
<td>12 (16)</td>
</tr>
<tr>
<td>3 (21)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>153 (84)</td>
</tr>
<tr>
<td>81 (85)</td>
</tr>
<tr>
<td>61 (84)</td>
</tr>
<tr>
<td>11 (79)</td>
</tr>
</tbody>
</table>
Clinical and Statistical Reviews
Drs. Suzman and Fernandes
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma
Source: ADRS, ADSL, CM, TU, ADAE datasets
1FA.xpt dataset Data Cutoff 10-24-2016
2Patients with metastatic disease may also have locally advanced disease.
3Defined as lung, liver, or bone disease
4Sums to >100% due to some patients receiving multiple types of platinum-based therapies

Reviewer Comment: The Bellmunt and MSKCC risk group scores are based on BICR evaluation and differ from those presented by the Applicant which are based on both the BICR and the investigator assessments.

Figure 2: Distribution of Mean Tumor Burden at Baseline as per BICR by the Responder Status

Plot of BICR Sum of Diameters by IRR Responses

Source: ADRS, ADSL datasets;

Reviewer Comment: Smaller tumor burden at baseline was associated with increased likelihood of a complete response, without accounting other confounding factors.
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Figure 3: Patient Enrollment by Country

Source: ADSL datasets;

Reviewer Comment: Majority of the patients were recruited in the US (49%) with the remainder from centers in Europe, Canada and Korea.

Efficacy Results – Primary Endpoint

The key primary endpoint was confirmed, BICR-assessed ORR per RECIST v1.1 in all patients. The ORR was based on the submitted dataset with the cutoff date of October 24, 2016 is shown in Table 10 for all the patients and by the PDL1 expression subgroup. The confirmed ORR was 17.0% (95% CI: 11.9%, 23.3%) in all treated patients. Both CRs and PRs were observed. Note that this, which was associated with a median follow-up time of 5.6 months.

As shown in Table 10, the confirmed ORR was 26.3% (95% CI: 17.8%, 36.4%) in 95 patients with high PD-L1 expression and 4.1% (95% CI: 0.9%, 11.5%) in 73 patients with low or negative PD-L1 expression. There were 14 patients who were not evaluable for PD-L1 status (in 13 cases, due to insufficient tumor biopsy samples and in one case due to a sample that had not been tested as of the DCO); response rate in these patients was 21.4% (95% CI: 4.7%, 50.8%).
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Table 10: Confirmed ORR as Assessed by BICR by PD-L1 Expression Status.

<table>
<thead>
<tr>
<th>PD-L1 Expression Subgroups</th>
<th>Overall N = 182</th>
<th>PD-L1 High N=95</th>
<th>PD-L1 Low/negative N=73</th>
<th>Not evaluable N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of BICR-assessed Confirmed Responders</td>
<td>31</td>
<td>25</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ORR % (95% CI)</td>
<td>17.0 (11.9, 23.3)</td>
<td>26.3 (17.8, 36.4)</td>
<td>4.1 (0.9, 11.5)</td>
<td>21.4 (4.7, 50.8)</td>
</tr>
<tr>
<td>Complete Response (CR) n (%)</td>
<td>5 (2.7)</td>
<td>3 (3.2)</td>
<td>1 (1.4)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Partial Response (PR) n (%)</td>
<td>26 (14.3)</td>
<td>22 (23.2)</td>
<td>2 (2.7)</td>
<td>2 (14.3)</td>
</tr>
</tbody>
</table>

Source: ADRS, ADS datasets;

The best objective response in the PD-L1 unselected cohort of patients (N=128) who were enrolled post amendment eight of the protocol is presented in Table 11 by the PD-L1 expression status. The ORR in this cohort of patients is 12.5% (95% CI: 7.3%,19.5%). The confirmed ORR was 19.0% (95% CI: 9.9%,31.4%) in 58 patients with high PD-L1 expression, 3.6% (95% CI: 0.4-12.3%) in 56 patients with low or negative PD-L1 expression and 21.4% (95% CI: 4.7%-50.8%) in 14 patients with non-evaluable PD-L1 expression.

The IRC charter allowed changes in response status. Among the 152 patients available for review as of the October 24 2016 DCO, 13 (9%) patients had a change in their response status. In no patients did this change result in an additional patient assessed as having a complete or partial response.

Reviewer Comments: The ORR as reported by the applicant was 17.5% (n=32, respondents). During the review it was determined that one patient who was considered a CR did not have measurable disease at baseline and hence was considered as NE. The final ORR was thus considered to be 17.0%, which is consistent with the response rates seen with other PD-L1/PD-1 inhibitors in this setting.

Table 11: Best Objective Response as Assessed by BICR in the PD-L1 Unselected Expansion Cohort of N=128 Patients.

<table>
<thead>
<tr>
<th>PD-L1 Expression Subgroups</th>
<th>Overall (N=128)</th>
<th>PD-L1 High (N=58)</th>
<th>PD-L1 Low/negative (N=56)</th>
<th>Not evaluable (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR) [95% CI]</td>
<td>12.5 (7.3, 19.5)</td>
<td>19.0 (9.9, 31.4)</td>
<td>3.6 (0.4, 12.3)</td>
<td>21.4 (4.7, 50.8)</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>25</td>
<td>68</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL datasets;

The impact of major protocol violations on ORR was assessed in all enrolled patients. Exclusion of the 10 patients from the analyses resulted with 29 responses in 172 patients providing an ORR of 16.9% (95% CI: 11.6%, 23.3%) in the overall study population. This ORR is similar to that reported in the overall population of Study 1108 in Table 10, suggesting that the detected ORR in all patients is sustainable.

The distribution of the best overall response (BOR) by investigator and IRR is presented in Table 12. There were 35 responders as per the investigator assessment and the ORR is 19.2% (95% CI: 13.8%, 25.7%).

Table 12: Distribution of the BOR as per Investigator and BICR in the Efficacy Population (N=182).

<table>
<thead>
<tr>
<th>BOR as per Investigator</th>
<th>BOR as per BICR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL datasets; NE: non-evaluable as reported.

Reviewer Comments: There were some minor differences between the investigator and BICR assessments of BOR but the ORR as determined by the BICR is used as the primary endpoint, since it provides a robust and unbiased assessment of efficacy in a single arm study.

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.
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Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was DOR. With the data used for the ORR analysis shown in Table 10, median DOR in responders was not reached and the observed response durations ranged from 0.92+ to 19.9+ months as presented in Table 12 and Figure 4. Of the 31 responders, 14 had ongoing responses of ≥6 months and 5 had ongoing responses of ≥12 months. Response durations tabulated by the PD-L1 subgroups are also present in Table 13 and Figure 4.

Table 13: Response Duration in Responders as per BICR in the Overall Efficacy Population.

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=182)</th>
<th>PD-L1 Expression Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PD-L1 High (N=95)</td>
</tr>
<tr>
<td>Number of Responders</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Duration of Response Median (mos) (Range)</td>
<td>NR (0.9+,19.9+)</td>
<td>NR (0.9+,19.9+)</td>
</tr>
<tr>
<td>Number of Patients Responding for ≥6 months n (%)</td>
<td>14/31 (35)</td>
<td>13/25 (52)</td>
</tr>
<tr>
<td>Number of Patients Responding for ≥12 months n (%)</td>
<td>5/31 (16)</td>
<td>4/25 (16)</td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL, ADTTE datasets; +: denotes a censored value; NR= Not reached, NE=Not Evaluable
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Figure 4: Duration of Response by the PD-L1 Status for Responders in the Overall Efficacy Population.

Source: ADRS, ADSL, ADTTE datasets;

The DOR in the PD-L1 unselected cohort of patients (N=128) who were enrolled post amendment eight of the protocol is presented in Table 14 and

Figure 5 by the PD-L1 expression status. The median DOR is 4.2 months in this cohort of patients ranging from 0.9+ to 4.2 months.

Table 14: Response Duration in Responders as per BICR in the PD-L1 Unselected Expansion Cohort of N=128 Patients.

<table>
<thead>
<tr>
<th></th>
<th>Overall  (N=128)</th>
<th>PD-L1 Expression Subgroups</th>
</tr>
</thead>
</table>

CDER Clinical Review Template 2015 for New NDA or BLA

Reference ID: 4068251
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<table>
<thead>
<tr>
<th></th>
<th>PD-L1 High (N=95)</th>
<th>PD-L1 Low/negative (N=73)</th>
<th>PD-L1 NE (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Responders</td>
<td>16</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Duration of Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mos)</td>
<td>4.2 (0.9+, 4.2)</td>
<td>4.2 (0.9+, 4.2)</td>
<td>NR (1.9+, 4.2+)</td>
</tr>
<tr>
<td>(Range)</td>
<td></td>
<td></td>
<td>(2.3+, 2.6+)</td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL, ADTTE datasets; +: denotes a censored value; Ne= Not reached, NE=Not Evaluable

Reviewer Comments: There were only 16 patients with a response in this cohort of 128 patients. Only two patients of the 11 responders in the PD-L1 high group had an event (disease progression) which limits the interpretability of the duration of response results in this subgroup and is reported as not evaluable in the label.

Figure 5: Duration of response by the PD-L1 status for responders in the PD-L1 Unselected Expansion Cohort of N=128 Patients.

KM Plot of Duration of Response by PDL1 status for PD-L1 Unselected Expansion cohort

![KM Plot of Duration of Response by PDL1 status for PD-L1 Unselected Expansion cohort](image-url)
Table 15 summarizes the ORR as assessed by BICR in overall efficacy population by various subgroups of interest.

### Table 15: ORR by PD-L1 status in the Overall Efficacy Population (N=182) for Various Subgroups of Interest

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall (N=182) n/N % (95% CI)</th>
<th>PD-L1 Expression Subgroups</th>
<th>PD-L1 High (N=95) n/N % (95% CI)</th>
<th>PD-L1 Low/negative (N=73) n/N % (95% CI)</th>
<th>PD-L1 NE (N=14) n/N % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (n=70)</td>
<td>14/70 20% (11.4, 31.3)</td>
<td>12/35 34.3% (19.1, 52.2)</td>
<td>1/30 3.3% (0.1, 17.2)</td>
<td>1/5 20% (0.5, 71.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;=65 (n=112)</td>
<td>17/112 15.2% (9.1, 23.2)</td>
<td>13/60 21.7% (12.1, 34.2)</td>
<td>2/43 4.7% (0.6, 15.8)</td>
<td>2/9 22.2% (2.8, 60)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=51)</td>
<td>5/51 9.8% (3.3, 21.4)</td>
<td>5/26 19.2% (6.6, 39.4)</td>
<td>0/22 0% (0, 15.4)</td>
<td>0/3 0% (0, 70.8)</td>
<td></td>
</tr>
<tr>
<td>Male (n=131)</td>
<td>26/131 19.8% (13.4, 27.7)</td>
<td>20/69 29% (18.7, 41.2)</td>
<td>3/51 5.9% (1.2, 16.2)</td>
<td>3/11 27.3% (6, 61)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (n=36)</td>
<td>6/36 16.7% (6.4, 32.8)</td>
<td>5/15 33.3% (11.8, 61.6)</td>
<td>0/18 0% (0, 18.5)</td>
<td>1/3 33.3% (0.8, 90.6)</td>
<td></td>
</tr>
<tr>
<td>Other (n=29)</td>
<td>8/29 27.6% (12.7, 47.2)</td>
<td>4/15 26.7% (7.8, 55.1)</td>
<td>2/11 18.2% (2.3, 51.8)</td>
<td>2/3 66.7% (9.4, 99.2)</td>
<td></td>
</tr>
<tr>
<td>White (n=117)</td>
<td>17/117 14.5% (8.7, 22.2)</td>
<td>16/65 24.6% (14.8, 36.9)</td>
<td>1/44 2.3% (0.1, 12)</td>
<td>0/8 0% (0, 36.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Geographical Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (n=90)</td>
<td>15/90 16.7% (9.6, 26)</td>
<td>3/47 27.7% (15.6, 42.6)</td>
<td>2/34 5.9% (0.7, 19.7)</td>
<td>0/9 0% (0, 33.6)</td>
<td></td>
</tr>
</tbody>
</table>
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### Subgroup
<table>
<thead>
<tr>
<th></th>
<th>Overall (N=182)</th>
<th>PD-L1 Expression Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N % (95% CI)</td>
<td>PD-L1 High (N=95) n/N % (95% CI)</td>
</tr>
<tr>
<td>Non-US (n=92)</td>
<td>16/92 (10.3, 26.7)</td>
<td>12/48 (13.6, 39.6) 1/39 (0.1, 13.5)</td>
</tr>
<tr>
<td></td>
<td>17.4%</td>
<td>25%</td>
</tr>
</tbody>
</table>

### ECOG Performance Status

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PD-L1 High</th>
<th>PD-L1 Low/negative</th>
<th>PD-L1 NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14/61 (13.2, 35.5)</td>
<td>12/34 (19.7, 53.5)</td>
<td>0/19 (0, 17.6)</td>
<td>2/8 (3.2, 65.1)</td>
</tr>
<tr>
<td>1</td>
<td>17/121 (8.4, 21.5)</td>
<td>13/61 (11.9, 33.7)</td>
<td>3/54 (1.2, 15.4)</td>
<td>1/6 (0.4, 64.1)</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>35.3%</td>
<td>0%</td>
<td>25%</td>
</tr>
</tbody>
</table>

### Number of Prior Chemotherapy Regimens

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PD-L1 High</th>
<th>PD-L1 Low/negative</th>
<th>PD-L1 NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/118 (12.8, 27.8)</td>
<td>18/61 (18.5, 42.6)</td>
<td>3/46 (1.4, 17.9)</td>
<td>2/11 (2.3, 51.8)</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>8/64 (5.6, 23.2)</td>
<td>7/34 (8.7, 37.9)</td>
<td>0/27 (0, 12.8)</td>
<td>1/3 (0.8, 90.6)</td>
</tr>
<tr>
<td></td>
<td>19.5%</td>
<td>29.5%</td>
<td>6.5%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

### Bellmunt (as per BICR)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PD-L1 High</th>
<th>PD-L1 Low/negative</th>
<th>PD-L1 NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n=42)</td>
<td>11/42 (13.9, 42)</td>
<td>9/20 (23.1, 68.5)</td>
<td>0/15 (0, 21.8)</td>
<td>2/7 (3.7, 71)</td>
</tr>
<tr>
<td></td>
<td>26.2%</td>
<td>45%</td>
<td>0%</td>
<td>28.6%</td>
</tr>
<tr>
<td>1 (n=69)</td>
<td>11/69 (8.2, 26.7)</td>
<td>8/39 (9.3, 36.5)</td>
<td>2/25 (1, 26)</td>
<td>1/5 (0.5, 71.6)</td>
</tr>
<tr>
<td></td>
<td>15.9%</td>
<td>20.5%</td>
<td>8%</td>
<td>20%</td>
</tr>
<tr>
<td>2 (n=52)</td>
<td>9/52 (8.2, 30.3)</td>
<td>8/22 (36.4, 17.2, 59.3)</td>
<td>1/28 (0.1, 18.3)</td>
<td>0/2 (0, 84.2)</td>
</tr>
<tr>
<td></td>
<td>17.3%</td>
<td>36.4%</td>
<td>3.6%</td>
<td>0%</td>
</tr>
<tr>
<td>3 (n=17)</td>
<td>0/17 (0, 19.5)</td>
<td>0/12 (0, 26.5)</td>
<td>0/5 (0, 52.2)</td>
<td>0/0 (0, 100)</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### MSKCC (as per BICR)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PD-L1 High</th>
<th>PD-L1 Low/negative</th>
<th>PD-L1 NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n=62)</td>
<td>24/62 (38.7%, 26.6%, 51.9)</td>
<td>18/36 (32.9%, 67.1)</td>
<td>3/19 (3.4, 39.6)</td>
<td>3/7 (9.9, 81.6)</td>
</tr>
<tr>
<td></td>
<td>38.7%</td>
<td>50%</td>
<td>15.8%</td>
<td>42.9%</td>
</tr>
<tr>
<td>1 (n=120)</td>
<td>7/120 (5.8%)</td>
<td>7/59 (11.9%)</td>
<td>0/54 (0)</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td></td>
<td>5.8%</td>
<td>11.9%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall (N=182)</th>
<th>PD-L1 Expression Subgroups</th>
<th>Liver Baseline (as per BICR)</th>
<th>Lung Baseline (as per BICR)</th>
<th>Bone Baseline (as per BICR)</th>
<th>Immune Mediated AE</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>PD-L1 High (N=95)</td>
<td>PD-L1 Low/negative (N=73)</td>
<td>PD-L1 NE (N=14)</td>
<td>No (n=120)</td>
<td>Yes (n=62)</td>
<td>No (n=103)</td>
</tr>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>n/N % (95% CI)</td>
<td>n/N % (95% CI)</td>
<td>n/N % (95% CI)</td>
<td>26/120 (21.7%) (14.7, 30.1)</td>
<td>5/62 (8.1%) (2.7, 17.8)</td>
<td>27/103 (26.2%) (18, 35.8)</td>
</tr>
<tr>
<td>PD-L1 High (N=95)</td>
<td>20/58 (34.5%) (22.5, 48.1)</td>
<td>3/49 (6.1%) (1.3, 16.9)</td>
<td>5/37 (13.5%) (4.5, 28.8)</td>
<td>21/60 (35%) (23.1, 48.4)</td>
<td>4/35 (11.4%) (3.2, 26.7)</td>
<td>24/78 (30.8%) (20.8, 42.2)</td>
<td>4/17 (5.9%) (0.1, 28.7)</td>
</tr>
<tr>
<td>PD-L1 Low/negative (N=73)</td>
<td>(0, 6.6) (0, 41)</td>
<td>(0, 14.2) (0, 97.5)</td>
<td>(6.6, 29.1) (10.2, 51.8)</td>
<td>(1.9, 23.7) (7.5, 70.1)</td>
<td>(0, 9) (0, 52.2)</td>
<td>(1.1, 14.4) (5.5, 57.2)</td>
<td>(1, 13.1) (0, 25.1)</td>
</tr>
<tr>
<td>PD-L1 NE (N=14)</td>
<td>(0, 21.8) (0, 84.2)</td>
<td>(0.975) (0, 97.5)</td>
<td>(0.975) (0, 97.5)</td>
<td>(0.975) (0, 97.5)</td>
<td>(0, 97.5) (0, 97.5)</td>
<td>(0.975) (0, 97.5)</td>
<td>(0.975) (0, 97.5)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall (N=182)</th>
<th>PD-L1 High (N=95)</th>
<th>PD-L1 Low/negative (N=73)</th>
<th>PD-L1 NE (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (% 95% CI)</td>
<td>n/N (% 95% CI)</td>
<td>n/N (% 95% CI)</td>
<td>n/N (% 95% CI)</td>
</tr>
<tr>
<td>PD-L1 Unselected</td>
<td>16/128 (12.5%)</td>
<td>11/58 (19%)</td>
<td>2/56 (3.6%)</td>
<td>3/14 (21.4%)</td>
</tr>
<tr>
<td>Expansion</td>
<td>(7.3, 19.5)</td>
<td>(9.9, 31.4)</td>
<td>(0.4, 12.3)</td>
<td>(4.7, 50.8)</td>
</tr>
</tbody>
</table>

Source: ADRS, ADSL, ADAE datasets; NE-not evaluable; NR-not reached

Reviewer Comments:
Some of these exploratory subgroup analyses, such as bone lesions, had a limited number of patients in the PD-L1 low/negative and NE expression groups. In addition, these analyses are exploratory with no multiplicity adjustment and no pre-specified hypotheses. In the few patients that had a Bellmunt score of three, there were no observed responses. The ORR appeared to be low for patients with a MSKCC score of one. Patients who experienced an immune-mediated AE had a numerically higher ORR than those who did not, as did patients with transitional cell carcinoma vs those with variant histology. Additionally, there did not appear to be differences in ORR by receipt of prior BCG therapy or site of disease (bladder vs upper tract).

One consideration was whether patients with a long duration between receipt of their prior line of chemotherapy and enrollment on Study 1108 may have either had a lower burden of disease or had biologically different and more indolent disease than those with a shorter duration between therapies. We evaluated ORR in the subset of 45 patients with more than 90 days between progression on prior systemic therapy and enrollment on Study 1108. Eight of these patients were responders (8.45; 17.8%), a similar proportion to the ORR for the entire cohort.

Table 167 shows the results of PFS and OS in the overall efficacy population. The median PFS in all patients was 1.4 months (95% CI: 1.4, 2.1). The median OS was 18.2 months (95% CI: 8.1, NR) in all patients.

Twenty-one (12%) patients received at least one subsequent therapy following durvalumab as summarized in Table 16: Subsequent Therapies post-PD.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Durvalumab (N = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>
Clinical and Statistical Reviews
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<table>
<thead>
<tr>
<th>Experimental Therapy</th>
<th>5 (3)</th>
<th>3 (2)</th>
<th>3 (2)</th>
<th>9 (5)</th>
</tr>
</thead>
</table>

*Source: ADCM dataset.*

Table 167: PFS and OS in the Efficacy Population by PD-L1 expression status.

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=182)</th>
<th>PD-L1 Expression Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PD-L1 High (N=95)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of events (%)</td>
<td>142 (78)</td>
<td>68 (72)</td>
</tr>
<tr>
<td>Median (mos)</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(1.4, 2.1)</td>
<td>(1.4, 3.5)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of events (%)</td>
<td>64 (35)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Median (mos)</td>
<td>18.2</td>
<td>18.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8.1, NR)</td>
<td>(11.6, NA)</td>
</tr>
</tbody>
</table>

*Source: ADRS, ADSL, ADTTE datasets; NE-not evaluable; NR-not reached*

Reviewer Comments:
The median OS in the PD-L1 high group appears to be longer than that observed in the PD-L1 low/negative group. The reason for this observed difference may be related to the baseline disease characteristics and/or better responses in the PD-L1 high subgroup. Nevertheless, in single arm trials time-to-event endpoints are difficult to interpret and implications of the observed OS and PFS in this study are not clear, thus no conclusions can be reliably made based on the results shown Table 16.

Dose/Dose Response

All patients with UC enrolled on Study 1108 received durvalumab 10 mg/kg Q2W, thus no conclusions regarding a dose-response association can be made.

Durability of Response

The response durability results are presented in Table 13 and Table 14 for the overall efficacy population and the PD-L1 Unselected Expansion Cohort. The median of DOR was not reached at the time of data cutoff time for the overall patient population and was not interpretable due
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to few events and low numbers in the PD-L1 Unselected Expansion Cohort.

Persistence of Effect
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The current estimates 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).

7 Integrated Review of Effectiveness

APPEARS THIS WAY ON ORIGINAL
7.1. Assessment of Efficacy Across Trials

Demonstration of the effectiveness of durvalumab for the proposed indication is based on the results of the 2nd-line post-platinum UC cohort of Study 1108. The key efficacy measures were ORR and DOR as assessed by BICR per RECIST v1.1. These measures serve as surrogates of effectiveness.

No additional studies were conducted in urothelial cancer. Thus, refer to Section 6.1.2 for further discussion of efficacy in Study 1108.

7.1.1. Dose and Dose-Response

All patients in the UC cohort received a dose of 10 mg/kg durvalumab. Therefore, no dose-response relationship can be explored.

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 182 patients with locally advanced or metastatic urothelial carcinoma who had prior platinum-containing chemotherapy, treatment with durvalumab elicited a confirmed ORR of 17.0% (95% CI: 11.9-23.3%), as assessed by BICR per RECIST v1.1. The responses appear durable. At the time of the ORR analysis, median DOR in responders was not reached (range: 0.9-19.9 months). Of the 31 responders, 14 (35%) patients had ongoing responses of ≥6 months and 5 (16%) had ongoing responses of ≥12 months.

The confirmed ORR was 26.3% (95% CI: 17.8-36.4%) in 95 patients with high PD-L1 expression as evaluated by the SP263 assay, and 4.1% (95% CI: 0.9-11.5%) in 73 patients with low or negative PD-L1 expression. Response durations in the PD-L1 subgroups were similar to those in the 182 patients, although there were only three responders available for evaluation in the PD-L1 low group.

Increasing Bellmunt risk score, indicating worse performance status, anemia, and the presence
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of liver metastases, appeared to correlate with poor outcome, including lower ORR. None of
the 22 patients with Bellmunt risk score of 3 had a response, while only 1/26 (3.8%) patients
with Bellmunt scores of 2 and low/negative PD-L1 had a response. These patients additionally
had a high risk of early progression or death. Consideration of alternative therapies, such as
chemotherapy or supportive care, may be appropriate in patients with a Bellmunt risk score of
3 or both Bellmunt score of 2 and low/negative PD-L1.

Overall, the durvalumab-induced ORR and DOR represent a clinically meaningful improvement
over existing chemotherapeutics used off-label in this disease setting and are similar to those
seen with atezolizumab (Table 2). To the review team, these improvements, along with the
safety profile (Section 8), provide substantial evidence to support accelerated approval of
durvalumab 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 durvalumab versus
durvalumab in combination with the CTLA-4 antagonist tremelimumab versus the Investigator’s
choice of chemotherapeutic may provide confirmatory evidence (NCT02516241).

8 Review of Safety

8.1 Safety Review Approach

The safety of durvalumab was primarily evaluated in the 2nd-line post-platinum UC cohort of
Study 1108. This review focused on these 182 patients with a data cut-off for the safety
population of July 24, 2016.

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

1. Study 1108 (all patients; n=1018); DCO of April 29, 2016 for non-UC patients, July 24,
   2016 for UC patients
2. ATLANTIC (n=444); a Phase 2, open-label trial of durvalumab in patients with PD-L1-high
   locally advanced or metastatic NSCLC with at least two prior systemic treatment
   regimens. DCO of June 3, 2016

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

The safety database included 182 patients with 2nd-line post-platinum UC who received at least one infusion of durvalumab at least 30 days prior to the BLA DCO of 7-24-2016. Additional analysis of AESIs was performed using the 90-day safety update with DCO of 10-24-2016.

The Applicant mapped and coded verbatim adverse events (AE) terms for Study 1108 using MedDRA version 19.0.

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 durvalumab 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 2nd-line post-platinum UC cohort of Study 1108 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. However, an OSI investigation of the top-enrolling site in the US demonstrated an approximately 50% rate of AEs that had not been entered on CRFs by the investigator. Review of two other US sites did not demonstrate evidence of a systemic discrepancy in AE reporting.

6. To review the AE datasets, the following terms were pooled:

Table 17: Pooled Terms

<table>
<thead>
<tr>
<th>Pooled term</th>
<th>Preferred Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Colitis</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>General physical health deterioration</td>
</tr>
<tr>
<td></td>
<td>Failure to thrive</td>
</tr>
<tr>
<td></td>
<td>Performance status decreased</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Dyspnea exertional</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain upper</td>
<td></td>
</tr>
<tr>
<td>Flank pain</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Oedema</td>
</tr>
<tr>
<td></td>
<td>Oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Localised oedema</td>
</tr>
<tr>
<td></td>
<td>Lymphoedema</td>
</tr>
<tr>
<td></td>
<td>Peripheral swelling</td>
</tr>
<tr>
<td></td>
<td>Scrotal oedema</td>
</tr>
<tr>
<td></td>
<td>Scrotal swelling</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Cystitis</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Candiduria</td>
</tr>
<tr>
<td></td>
<td>Urosepsis</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td>Tumor-associated fever</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Glomerular filtration rate decreased</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Hypophagia</td>
</tr>
<tr>
<td>Constipation</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Faecalaloma</td>
</tr>
<tr>
<td>Anemia</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin decreased</td>
</tr>
<tr>
<td></td>
<td>Anaemia of chronic disease</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Neck pain</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal discomfort</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal chest pain</td>
</tr>
<tr>
<td>Confusional state</td>
<td>Confusional state</td>
</tr>
<tr>
<td></td>
<td>Metabolic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Mental status changes</td>
</tr>
<tr>
<td></td>
<td>Delirium</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Thyroxine decreased</td>
</tr>
<tr>
<td></td>
<td>Thyroiditis subacute</td>
</tr>
</tbody>
</table>

CDER Clinical Review Template 2015 for New NDA or BLA

Reference ID: 4068251
<table>
<thead>
<tr>
<th>Thyroiditis chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Dermatitis</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
</tr>
<tr>
<td>Dermatitis psoriasiform</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Rash maculopapular</td>
</tr>
<tr>
<td>Rash pruritic</td>
</tr>
<tr>
<td>Rash papular</td>
</tr>
<tr>
<td>Rash pustular</td>
</tr>
<tr>
<td>Skin toxicity</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Rash erythematous</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
</tr>
<tr>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Alanine aminotransferase elevated</td>
</tr>
<tr>
<td>Aspartate aminotransferase elevated</td>
</tr>
<tr>
<td>Transaminases increased</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td>GGT increased</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Productive cough</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Lung infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intestinal obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestinal obstruction</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td>Ileus</td>
</tr>
<tr>
<td>Subileus</td>
</tr>
<tr>
<td>Large intestinal obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureteric obstruction</td>
</tr>
<tr>
<td>Hydroureter</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Bladder outlet obstruction</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
8.2.1. Overall Exposure

The median number of doses received was 4 (1 to 27) and the median duration of therapy was 10.2 weeks (0.14-52.4 weeks) as of the July 24, 2016 cutoff date (Table 18). All 182 subjects received at least one dose of durvalumab at least 30 days prior to the DCO.

Table 18: Safety Population Exposure (DCO 7-24-2016)

<table>
<thead>
<tr>
<th>Clinical Trial Groups</th>
<th>Durvalumab 2nd-line post-platinum cohort (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of doses received</td>
<td>Mean (SD) 6.1 (6.3)</td>
</tr>
<tr>
<td></td>
<td>Median (Min, Max) 4 (1, 27)</td>
</tr>
<tr>
<td>Treatment duration (weeks)</td>
<td>Mean (SD) 12.2 (12.6)</td>
</tr>
<tr>
<td></td>
<td>Median (Min, Max) 10.2 (0.14, 52.4)</td>
</tr>
<tr>
<td>Treatment duration (weeks)</td>
<td>0-8 96</td>
</tr>
<tr>
<td></td>
<td>&gt;8-16 53</td>
</tr>
<tr>
<td></td>
<td>&gt;16-24 11</td>
</tr>
<tr>
<td></td>
<td>&gt;24-52 13</td>
</tr>
<tr>
<td></td>
<td>&gt;52 9</td>
</tr>
<tr>
<td>Dose Interruptions/Delays</td>
<td>Any delay 30 (16%)</td>
</tr>
<tr>
<td></td>
<td>Delay due to AE 26 (14%)</td>
</tr>
</tbody>
</table>

Note that per ADEX.xpt dataset, 56/182 (31%) patients experienced an AE leading to dose interruption.

At the time of the database lock for safety, 24% of patients were continuing with study treatment.

**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 durvalumab in the target population. However, there were small numbers of patients with urothelial carcinoma followed for over 6 months and over 12 months. In the combined safety database,
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there were 437 patients followed for at least 6 months and 98 patients followed for at least 12
months. The duration of exposure for the safety population was less than that for the efficacy
population due to the timing of the data cut-off for response. It is expected that the incidence of
adverse events will be somewhat higher with additional follow-up of patients remaining on
therapy.

8.2.2. Relevant characteristics of the safety population:

The safety and efficacy populations were identical aside from duration of follow-up. Refer to
Section 6.1.2 for additional details regarding the efficacy population.

The trial excluded patients with a history of autoimmune disease within the past two years
prior to enrollment with the exception of autoimmune hypothyroidism (Grave’s disease or
Hashimoto’s disease), vitiligo, or psoriasis not requiring systemic treatment within the past two
years.

Reviewer Comments: 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 with a few exceptions. The trial additionally excluded those with HIV, HBV,
or HCV infection. There were relatively few patients with baseline metastases to the CNS. The
trial did not enroll large numbers of non-Caucasian patients. There were few 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 durvalumab exposure were sufficient to
characterize the safety of durvalumab 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, DANUBE. DANUBE will evaluate durvalumab, either as monotherapy or in
combination with the CTLA-4 antagonist tremelimumab, with chemotherapy in 1st-line
platinum-eligible UBC patients.

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
durvalumab 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
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On January 4, 2017, the Office of Scientific Investigations reported that the University of Chicago site, which had enrolled 10 patients, the most of any US site, had many under-reported AEs to the sponsor. These AEs were found in numerous source documents at the site, but were not properly entered into the CRFs. Additionally, several patients were documented as “withdrew consent” rather than followed per protocol. The medical monitor had not noted these issues. The approximate rate of missing AEs was 50%. Inspections of two other high-enrolling US sites, including UCSF, which had the lowest rate of AEs per patient among sites enrolling at least 5 patients, did not demonstrate significant systemic issues with regards to AE reporting.

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 19.0. 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 based on the known mechanism of action of durvalumab. These events were not pre-determined. 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 Comments: 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

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In Study 1108 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).
- Coagulation panel (results to be obtained prior to dosing on infusion days)
- Thyroid function testing including TSH and free T3 and T4 (results to be obtained prior to dosing on infusion days)
- Radiographic disease assessments after 6 weeks, then after 12 weeks, 16 weeks, then every 8 weeks
- Pregnancy screening for women of childbearing potential every cycle.

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 90 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 who discontinued durvalumab due to completion of treatment and sustained disease control or due to toxicity were followed in clinic every 30 days for 3 months. 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 Comments:
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. Patients were followed closely for AEs for 90 days, which is likely sufficient to determine late-onset immune-mediated AEs, although the median duration of follow-up for the UC patients on Study 1108 was short.

8.4. Safety Results
Clinical and Statistical Reviews  
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Table 43 presents the overview of safety in the 2nd-line post-platinum cohort as well as the pooled safety population, including all durvalumab-treated patients on Study 1108 and ATLANTIC.

Table 19: Integrated Summary of Safety

<table>
<thead>
<tr>
<th>Total number of patients with at least one:</th>
<th>2nd-line Post-platinum UC Cohort</th>
<th>All patients (N = 1414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 1108 (N = 182)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>12 (6.6%)</td>
<td>264 (19%)</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>84 (46%)</td>
<td>682 (48%)</td>
</tr>
<tr>
<td>SAE</td>
<td>84 (46%)</td>
<td>634 (45%)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>6 (3.3%)</td>
<td>102 (7.2%)</td>
</tr>
<tr>
<td>imAE</td>
<td>15 (8.2%)</td>
<td>160 (11%)</td>
</tr>
</tbody>
</table>

Source ADAE dataset; ISS ADAE dataset

8.4.1. Deaths

Table 20 summarizes total deaths in the second-line post-platinum cohort of Study 1108. Listed deaths include deaths during treatment and occurring up to 90 days of the last dose of study drug as of the database lock date (July 24, 2016). Patient narratives were reviewed for attribution of death to either disease progression or toxicity. Thus, while 12 patients were assessed by the investigator as experiencing Grade 5 adverse events, these included several patients in which the cause of death was assessed by the reviewer as due to disease progression. The reviewer considered seven patients to have experienced death that was reasonably likely to be due to study drug toxicity.

Table 20: Deaths on Study

<table>
<thead>
<tr>
<th></th>
<th>2nd-line Post-platinum cohort (N = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
</tbody>
</table>

CDER Clinical Review Template 2015 for New NDA or BLA  
Reference ID: 4068251
Clinical and Statistical Reviews
Drs. Suzman and Fernandes
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Total deaths</th>
<th>46 (25.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths within 30 days of last dose</td>
<td>23 (12.6%)</td>
</tr>
<tr>
<td>Death attributed to disease progression</td>
<td>16 (8.8%)</td>
</tr>
<tr>
<td>Death attributed to other/unknown/toxicity (including those occurring up to 90 days after last dose of study drug)</td>
<td>7 (3.8%)</td>
</tr>
</tbody>
</table>

Source: ADAE dataset

The Applicant considered two patients to have died due to durvalumab-related toxicity, one patient with autoimmune hepatitis and one patient with pneumonitis. Due to the potential for late-onset immune-related toxicity, deaths occurring up to 90 days after the last dose of durvalumab were studied.

The reviewer did not agree with the Applicant on the attribution of death in five patients. These patients, who are discussed in Table 21, were considered to have died due to durvalumab-related toxicity.

Table 21: Brief Summaries of Related Deaths

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Brief case description</th>
<th>Days from last dose to death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune Hepatitis</strong></td>
<td>A 71 year-old woman with metastatic disease to the local lymph nodes and brain developed Grade 2 elevated AST and ALP on Day 28, 14 days after the last infusion. This elevated was then considered to be Grade 3 autoimmune hepatitis on Day 42. The patient did not receive any treatment for autoimmune hepatitis and was admitted to hospice. She died on Day 65, 51 days after the last infusion.</td>
<td>51</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td>A 51 year-old man developed Grade 3 pneumonitis on Day 25,</td>
<td>29</td>
</tr>
</tbody>
</table>

Reference ID: 4068251
Reviewer note: Pneumonitis is a known toxicity from anti-PD-1 and anti-PD-L1 drugs.

<table>
<thead>
<tr>
<th>Additional Durvalumab-related toxic deaths per the Reviewer</th>
<th>Sepsis</th>
<th>Patient 2000136927</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer note: Infection, including sepsis, has been noted as a toxicity of anti-PD-1 and anti-PD-L1 drugs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 days after the last infusion. He was hospitalized and started on supplemental oxygen and antibiotics, although work-up was negative for infection. He was then treated with methylprednisolone 2 mg/kg, however his pneumonitis worsened and he died on Day 29.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Sepsis | A 68 year-old woman with metastatic disease to the adrenals, liver, lung, and lymph nodes and eight prior lines of systemic therapy developed a Grade 3 urinary tract infection 10 days after her first dose of durvalumab. She was hospitalized and treated with antibiotics, pressors, and steroids. Her infection improved and she was discharged to a nursing facility, however she was re-admitted on Day 28 with sepsis. She died on Day 30. |
| Patient 20010902512 |

| Sepsis | A 58 year-old man with metastatic disease to the liver and bone developed Grade 4 sepsis on Day 32. He was hospitalized and treated with antibiotics. He was determined to have disease progression by RECIST on Day 34. Although the sepsis was considered to be resolved on Day 50 and he was discharged from the hospital on the same day, the patient died on Day 53. Death was reported to be due to bladder cancer. |
| Patient 200223712474 |

| Sepsis | A 77 year-old man with metastatic disease to the retrocaval lymph nodes developed progression of disease including new liver metastases on |
| Patient 200223712474 | 25 |
Although this patient developed progression of disease prior to death, the time between these events was sufficiently short that death due to toxicity is more likely than death due to disease progression. Additionally, infection has been noted as a toxicity of anti-PD-1 and anti-PD-L1 drugs.

Day 39, 12 days after the last infusion. Durvalumab was discontinued. Ten days later, on Day 49, he developed Grade 4 sepsis that his critical care team felt may have been associated with an ongoing urinary tract infection. He died on Day 52.

Pneumonia
Patient 20006782366

Reviewer note: There is no evidence to support disease progression as a cause of death in this patient. Infection, including pneumonia, is a known toxicity of anti-PD-1 and anti-PD-L1 drugs and is a more likely cause of death.

A 48 year-old man with metastases to the bone developed Grade 3 pneumonia on Day 29, 15 days after the last infusion. He was hospitalized and treated with pressors, fluids, and antibiotics. Per the investigator, the family did not desire aggressive treatment and no additional imaging was performed; the investigator considered disease progression to have occurred based on clinical judgment. The patient was discharged to hospice and died on Day 34. Death was reported to be due to bladder cancer.

Pneumonia
Patient 20001672526

Reviewer note: There is no evidence to support disease progression as a cause of death in this patient. Infection, including pneumonia, is a known toxicity of anti-PD-1 and anti-PD-L1 drugs and is a more likely cause of death.

A 75 year-old man with metastatic disease to the lung, liver, peritoneum, and bone developed Grade 4 acute respiratory failure on Day 14. He was treated with BiPAP, fluids, and antibiotics for presumed hospital-acquired pneumonia. No imaging is available for the
8.4.2. Serious Adverse Events

Non-fatal serious adverse events (SAEs) occurred in 46% of patients. Refer to Table 40 for pooled terms. The most frequent serious adverse reactions (≥2% of patients) were urinary tract obstruction, musculoskeletal pain, acute kidney injury, liver injury, general physical health deterioration, sepsis, abdominal pain, pyrexia, pneumonia, and intestinal obstruction. Table 22 summarizes these common SAEs.

Table 22: Serious Adverse Events Occurring in ≥2%

<table>
<thead>
<tr>
<th>Pooled term</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>12 (6.6%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (4.9%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>8 (4.4%)</td>
</tr>
<tr>
<td>Liver injury</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>5 (2.7%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (2.7%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (2.7%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (2.7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>4 (2.2%)</td>
</tr>
</tbody>
</table>

Source: ADAE dataset; Data Cutoff: 7-24-2016
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 23 below provides information on the 6 patients who permanently discontinued durvalumab due to an adverse event. This includes four patients listed as either withdrawal of consent or discontinuation due to patient request who, on review, had actually experienced a discontinuation due to drug-related adverse event. Five additional patients in the ADAE.xpt dataset are documented as experiencing discontinuation due to an adverse event, however on review of the narratives for these patients, the event actually reflected disease progression. These included one case that was documented as autoimmune hepatitis for which the patient (12455011922) received corticosteroids, however on review there was concomitant development of extensive hepatic metastases. One of these patients was documented as discontinuing durvalumab due to sub-ileus. On review, this patient had concomitant disease progression in the peritoneum that was more likely responsible for the event.

In the 2 remaining patients, one experienced Grade 3 acute kidney injury. Renal biopsy demonstrated diffuse tubulointerstitial nephritis with prominent neutrophilic inflammation and intratubular aggregates of neutrophils. The nephritis was considered to be immune-mediated and the patient was started on high-dose corticosteroids with subsequent improvement in renal function. One patient from South Korea experienced pulmonary tuberculosis approximately one month prior to discontinuation and had Grade 3 ALT at the end of study visit. This patient had not previously received high dose corticosteroids and did not have liver metastases. The other patient experienced general physical health deterioration 21 days after the first dose of durvalumab with concomitant decreased appetite and fatigue. The patient died on Day 39 due to disease progression. Two other patients experienced drug-related elevations in transaminases and one experienced acute kidney injury.

Dose interruptions or delays occurred in 56 (31%) patients in the AE dataset (note that, in the exposure dataset, only 16% of patients are listed as having dose modifications). These interruptions are discussed further in Section 8.5.

Table 23: Adverse Events Resulting in Permanent Discontinuation

<table>
<thead>
<tr>
<th>Any Adverse Event Leading to Permanent Discontinuation</th>
<th>6 (3.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic Disorders</td>
<td></td>
</tr>
<tr>
<td>Elevated Transaminases</td>
<td>2</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Renal Disorders</td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2</td>
</tr>
</tbody>
</table>

Source ADAE dataset; Data Cutoff: 7-24-2016
8.4.4. Significant Adverse Events

Adverse events of special interest (AESIs) were defined as events of scientific and medical interest specific to the durvalumab safety profile and may be serious or non-serious. Specific MedDRA terms were not pre-specified, but were defined ad hoc during Study 1108 and included the following events:

1. Colitis
2. Pneumonitis,
3. ALT/AST increases, hepatitis, hepatotoxicity
4. Neuropathy/neuromuscular toxicity
5. Endocrinopathy
6. Dermatitis
7. Nephritis
8. Pancreatitis

Overall, 85 patients (47%) of patients in the 2nd-line post-platinum UC cohort experienced an AESI. Twenty-four of these patients (13%) experienced a Grade 3-4 AESI. The most common AESIs were diarrhea/colitis (18%) and liver enzyme elevation (13%). 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, back pain, and constipation. The most common Grade 3-4 adverse events (>2% of patients) were anemia, liver injury, fatigue, hyponatremia, acute kidney injury, back pain, urinary tract infection, abdominal pain, general physical health deterioration, dehydration, dyspnea, hyperkalemia, and hypercalcemia (Table 25). Note that adverse events based predominantly on laboratory abnormalities, specifically hepatic and renal events, are excluded from Table 25, but are presented in Table 27. Table 26 summarizes the most common adverse events in >10% of patients in the 2nd-line post-platinum cohort compared to the combined safety database (n=1414). Note that Table 26 reports adverse events in the UC population as of the 90-day safety update (DCO = 10-24-2016). The incidence of common adverse events was generally similar between the UC cohort and the combined safety database. Acute kidney injury was more common in the UC cohort while dyspnea and cough were more common in the combined safety database, likely due to a high proportion of patients with non-small cell lung cancer.
# Table 24: Grade 1-4 Adverse Reactions in ≥ 10% or Grade 3-4 Adverse Reactions in ≥ 2% of Patients with 2nd-line Post-platinum Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3 – 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Reactions</td>
<td>96</td>
<td>46</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td><strong>General Disorders and Administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

*Source: ADAE dataset*
**Table 25: Grade 1-4 Adverse events in >10% of Patients in Either Group**

<table>
<thead>
<tr>
<th>Category</th>
<th>Durvalumab (N = 182)</th>
<th>Safety Database (N = 1414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Any</td>
<td>180 (99)</td>
<td>96 (53)</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia/Hemoglobin Decreased¹</td>
<td>35 (19)</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism²</td>
<td>14 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation/Fecaloma</td>
<td>48 (26)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>39 (21)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>31 (17)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort</td>
<td>23 (13)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Vomiting/Retching</td>
<td>21 (12)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions/Lethargy</td>
<td>79 (43)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Peripheral Edema³</td>
<td>30 (16)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection⁴</td>
<td>36 (20)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Liver Injury⁵</td>
<td>30 (16)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite/Hypophagia</td>
<td>42 (23)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain⁶</td>
<td>51 (28)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (10)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Headache⁷</td>
<td>7 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Kidney Injury⁸</td>
<td>30 (16)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea/Exertional Dyspnea</td>
<td>24 (13)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Cough/Productive Cough</th>
<th>24 (12)</th>
<th>0</th>
<th>301 (21)</th>
<th>6 (0.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>29 (16)</td>
<td>1 (0.5)</td>
<td>225 (16)</td>
<td>10 (0.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (7)</td>
<td>0</td>
<td>163 (12)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Data Cutoff</td>
<td>10-24-2016</td>
<td>4-29-2016, 6-3-2016, 7-24-2016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ADAO dataset; ISS ADAO dataset

1Includes anemia of chronic disease, hemolysis, hemolytic anemia, and iron deficiency anemia
2Includes autoimmune hypothyroidism, autoimmune thyroiditis, thyroiditis, chronic and subacute thyroiditis, thyroxine and free thyroxine decreased, triiodothyronine and free triiodothyronine decreased, and TSH increased
3Includes edema, localized edema, lymphedema, scrotal edema, and scrotal swelling
4Includes cystitis, leukocyturia, pyuria, and urinary tract infection fungal
5Includes ALT/AST, bilirubin, GGT, and transaminases increased, autoimmune hepatitis, hepatic enzymes increased, hepatic failure, hepatic function abnormal, hepatocellular injury, and hyperbilirubinemia
6Includes back and neck pain, musculoskeletal chest pain, pain, and discomfort, and myalgia
7Includes migraine, sinus headache, and tension headache
8Includes anuria, autoimmune nephritis, blood creatinine increased, glomerular filtration rate decreased, glomerulonephritis, nephritis, oliguria, renal failure, and tubulointerstitial nephritis
9Includes acne, dermatitis, dermatitis acneiform, dermatitis psoriasiform, eczema, erythema, erythema multiforme, lichen planus, seborrheic dermatitis, seborrhea, and erythematous, generalized, macular, maculopapular, pruritic, papular, and pustular rash

8.4.6. Laboratory Findings

Laboratory events in the albxpt database 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 hyponatremia (12%) and lymphopenia (10%) (Table 26). 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 (4%) and increased AST (3%). There were three cases of Hy’s Law identified through laboratory screening, however these patients had alternative etiologies for their liver test abnormalities. Grade 3-4 increased creatinine occurred in 2% of patients. The most common Grade 3-4 electrolyte abnormalities were hyponatremia (12%) and hyperglycemia (4%).

Table 26: Incidence of Grade 3-4 Laboratory Abnormalities in ≥1% of Patients with 2nd-line Post-platinum Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>12</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
</tr>
</tbody>
</table>
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 durvalumab.

8.4.8. Electrocardiograms (ECGs)

Safety ECGs were collected in ATLANTIC (D4191C00003). The QT-IRT team reviewed the data with a cut-off of 9/25/2015. A total of 256 of 265 patients in the QTc substudy had baseline ECG recorded. There was no exposure-response relationship between durvalumab plasma concentrations and ΔQTcF or other ECG-related changes.

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 Study 1108. Among patients receiving durvalumab 10 mg/kg and using an early data cutoff of April 29, 2016, baseline and post-baseline anti-therapeutic antibodies (ATAs) levels were available in 1124 pts. Among the 1124 pts, 37 had ATAs. The 37 patients include 34 who developed ATA on durvalumab and 3 pts who had a positive titer at baseline and a four-fold increase in titer on durvalumab. Most titers were low. Two patients had neutralizing antibodies, one at Day 29, and one 6 months after discontinuation of durvalumab. However, the neutralizing assay is thought to be insufficiently sensitive and these results should be interpreted with caution. The one patient had an infusion reaction on the same day the titer was 1024. This patient also had a neutralizing antibody. A second patient had a positive titer at baseline and wheezing on Day 1 and fever on Day 2.

In patients with urothelial cancer who received 10 mg/kg (a subset of the 1124 pts above), 102 patients have baseline and post-baseline results and 7 had ATAs. All had negative baseline titers and developed ATA after exposure to durvalumab. One patient had a neutralizing antibody. The
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patient with wheezing and fever on Days 1 and 2 described above had an underlying urothelial
cancer. Among the seven patients with 2nd-line post-platinum UC and ATA titers, there were
no responses.

Among the 39 patients who received a dose other than 10 mg/kg durvalumab and had both
baseline and post-baseline results, four patients developed ATA on durvalumab. One had a titer
of 1:4096. Neutralizing antibodies were found in two patients. There were no AEs of concern.

Reviewer Comments: 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, pembrolizumab,
and atezolizumab are primarily immune-related and include pneumonitis, colitis, hepatitis,
hypophysitis, renal failure/nephritis, hyper/hypothyroidism. In Study 1108, 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 groupings were identified on an ad hoc basis, subsequent to the clinical study protocol
but prior to the database lock. The following AESI groups were identified:

1. Adrenal insufficiency
2. Diarrhea/colitis
3. Select hepatic events
4. Infusion-related/hypersensitivity/anaphylactic reactions
5. Pneumonitis
6. Hyperthyroidism
7. Hypophysitis
8. Hypothyroidism
9. Dermatitis
10. Rash
11. Select pancreatic events
12. Select renal events
13. Infection
14. Other rare events of potential immune-mediated nature

In the 2nd-line post-platinum cohort, the Applicant identified 85 patients (47%) who
experienced at least one AESI. The most common AESIs were diarrhea/colitis (18%) and liver
enzyme elevations (13%). The most common Grade 3-4 events were acute kidney injury (5%)
and liver enzyme elevation (5%).

In the combined safety cohort, 818 patients (56%) experienced at least one AESI and 186
patients (13%) experienced a Grade 3-4 AESI. The most common Grade 3-4 AESI was liver
enzyme elevation (8%).
Additionally, the Applicant identified immune-mediated adverse events (imAEs) as those in which an AESI (excluding infusion-related, hypersensitivity, or anaphylactic reaction) consistent with an immune-mediated mechanism of action that required treatment with systemic corticosteroids, other immunosuppressives, or endocrine therapy and had no clear alternate etiology. The incidence of these events is shown in Table 51 below. In the safety population, 5.5% of patients experienced an imAE. Across the integrated safety database, including mUC patients and patients with other malignancies treated on Study 1108 and ATLANTIC, 6.2% of patients experienced an imAE. Overall, 23% of the UC safety population and 36% of the safety database received systemic steroids, of which 11% and 16% were high-dose (at least 40 mg/day of prednisone-equivalent). The incidence of steroid use was higher (49%) in the ATLANTIC trial of NSCLC patients, potentially reflecting use for COPD, brain metastasis/edema, and dyspnea symptoms. Incidence of corticosteroid administration is discussed in more detail in section 8.5.16.

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

<table>
<thead>
<tr>
<th>ImAEs</th>
<th>2nd-line Post Platinum UC (N = 182) n (%)</th>
<th>All patients (N = 1414) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total imAEs (including endocrine events)</td>
<td>15 (8.2%)</td>
<td>160 (11%)</td>
</tr>
<tr>
<td>Total imAEs treated with steroids</td>
<td>10 (5.5%)</td>
<td>88 (6.2%)</td>
</tr>
<tr>
<td>Total Grade 3 or greater imAEs</td>
<td>5 (2.7%)</td>
<td>32 (2.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.0%)</td>
<td>19 (1.3%)</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>1 (0.5%)</td>
<td>21 (1.5%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3 (1.6%)</td>
<td>16 (1.1%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7 (3.7%)</td>
<td>87 (6.2%)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1 (0.5%)</td>
<td>18 (1.3%)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (0.5%)</td>
<td>7 (0.5%)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (0.5%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (0.5%)</td>
<td>17 (1.2%)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (0.1%)</td>
</tr>
</tbody>
</table>

*Source: ADIMAE dataset; ISS ADIMAE dataset*
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8.5.1. Pneumonitis

2nd-line Post-platinum UC Cohort

One patient (0.5%) developed pneumonitis or interstitial lung disease. This patient died due to pneumonitis. The patient did not have baseline lung disease or lung metastases, but did have a remote 60 pack-year smoking history and Grade 1 dyspnea at baseline. The event occurred on Day 26. He received treatment for the pneumonitis including antibiotics and high-dose corticosteroids (2 mg/kg methylprednisolone) on Day 29. The patient’s respiratory status improved transiently but then worsened and the patient died due to the pneumonitis on Day 30.

Dyspnea or exertional dyspnea was reported in 29 patients of whom 5 cases were Grade 3-4. Eight of these patients were treated with corticosteroids, however there was no clear radiographic evidence of pneumonitis in these cases.

Combined Safety Cohort

Forty-one events of pneumonitis or interstitial lung disease developed in 31 patients (excluding the patient discussed above). Of these, one patient died due to pneumonitis and eight patients experienced Grade 3-4 events. The median day of onset was Day 73 (range 24-423). The drug was interrupted in 15 patients and discontinued in five patients. Fourteen patients were treated with high-dose systemic steroids (prednisone equivalent of >40 mg/day). The event was considered to have resolved in 27 patients with a median duration of 38 days (range 2-183).

Reviewer Comments: In conclusion, the incidence of pneumonitis was 1/182 (0.5%) in the 2nd-line post-platinum UC population. The one patient died on Day 30 despite high-dose steroid administration within 3 days of the onset of the event. In the combined safety cohort, the incidence was 31/1414 (2.2%), including one additional fatal case. Of note, a high proportion of these patients had NSCLC, which has been associated with an increased risk for pneumonitis. In the combined safety cohort, durvalumab was permanently discontinued in 6/1462 patients and interrupted in 15/1462 patients. Steroids were used in 14 of the 31 patients. Overall, the incidence of pneumonitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors.

8.5.2. Hepatitis

Safety Database
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Table 28 below presents the incidence of Grade 3-4 liver function test abnormalities in the 2nd-line post-platinum cohort and the combined safety cohort, comprising 1462 patients with multiple tumor types in several studies. On-study labs were not available for all patients. Of note, the combined safety cohort includes a high proportion of patients with gastrointestinal malignancies; these patients have a high incidence of transaminase and bilirubin abnormalities.

Table 28: Liver Function Test Abnormalities in the Adverse Event Datasets

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Grade 3-4 AST n/N (%)</th>
<th>Grade 3-4 ALT n/N (%)</th>
<th>Grade 3-4 bilirubin n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-line Post-platinum Cohort N = 182</td>
<td>6/174 (3.4%)</td>
<td>2/171 (1.2%)</td>
<td>3/173 (1.7%)</td>
</tr>
<tr>
<td>Combined Safety Cohort N = 1414</td>
<td>64/1336 (4.8%)</td>
<td>43/1340 (3.2%)</td>
<td>39/1344 (2.9%)</td>
</tr>
</tbody>
</table>

Source: ADLB dataset

2nd-line Post-platinum UC Cohort

Table 53 below provides information on the incidence of hepatic adverse events, including laboratory abnormalities that were reported as adverse events. Fifty-three (53) events occurred in 26 patients. One patient had an isolated elevation in alkaline phosphatase and is not included in the table. The median day of onset for the first event for the 26 patients was day 26 (range: 2-252). Many events were ongoing and a date of resolution (and therefore duration) was not available for 16 patients. The median duration of the first event was 17 days (range: 1-120) in the remaining 10 patients. Durvalumab was discontinued for a hepatic event in one patient and delayed in 9 patients. Sixteen of these patients had liver metastases at baseline.

Three patients developed liver enzyme elevations that appeared to be immune-mediated. Patient 20011172378 had liver metastases at baseline and developed Grade 1 increased transaminases on Day 6. The event continued to worsen and was considered autoimmune hepatitis on Day 28. He then received high dose corticosteroids beginning on Day 32 and durvalumab was discontinued. His hepatic function continued to worsen and he developed encephalopathy and coagulopathy. He was hospitalized and placed on dialysis, however he died on Day 37. Patient 20001122442 developed Grade 3 AST and ALT elevations on day 42. He was hospitalized and received system corticosteroids. Durvalumab was not withheld and the transaminase elevations resolved by Day 84. Patient 20010772237 developed Grade 1 AST and ALT increase on Day 111. Durvalumab was temporarily held and the transaminase elevations resolved to normal by Day 154.
Patient 12455011922 developed Grade 2 transaminase elevation on Day 28, which was then considered Grade 3 autoimmune hepatitis on Day 42. However, bilirubin did not rise higher than the ULN, whereas alkaline phosphatase was elevated up to >10xULN. She was started on prednisone 60mg/day. CT demonstrated extensive new liver metastases. Durvalumab was discontinued and she entered hospice care. Given the new liver metastases and the lack of a clear picture of hepatitis, it is more likely that the elevated liver enzymes were due to disease progression rather than an autoimmune mechanism.

Table 29: Incidence of Hepatic Adverse Events in 2nd-line Post-platinum cohort (Data cut-off July 24, 2016)

<table>
<thead>
<tr>
<th>2nd-line Post-platinum (N=182)</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>26 (14%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>AST Increased</td>
<td>13 (7.1)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>10 (5.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>AKP Increased</td>
<td>7 (3.8)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Elevated Bilirubin/Hyperbilirubinemia</td>
<td>3 (1.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>GGT Increased</td>
<td>7 (3.8)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>

Source: ADAE dataset?

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). However, these cases were not considered as Hy’s Law cases due to the presence of an alternative etiology rather than durvalumab-related toxicity. Figure 5 below highlights these three cases. Patient 10025011792 experienced Grade 3 increases in AST, Grade 2 increase in bilirubin, and Grade 1 increase in ALT beginning on Day 14. However, the patient then developed elevated alkaline phosphatase and was determined to have experienced disease progression that better explained the enzyme elevations. Patient 13711012235 had baseline liver metastases and developed elevated transaminases on Day 13. On Day 69, her transaminases worsened and she developed an elevation in bilirubin. However, she had concomitant septic cholangitis and MRCP demonstrated hepatic disease progression. Patient 2000199986 had liver metastases at baseline and developed Grade 1 increased transaminases and alkaline phosphatase prior to the first dose of durvalumab. On Day 53, he experienced Grade 3 increased bilirubin and CT
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imaging demonstrated intrahepatic biliary dilation but decreased size of his hepatic metastases. Alkaline phosphatase was concomitantly elevated. A biliary drain was placed that did not result in improvement in his hepatic lab abnormalities. He received high dose corticosteroids and underwent liver biopsy, which reportedly demonstrated “progressive liver disease that was considered not related to immunotherapy/drug-induced liver injury.” He developed worsening liver function and encephalopathy and the investigator felt that the clinical course was most consistent with worsening metastatic disease and the patient was placed on comfort care measures. He died on Day 68.

Figure 6: Hy’s Law Cases in 2nd-line Post-platinum cohort

![Graph showing Hy's Law Cases]

Source: ADLB dataset

Combined safety cohort

Table 30 below provides information on the incidence of hepatic adverse events, including laboratory abnormalities that were reported as adverse events. Seventeen 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 233 patients was Day 30 (range: 1-309). Many events were ongoing and a date of resolution (and therefore duration) was not available for 117 patients. The median duration of the first event for the remaining 116 patients was 15 days (range: 1-183). Durvalumab was discontinued in 12 patients and interrupted/delayed in 69 patients.
Sixteen patients (including the two patients discussed under the 2nd-line post-platinum cohort) received corticosteroids for 29 hepatic events that were presumed to be immune-related. With the exception of the death of patient 2001172378 discussed above, the highest toxicity grade for these events was Grade 3. These events resolved in twenty cases and did not resolve as of the DCO in 9 cases. The median duration of steroid use was 39 days (range 3-125).

Table 30: Incidence of Hepatic Adverse Events in Combined Safety Cohort

<table>
<thead>
<tr>
<th>Combined Safety Cohort (N = 1414)</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>233 (16%)</td>
<td>108 (7.6%)</td>
</tr>
<tr>
<td>AST Increased</td>
<td>163 (11%)</td>
<td>33 (2.3%)</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>132 (9%)</td>
<td>23 (1.6%)</td>
</tr>
<tr>
<td>GGT Increased</td>
<td>107 (7.3%)</td>
<td>57 (4.0%)</td>
</tr>
<tr>
<td>AKP Increased</td>
<td>89 (6.1%)</td>
<td>20 (1.4%)</td>
</tr>
<tr>
<td>Elevated Bilirubin/Hyperbilirubinemia</td>
<td>88 (6%)</td>
<td>40 (2.8%)</td>
</tr>
<tr>
<td>Transaminases Increased</td>
<td>16 (1.1%)</td>
<td>8 (0.6%)</td>
</tr>
<tr>
<td>Hepatic Function Abnormal</td>
<td>7 (0.5%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Hepatic Enzymes Increased/abnormal</td>
<td>5 (0.3%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Hepatocellular injury</td>
<td>8 (0.5%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>6 (0.4%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>5 (0.3%)</td>
<td>5 (0.4%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>5 (0.3%)</td>
<td>5 (0.4%)</td>
</tr>
<tr>
<td>Liver function test increased</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hepatobiliary disease</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Liver injury</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hepatitis toxic</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: ADAE dataset

Laboratories and adverse events were examined for concurrent reports of bilirubin > 2xULN (grade 2) and ALT/AST > 3xULN (grade 2). 37 patients had concurrent elevations, including the three bladder cancer patients discussed above. Data regarding baseline liver metastases was available only in five of these patients (patients 10025011792, 13711012235, 2000199986, E3305001, and E6601003), three of whom were patients with bladder cancer and two of whom were patients with NSCLC. All five had baseline liver metastases. Additionally, eight patients had hepatocellular carcinoma.
Reviewer Comments: In conclusion, hepatic adverse events occurred in 26 (14%) patients in the 2nd-line post-platinum UBC cohort, including 11/182 (6%) with Grade 3-4 hepatic adverse events. The median day of onset for the first event was Day 26 and the event resolved in 10 patients with a median duration of 17 days. In the 2nd-line post-platinum patients with bladder cancer treated with durvalumab for whom on-study laboratory values were available, the incidence of Grade 3-4 AST, ALT, and total bilirubin elevation were 6/174 (3.4%), 2/171 (1.2%), and 3/173 (1.7%) respectively. There was one case of fatal immune-mediated hepatitis. Durvalumab was permanently discontinued for hepatic events in 1/182 patients and interrupted in 9/182 patients. Steroids were used for hepatic events in 4/182 (2.2%) of patients, of whom two patients died (including one case more likely due to disease progression than study drug toxicity) and two patients experienced resolution of the event. In the combined safety cohort, which included patients with hepatic and GI malignancies, the incidence of hepatic enzyme abnormalities was slightly higher than in the bladder cancer population. Overall, the incidence of hepatitis appears consistent or lower than that noted with other PD-1/PD-L1 inhibitors.

8.5.3. Diarrhea/Colitis

2nd-line post-platinum UBC

Table 31 below provides information on the incidence of diarrhea.

<table>
<thead>
<tr>
<th></th>
<th>2nd-line Post-platinum UBC (N = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
</tr>
<tr>
<td>All</td>
<td>23 (13%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (13%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

Source: ADAE dataset; Data Cutoff: 7-24-16

Thirty-three events of diarrhea occurred in 23 patients. The median day of first event onset was day 16 (range: 1-266). Seven events were unresolved. Among the 16 patients in whom the event had resolved and in whom data was available, the median duration was 3 days (range: 1-325). Drug was interrupted in one patient; no patient withdrew due to diarrhea. Among the two patients with Grade 3 diarrhea, durvalumab was not interrupted in either patient. One event occurred 34 days after the last infusion, at which time durvalumab had been discontinued due to worsening performance status. In the other patient (20002092413), diarrhea occurred concomitant with vomiting and was thought to have been associated with infection. Steroids were not administered for either event. One patient (20001122442)
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received steroids for Grade 2 diarrhea. Durvalumab was not held and the event resolved after 31 days.

Combined Safety Cohort

Table 32 below provides information on the incidence of diarrhea/colitis. There were 386 events of diarrhea/colitis in 252 patients. The median day of the first event onset was day 41 (range 1-417). Forty-two events were unresolved. Among the 205 patients in which the event had resolved and in whom data was available, the median duration was three days (range; 1-325). Durvalumab was permanently discontinued in six patients and interrupted/delayed in 19 patients. Corticosteroids or immunosuppresants (one patient each received infliximab and mycophenelate mofetil) were administered in 21 patients. In these patients, the median duration of the event was 26 days (range 2-109), the time to first steroid dose was six days (range 1-93), steroids were administered for a median of 36 days (range 6-280), and the event resolved in 12 patients. In the remaining seven patients, durvalumab was permanently discontinued in two patients and unchanged in five patients.

Table 32: Diarrhea/colitis Events in the Combined Safety Cohort

<table>
<thead>
<tr>
<th></th>
<th>Combined Safety Cohort (N = 1414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
</tr>
<tr>
<td>All</td>
<td>252 (17%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>238 (16%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>11 (0.8%)</td>
</tr>
<tr>
<td>Colitis ischemic</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>9 (0.6%)</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>2</td>
</tr>
<tr>
<td>Enteritis</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: ADAE dataset

Reviewer Comments: In conclusion, the incidence of diarrhea was 13% in the 2\textsuperscript{nd}-line post-platinum cohort. The median date of onset was Day 16. In the combined safety cohort, the incidence was 252/1414 (17.8%). The majority of these events were grade 1-2 and most were of short duration. No patients died due to diarrhea/colitis. In the 2\textsuperscript{nd}-line post-platinum cohort, durvalumab was not discontinued due to diarrhea/colitis and was interrupted in 1/182 patients. Steroids were used in only one patient in the 2\textsuperscript{nd}-line post-platinum cohort and 19/1462 (1.3%) patients in the combined safety cohort.
2nd-line Post-platinum UC Cohort

Hypothyroidism (including increased TSH, autoimmune hypothyroidism, decreased thyroxine, or thyroiditis leading to hypothyroidism) was reported in ten (5.5%) patients. This includes three patients with a preferred term of “endocrinopathy” who were considered to have experienced hypothyroidism. The median time of onset was 42 days (range: 15-239). Three cases were reported as resolved with a median duration of 35 days. Seven of the patients were treated with levothyroxine.

Hyperthyroidism (including decreased TSH, Basedow’s disease, increased thyroxine, or thyroiditis leading to hyperthyroidism) was reported in nine (4.9%) patients. This includes three patients with a preferred term of “endocrinopathy” who were considered to have experienced hyperthyroidism. The median time to first onset was 43 days (range: 14-71). Thyroid stimulating hormone was decreased and below the patient’s baseline in 25 (16%) of 163 patients with a follow-up measurement.

Table 33 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. Twenty-five patients had both an on-study TSH value that was elevated and above their baseline.

**Table 33: Thyroid Stimulating Hormone (TSH) Changes in 2nd-line Post-platinum Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N=174) n (%)</th>
<th>On Study (N=163) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH &gt; ULN</td>
<td>19 (11%)</td>
<td>25 (14%)</td>
</tr>
<tr>
<td>TSH &gt; 3x ULN</td>
<td>2 (1.1%)</td>
<td>8 (4.6%)</td>
</tr>
<tr>
<td>TSH &gt; 10xULN</td>
<td>0</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>TSH &lt; ULN</td>
<td>5 (2.7%)</td>
<td>26 (16%)</td>
</tr>
</tbody>
</table>

*Source: ADLB dataset*

Combined Safety Cohort

Hypothyroidism (including increased TSH, autoimmune thyroiditis, decreased thyroxine, or thyroiditis leading to hypothyroidism) was reported in 135 (9.5%) patients. All events were Grades 1-2, except for one Grade 3 event in a patient with pancreatic adenocarcinoma in which the patient developed concomitant edema. The median day of onset was 57 (range: 1-423). 83 cases were reported as resolved with a median duration of 29 days (range: 1-660).

Hyperthyroidism (including decreased TSH, Basedow’s disease, increased thyroxine, or thyroiditis leading to hyperthyroidism) was reported in 81 (5.7%) patients. The median day of onset was 42 days (range: 1-438). The event was documented as resolved in 52 patients. In
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the median duration of the event was 29 days (range: 1-113). All events were
Grade 1-2.

Thyroiditis occurred in 10 patients, including a Grade 3 event in one patient who subsequently
experienced a myocardial infarction due to hyperthyroidism. In nine patients with thyroiditis,
transient hyperthyroidism preceded hyperthyroidism (and are captured in the incidence of
hypothyroidism or hyperthyroidism above). Three of these patients were treated with a beta-
blocker and/or thioamide.

<table>
<thead>
<tr>
<th>Table 34: Thyroid Events in Combined Safety Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Combined Safety Cohort</td>
</tr>
<tr>
<td>(N=1414)</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hypothyroidism or Elevated TSH</td>
</tr>
<tr>
<td>176 (12%)</td>
</tr>
<tr>
<td>Hyperthyroidism or Decreased TSH</td>
</tr>
<tr>
<td>75 (5.3%)</td>
</tr>
<tr>
<td>Thyroiditis</td>
</tr>
<tr>
<td>10 (0.7%)</td>
</tr>
</tbody>
</table>

(Source: ADAE dataset)

**Reviewer Comments:** In conclusion, the incidence of hypothyroidism was 10/182 (5.5%) in the
2nd-line post-platinum UBC cohort as reported by investigators. Twenty-five patients (14%) had
an elevated TSH while on study that was increased from baseline, indicating that investigator
report of hypothyroidism may underestimate the incidence of sub-clinical hypothyroidism.
Seven patients (3.8%) were treated with levothyroxine. The median day of onset was Day 58. In
the combined safety cohort, the incidence of hypothyroidism was 9.5% (165/1414), while there
were 445 patients (32%) who had an elevated on-study TSH value. TSH was elevated at least
10-fold over upper limit of normal in 6/1397 (0.4%) of patients with available baseline
laboratories and in 67/1407 (4.8%) of patients with available on-study laboratories. Overall, the
incidence of hypothyroidism appears consistent with other PD-1/PD-L1 agents.

8.5.5. Hyperglycemia/Diabetes Mellitus

2nd-line Post-platinum Cohort

No cases of likely immune-mediated diabetes mellitus (as identified by low C-peptide and/or
auto-antibodies) were noted in the 2nd-line post-platinum cohort. There were eight events of
hyperglycemia (including “hyperglycemia,” “glycosylated hemoglobin increased,” “glucose urine
present,” and “blood glucose increase”) in eight patients. All were Grades 1-2. The median day
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of onset was Day 30 (range: 15-97). All but two events were reported as unresolved. One patient had a medical history of hyperglycemia and three other patients experienced hyperglycemia either in the setting of corticosteroids or concomitant infection.

Combined Safety Cohort

Sixty-eight events of hyperglycemia or diabetes mellitus were reported in 49 patients. Fifty events were Grade 1-2, while 17 events in 13 patients were Grade 3-4. Among the patients with Grade 3-4 events, the median date of onset was Day 49 (range: 10-406) and 13 were reported as resolved. Patient 2000133915 developed autoimmune-mediated diabetes mellitus on Day 127. She was treated with IV insulin and then transitioned to subcutaneous insulin. Durvalumab was interrupted and then resumed. Eleven patients either had a baseline history of diabetes mellitus or developed hyperglycemia in the context of infection or corticosteroids for a concomitant event. In one patient, there were no apparent baseline or precipitating factors, however the event was transient and thus unlikely to represent true autoimmune diabetes.

Reviewer Comments: In conclusion, there were no cases of likely immune-mediated diabetes mellitus that occurred in the 2nd-line post-platinum cohort. The incidence of hyperglycemia was 8/182 patients (4.4%). There was one patient in the combined safety cohort with new-onset diabetes mellitus likely to represent immune-mediated diabetes. Overall, the incidence of diabetes mellitus is consistent with other PD-1/PD-L1 inhibitors.

8.5.6. Adrenal Insufficiency

2nd-line Post-platinum Cohort
One patient experienced new adrenal insufficiency. This occurred on Day 69 during a concomitant episode of septic cholangitis. The patient received antibiotics as well as hydrocortisone. During the course of evaluation, disease progression was noted and the patient was discharged to hospice care. It is unclear whether the adrenal insufficiency resolved.

There were three patients with concomitant reports of hyperkalemia and hyponatremia. In these patients, there were no reports of hypotension. One event occurred in the context of obstructive uropathy and acute kidney injury and one event occurred in the context of urosepsis.

Combined Safety Cohort

Fourteen patients in the combined safety cohort, including the patient described above, experienced new adrenal insufficiency. One event was considered Grade 3, the others were Grades 1-2. The median day of onset was Day 177 (range: 40-413). Three events were
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documented as resolving. Durvalumab was interrupted in 3 patients and unchanged in the
remaining patients. Seven patients received corticosteroids.

Reviewer Comments: There was one case of likely immune-mediated adrenal insufficiency in a
patient with bladder cancer treated with durvalumab. 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 the 2nd-line post-platinum
cohort.

Combined Safety Cohort

One patient in ATLANTIC developed Grade 3 hypophysitis that began on Day 44 in the setting of
aseptic meningitis, which was assumed to be immune-mediated. His ACTH and cortisol were
low, as was his antidiuretic hormone, indicating diabetes insipidus. CSF analysis demonstrated
high protein and lymphocytosis without evidence of malignancy or infection. He was treated
with corticosteroids and desmopressin. Durvalumab was interrupted, however the patient
continued on study.

Reviewer Comments: There were no cases of hypophysitis in the 2nd-line post-platinum UBC
cohort. There was one case of likely immune-mediated hypophysitis in the combined safety
cohort as described above. Overall, the incidence of hypophysitis appears similar to other PD-
1/PD-L1 inhibitors.

8.5.8. Other Endocrinopathies

2nd-line Post-platinum Cohort

One patient experienced decreased blood testosterone on Day 22 and was treated with
transdermal testosterone. The event was ongoing as of the DCO. No other endocrinopathies
were noted in this patient.

Combined Safety Cohort

Four patients experienced primary hypogonadism or decreased blood testosterone. All were
considered Grade 2. One event was considered resolved. None of these patients experienced
any additional endocrinopathy including hypothyroidism.

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.

2nd-line post-platinum

One patient experienced Grade 3 confusion state. This patient had brain metastases at baseline. A non-contrast CT scan was consistent with increased vasogenic edema secondary to his known brain metastases.

Nine patients experienced peripheral neuropathy. All events were Grade 1-2.

There was one case of Grade 1 opsoclonus myoclonus. On review, this appeared to be related to a metabolic encephalopathy.

Combined Safety Cohort

One patient experienced Grade 3 hemiplegia due to stroke. Two patients are reported as experiencing paralysis; in both cases these were Grade 1 mononeuropathies.

Three patients experienced Grade 3 neuropathies. In two cases, these were associated with new-onset brain metastases.

Three patients experienced Grade 3 seizure or partial seizure. In all three patients, this was associated either with primary glioma or brain metastases.

Table 35: Neurologic Events in PCD4989g and IMVigor Cohorts 1 and 2

<table>
<thead>
<tr>
<th>Event</th>
<th>2nd-line Post-platinum UBC (N=182)</th>
<th>Combined Safety Cohort (N=1414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusional state^{1}</td>
<td>Grade 1-4: 9 (6%)</td>
<td>Grade 1-4: 60 (4.2%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: 1 (0.5%)</td>
<td>Grade 3-4: 11 (0.8%)</td>
</tr>
<tr>
<td>Cerebral ischemia^{2}</td>
<td>Grade 1-4: 1 (0.5%)</td>
<td>Grade 1-4: 10 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: 1 (0.5%)</td>
<td>Grade 3-4: 6 (0.4%)</td>
</tr>
<tr>
<td>Neuropathy^{3}</td>
<td>Grade 1-4: 9 (6%)</td>
<td>Grade 1-4: 90 (6.4%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: 0</td>
<td>Grade 3-4: 3 (0.2%)</td>
</tr>
<tr>
<td>Opsoclonus myoclonus</td>
<td>Grade 1-4: 1 (0.5%)</td>
<td>Grade 1-4: 1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: 0</td>
<td>Grade 3-4: 0</td>
</tr>
<tr>
<td>Seizure</td>
<td>Grade 1-4: 0</td>
<td>Grade 1-4: 9 (0.6%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: 0</td>
<td>Grade 3-4: 3 (0.2%)</td>
</tr>
<tr>
<td>Deafness</td>
<td>Grade 1-4: 0</td>
<td>Grade 1-4: 4 (0.3%)</td>
</tr>
</tbody>
</table>
Clinical and Statistical Reviews

Reviewer Comments: In conclusion, the incidence of neurologic adverse events in the 2nd-line post-platinum UC cohort was 20/182 (10.9%), of which 2/182 (1.1%) 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. Steroids were not used to treat neurologic events in these patients. There were no clear cases of immune-mediated neurologic events in the combined safety cohort. Overall, the incidence of neurologic events appears consistent with other PD-1/PD-L1 inhibitors.

8.5.10. Musculoskeletal Disorders

2nd-line post-platinum

One patient (20022522574) experienced Grade 2 myositis on Day 139 manifested as left hip pain. MRI demonstrated a large heterogeneous enhancing mass, considered a new metastatic lesion, in the left iliopsoas muscle near the left hip joint with diffuse edema throughout the muscle. The patient received low-dose prednisone and the dose of durvalumab was not changed. The myositis was ongoing at the time of death.

An additional patient experienced Grade 1 arthritis.

Combined Safety Cohort

Five patients reported arthritis; all events were Grades 1-2. One patient (13711011923) was treated with corticosteroids.

Terms used to report arthralgias, myalgias, and musculoskeletal weakness were reviewed. There were no terms which raised suspicion of an autoimmune event.

8.5.11. Skin Disorders
There were 53 dermatologic events in 26 patients. The median day of onset of the first event was Day 41 (range: 2-323). Durvalumab was delayed in 2 patients due to dermatologic events. The event was considered recovered in 14 patients. In these patients, the median duration of the event was 15 days (range: 1-36). Grade 3 rash was reported in one patient (2004392431) beginning on Day 11, although he had an ongoing Grade 1 rash beginning prior to study entry. He received systemic corticosteroids and topical corticosteroid and urea creams. Durvalumab dosing was not changed. The Grade 3 rash was considered resolved after 8 days, however the patient continued on intermittent ongoing systemic corticosteroids for the initial rash.

Nine patients with dermatologic events received systemic steroids, while 12 received topical steroids.

\ Combined Safety Cohort

There were 615 dermatologic events in 347 patients. Durvalumab was interrupted due to the event in 22 cases in 18 patients. Durvalumab was permanently discontinued in one case of Grade 1 erythema nodosum. Previous to this, the patient had experienced multiple episodes of pruritic rash while on study, treated with topical corticosteroids. She was subsequently lost to follow-up and the events were considered ongoing.

There were 14 Grade 3 events in 12 patients. These Grade 3 events included 10 events of rash and one event each of dermatitis acneiform, pruritis, eczema, and alopecia. The median day of onset was Day 37 (range: 4-354). Ten events were documented as resolving. In these events, the median duration was 16 days (range: 6-57).

<table>
<thead>
<tr>
<th>Table 36: Dermatitis Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-line Post-platinum Cohort (N=182) n/%</td>
</tr>
<tr>
<td>Rash³</td>
</tr>
<tr>
<td>Rash³</td>
</tr>
<tr>
<td>Dermatitis Acneiform²</td>
</tr>
<tr>
<td>Alopecia³</td>
</tr>
<tr>
<td>Eczema⁴</td>
</tr>
<tr>
<td>Epidermolysis⁵</td>
</tr>
<tr>
<td>Lichen Planus</td>
</tr>
<tr>
<td>Seborrheic Dermatitis</td>
</tr>
<tr>
<td>Hypopigmentation⁶</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Photosensitivity reaction</th>
<th>0</th>
<th>0</th>
<th>1 (&lt;0.1%)</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>3</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/Generalized Pruritus</td>
<td>11</td>
<td>215</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>41</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>0</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>6</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Source: ADE database

1 Including macule, papule, erythema multiforme, erythematous, maculo-papular, pustular, popular, and pruritic rash and dermatitis; dermatitis contact, and dermatitis allergic
2 Including dermatitis psoriasiform, acne
3 Includes alopecia and madarosis
4 Includes eczema, dyshidrotic eczema, and eczema astematic
5 Includes epidermolysis, dermatitis bullous, dermatitis exfoliative, and skin exfoliation
6 Includes vitiligo, skin hypopigmentation, and skin discoloration
7 Includes erythema, palmar erythema, palmar-planter erythrodysesthesia syndrome
8 Including skin reaction, yellow skin, pityriasis rubra pilaris, skin fissures, skin fragility, skin disorder, and purpura

**Reviewer Comments:** In conclusion, the incidence of skin disorders (including pruritus) was 26/182 (14.3%) in the 2nd-line post-platinum UC cohort. The median date of onset was Day 41. Durvalumab was interrupted in two patients. Systemic steroids were used in nine patients and topical steroids were used in 12 patients. In the combined safety cohort, the incidence was 347/1462 (23.7%). The majority of these events were Grade 1-2 and most were of short duration. Twelve patients developed Grade 3 rash. Durvalumab was permanently discontinued in one patient and interrupted in 18 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.

**2nd-line Post-Platinum UC Cohort**

Amylase and lipase were not routinely assessed in either Study 1108 or ATLANTIC. There were no cases of pancreatitis or increased amylase or lipase reported in the 2nd-line post-platinum cohort.

**Combined Safety Cohort**

There were 13 patients with pancreatitis or elevated amylase/lipase in the combined safety cohort. There were 7 patients with Grade 3-4 events. The median day of onset was Day 197 (range: 23-365). Durvalumab was discontinued in one patient and interrupted in four.
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Systemic steroids were administered in three patients. The event resolved in 11 patients with a median duration of 15 days (range 2-74 days).

Among the patients with Grade 3-4 events, gallstones as a likely etiology were demonstrated in two patients. There were no patients with clear evidence of immune-mediated pancreatitis. However, there were two patients with otherwise unexplained amylase/lipase elevations. Patient 13717011695 had MSI-high colon cancer and developed Grade 4 elevated lipase/amylase on Day 364 associated with G1 abdominal pain. Durvalumab was delayed and the event resolved without further therapy. Patient 20001352214 had ovarian cancer and developed Grade 1 lipase elevation on Day 68, which worsened to Grade 3 on Day 82 and was associated with Grade 3 amylase. Durvalumab was delayed and the events resolved by Day 96. Of note, she had received dexamethasone prior to the event for abdominal pain.

**Reviewer Comments:** There were no cases of pancreatitis or increased amylase/lipase in the 2nd-line post-platinum UC cohort. There were 13 patients with amylase or lipase elevations or pancreatitis in the combined safety cohort. No cases were clearly immune-mediated, however two cases did not have a clear alternate etiology. Overall, the incidence of pancreatitis appears consistent with other PD-1/PD-L1 inhibitors.

8.5.13. Renal Abnormalities

2nd line Post-platinum Cohort

Renal Failure/impairment and acute kidney injury were reported as 38 events in 26 patients. The median day of onset was day 57 (range: 29-120). Durvalumab was interrupted in five patients and discontinued in one patient. Eighteen of the events were considered resolved with a median duration of 11 days (range: 2-148). Ten events in nine patients were considered Grade 3 or greater, including one patient (20010622297) who died in the setting of pneumonia with acute kidney failure thought to be associated with vancomycin toxicity.

One patient was treated with corticosteroids indicated for treatment of acute kidney injury. Patient 20001121221 developed Grade 3 acute tubulointerstitial nephritis on Day 90, confirmed by renal biopsy that demonstrated prominent neutrophilic inflammation and intratubular aggregates of neutrophils. Durvalumab was discontinued and he was treated with corticosteroids. The acute kidney injury improved, but was not fully resolved at the time the subject withdrew consent.

**Table 37: Creatinine Changes in the 2nd line post-platinum cohort**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N=182)</th>
<th>On Study (N=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>56 (31%)</td>
<td>0</td>
</tr>
</tbody>
</table>

CDER Clinical Review Template 2015 for New NDA or BLA

Reference ID: 4068251
Combined Safety Cohort

Renal Failure/impairment and acute kidney injury were reported as 113 events in 83 patients. The median day of onset for the first event was Day 44 (range 1-433). The event was considered as resolved in 46 patients with a median duration of 14.5 days (range: 2-212). Nineteen events in 17 patients were considered Grade 3 or greater. Durvalumab was interrupted in 17 patients due to kidney injury and discontinued in two patients.

Two additional patients received systemic corticosteroids for interstitial or autoimmune nephritis. Patient 1351901698 experienced Grade 3 tubulointerstitial nephritis and concomitant pneumonia and was treated with antibiotics and prednisone. Prednisone was tapered over three months, at which point the nephritis had resolved. Durvalumab was discontinued due to the nephritis. Patient 200136936 developed Grade 2 autoimmune nephritis on Day 238 and was treated with prednisone. Durvalumab was discontinued due to nephritis, which was documented as resolving four months later.

Table 37 provides information on laboratory abnormalities at baseline and during the treatment period/30 day follow-up.

Reviewer Comments: In conclusion, the incidence of renal abnormalities was 26/182 (14.3%) in the 2nd-line post-platinum cohort. The median date of onset was Day 57. In the combined safety cohort, the incidence was 83/1414 = 5.9%. The majority of these events were grade 1-2 and most were of short duration. In the 2nd-line post-platinum UC cohort, durvalumab was interrupted due to a renal event in 5/182 patients and discontinued in 1/182 patients, while in the combined safety cohort, durvalumab was interrupted in 17/1414 patients and discontinued in 2/1414 patients. One patient in the 2nd-line post-platinum cohort and two additional patients in the combined safety cohort were treated with corticosteroids for a renal event. Overall, the incidence of renal abnormalities appears consistent with other PD-1/PD-L1 inhibitors.

8.5.14. Infection

2nd-line Post-platinum Cohort

Using the system organ class term “infections and infestations,” 54 (29.7%) patients in the 2nd-line post-platinum cohort were considered to have experienced infection. Grade 3 or 4 infection occurred in 11 (6.0%) patients while five (2.7%) patients were experiencing infection at the time of death. These patients are discussed in Table 22. Urinary tract infections were
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the most common cause of Grade 3 or higher infection, occurring in eight (4.4%) patients. One patient experienced Grade 2 pulmonary tuberculosis in a South Korean patient and one patient experienced a Grade 2 epidural abscess. Durvalumab was interrupted in 12 patients due to infection and was not discontinued due to infection in any patient.

Combined Safety Cohort

Using the system organ class term “infections and infestations,” 567 (40%) patients in the combined safety cohort were considered to have experienced infection. Grade 3 or 4 infection occurred in 128 (9.1%) patients, while 13 (0.9%) patients died due to infection. One patient experienced Grade 4 necrotizing fasciitis. Dose interruptions due to infection occurred in 85 patients, while durvalumab was discontinued in 11 patients due to infection.

Reviewer Comments: In conclusion, the incidence of infection was 54/182 (29.7%) in the 2nd-line post-platinum cohort, including 11 Grade 3 or 4 events and five events that were considered fatal, in that they were ongoing at the time of death. Urinary tract infections were the most common cause of high-grade infection, which is consistent with the pattern of infection seen with other PD-1/PD-L1 inhibitors. In the combined safety cohort, 567/1414 patients (40%) experienced infection. Although there was one case of pulmonary tuberculosis, there did not appear to be an increased risk of mycobacterial infections. Overall, the incidence of infection appears consistent with other PD-1/PD-L1 inhibitors.

8.5.15. Infusion Reactions

2nd-line Post-platinum Cohort

The terms “infusional-related reaction” or “urticaria” that occurred on an infusion day were reported in two patients. One event was Grade 1 and one event was Grade 3. Patient 2004391740 experienced a Grade 3 infusion-related reaction characterized by fever and tachycardia. He was found to have a concomitant urinary tract infection. He was hospitalized and treated with antibiotics with resolution of his symptoms. Two weeks later, he experienced sepsis and durvalumab was discontinued at the time of his subsequent CT scan which demonstrated disease progression.

Combined Safety Cohort

Infusion-related reaction or urticarial that occurred on an infusion day were reported in 25 patients. Five events were considered Grade 3. There were no Grade 4 reactions. Durvalumab was discontinued in one patient and interrupted in eight patients.
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**Reviewer Comments:** In conclusion, the incidence of infusion reactions (as defined by the terms “infusion-related reaction” or “urticarial” occurring on the date of infusion) was 2/182 (1.1%) in the 2nd-line post-platinum cohort, including one Grade 3 event that may have been related to an underlying urinary tract infection. No patients required steroids for an infusion reaction. In the combined safety cohort, 25/1414 patients (1.8%) experienced an infusion-related reaction resulting in dose interruption in 8 patients and discontinuation in one patient. Overall, the incidence of infusion-related reaction appears consistent with other PD-1/PD-L1 inhibitors.

8.5.16. Corticosteroid Use

2nd-line Post-platinum Cohort

Thirty-nine (21.4%) patients in the 2nd-line post-platinum cohort received systemic corticosteroids within 30 days of an AE. Twenty-seven (14.8%) patients received at least 10 mg/day of prednisone-equivalent steroids, while 20 (11%) received at least 40 mg/day of prednisone-equivalent steroids. Nine patients (4.9%) were treated with corticosteroids and were considered to have experienced an imAE, including five patients with a Grade 3 or greater AE and four patients with Grade 1-2 AEs. Of the 28 patients who received systemic steroids but were not considered to have experienced an imAE, the most common associated AEs were pain (11 patients), pruritis/rash (44 patients), and pre-medication for chemotherapy or contrast (four patients).

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 mycophenolate.

Combined Safety Cohort

Five hundred and two patients received corticosteroids during the treatment period, of whom 368 received at least 10 mg/day of prednisone-equivalent steroids and 219 received at least 40 mg/day of prednisone-equivalent steroids. Three patients received non-steroidal immunosuppressants, including infliximab and mycophenolate. Systemic steroid use was higher in ATLANTIC (48.6%) than in Study 1108 (29.5%) due to higher use in treating complications of NSCLC including chronic obstructive pulmonary disease, dyspnea, cough, and brain metastases. Eighty-eight patients (6.2%) received steroids for the treatment of an imAE, including 72 patients (5.1%) who received at least 10 mg/day prednisone-equivalent and 49 (3.5%) who received at least 40 mg/day prednisone equivalent.

**Reviewer Comments:** In conclusion, the incidence of corticosteroid use was 21.4% in the 2nd-line post-platinum cohort, of which 99 patients (4.9%) of patients received steroids for an adverse event considered possibly immune-mediated. In the combined safety cohort, the incidence of corticosteroid use was 502/1414 (35.5%), of whom 88 (6.2%) patients received steroids for a
Specific Safety Studies/Clinical Trials

Subgroup analysis based on race was not performed as the study population was largely Caucasian. Subgroup analyses based on age and gender in the 2nd-line post-platinum cohort 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 38: Grade 1-4 Adverse Events in >15% of Patients by Age

<table>
<thead>
<tr>
<th></th>
<th>&lt; 65 years (N = 70) n (%)</th>
<th>≥ 65 years (N = 112) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>All</td>
<td>69 (99%)</td>
<td>40 (57%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28 (40%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>16 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (13%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (23%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>11 (16%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>18 (26%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Source: ADAE dataset;

Table 39: Grade 1-4 Adverse Events in > 15% of Patients by Sex

<table>
<thead>
<tr>
<th>Grade 1-4 Adverse Events in &gt; 15% of Patients by Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N = 131)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Grade 1-4</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Decreased Appetite</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Peripheral Edema</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
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</tbody>
</table>

Source: ADAE dataset;
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, durvalumab 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 durvalumab and for at least five months after the last dose.

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

Durvalumab 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 dose-escalation phase of Study 1108, the maximum tolerated dose of durvalumab 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 durvalumab should be considered overdose. There was no evidence that suggests a risk for dependence of durvalumab. 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**

Durvalumab has not yet been approved in any market.

8.9.2. **Expectations on Safety in the Postmarket Setting**
Clinical and Statistical Reviews  
Drs. Suzman and Fernandes  
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma  
Patients with autoimmune disorders, except those with Type 1 diabetes mellitus or hypothyroidism on stable hormone replacement, were excluded from trials evaluating durvalumab. Thus, off-label use in these patients would constitute a safety concern regarding immune-mediated adverse events.

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 durvalumab 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 durvalumab exposure were sufficient to characterize the safety of durvalumab for treatment of a serious and life-threatening condition with the exception of updated safety data from the ongoing Phase 3 trial, which will be obtained via a PMR. Notable toxicities included a high incidence of infections, including severe urinary tract infections and sepsis, although this is difficult to interpreting the setting of a single-arm trial. Incidences of immune-mediated adverse events, including pneumonitis, hepatitis, and diarrhea/colitis, were similar to other checkpoint inhibitors such as atezolizumab, nivolumab, and pembrolizumab. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of durvalumab and the experience of the medical community in managing immune-mediated adverse reactions, based on use of other FDA-approved immune-modulating agents. Recommendations for safe and effective use of durvalumab, 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

There were no safety or efficacy issues identified for the proposed indication and the product itself. The safety profile of durvalumab is similar to that of three similar products currently marketed in the USA. The demonstrated benefit-risk profile for durvalumab is favorable in the intended patient population. Therefore, this application was not referred to the Oncologic Drugs Advisory Committee.

10 Labeling Recommendations

10.1. Prescribing Information
Clinical and Statistical Reviews
Drs. Suzman and Fernandes
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma
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 durvalumab for this BLA.

a) Section 1:
   Revised the proposed indication regarding prior neoadjuvant/adjuvant therapy to be consistent with other PD-1/PD-L1 agents.

b) Section 2:
   Removed (3) (4) from dose modification table.
   Added “Infection” and “Other” to dose modification table.

c) Section 5:
   - **Pneumonitis**
     - Included data from combined safety database
     - Provided additional data regarding outcome of cases.
   - **Hepatitis**
     - Included data from combined safety database
     - Provided additional details on management and outcome of all cases
   - **Colitis**
     - Included data from combined safety database
     - Provided additional details on management and outcome of all cases
   - **Thyroid Disorders**
     - Included data from combined safety database
     - Included data on patients with elevated or decreased TSH regardless of whether they experienced an AE
     - Included patients with a PT of “endocrinopathy” who had experienced thyroid toxicity
   - **Adrenal Insufficiency**
     - Included data from the safety database regarding incidence
   - **Diabetes Mellitus**
     - Included data from the safety database regarding incidence.
   - **Other Immune-Related Adverse Reactions**
     - Included several rare events from the combined safety database, including ocular toxicity, immune thrombocytopenic purpura, myocarditis, nephritis, and aseptic meningitis.
   - **Infection**
     - Included a new Warning since the high incidence of infection seen in trials of PD-L1 agents may be immune-mediated

d) Section 6:
   - Grade 5 AEs and infections occurring at the time of disease progression and death were included
   - Adverse events, including serious adverse events, were updated to reflect
Clinical and Statistical Reviews
Drs. Suzman and Fernandes
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pooled terms.
  • A table was added to include Grade 3-4 laboratory abnormalities.

e) Section 8:
   Included overall response rate and incidence of Grade 3-4 AEs in patients 65 and 75
   years or older

f) Section 14:
   • Clarified that Study 1 refers to the 182 2nd-line post-platinum cohort of Study
     1108
   • Updated data to reflect the DCO of October 24, 2016 including efficacy data from
     182 patients
   • Clarified that the assay performance was evaluated in the 128 patients who were
     enrolled without regards to PD-L1 status and after the assay was finalized (i.e.,
     post-Amendment 8). Response rates and duration of response in the PD-L1
     subgroups was added to Table 4.

g) Patient Counseling Information:
   • Highlighted immune-related adverse reactions and inserted subtitle concerning
     Embryo-Fetal Toxicity
   • Included the risk of infection and rash 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)

No REMS is indicated for the proposed indication.

12 Postmarketing Requirements and Commitments
Clinical and Statistical Reviews
Drs. Suzman and Fernandes
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma
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:
1. Provide data from Study D419BC00001 (DANUBE) concerning PD-L1 status and patient outcome to Ventana to update the device label.

PMCs:
1. Provide the median and updated information on the range of duration of response in the 182 patients in the urothelial cancer cohort of Study 1108 who have received prior platinum-based therapy. This should be provided for all patients, patients with PD-L1 high tumor staining, and patients with PD-L1 low tumor staining.
2. Re-evaluate the ADA confirmatory and triple mutation assay cut points using a 1.0% false positive rate.
3. Conduct drug tolerance studies for the screening, confirmatory, tittering, and triple mutation assay that are in the range of the Ctrough of 182 μg/mL to better demonstrate that the assay can detect ADA in the presence of drug.
4. Confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose by performing microbiological challenge studies with diverse microorganisms to support the 24 hour storage time. Your study should include gram-negative microorganisms (such as E. coli and/or E. cloacae) which are known to proliferate in these solutions. The challenge studies should include, at a minimum, time points at twice the label claim storage time.

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 the urothelial cancer cohort of Study 1108. Since this study relied on independent-review determined objective responses, financial issues are less likely to affect the analyses of the effectiveness of durvalumab in the intended patient population.

Covered Clinical Study (Name and/or Number): Study 1108
Clinical and Statistical Reviews  
Drs. Suzman and Fernandes  
BLA 761069 for Durvalumab for Use in Advanced Urothelial Carcinoma

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<tr>
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<td>Proprietary interest in the product tested held by investigator:</td>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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03/10/2017

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