APPLICATION NUMBER:

761069Orig1s000

SUMMARY REVIEW
Office Director and Division Director Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>From</td>
<td>Julia Beaver, MD, Division Director (Acting) &amp; Richard Pazdur, MD Office Director (Acting)</td>
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<tr>
<td>Subject</td>
<td>Office Director and Division Director Summary Review</td>
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<td>NDA/BLA #</td>
<td>761069</td>
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<td>Supplement #</td>
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<td>Applicant</td>
<td>AstraZeneca UK Ltd</td>
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<tr>
<td>Date of Submission</td>
<td>October 13, 2016</td>
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<td>PDUFA Goal Date</td>
<td>June 13, 2017</td>
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<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>Imfinzi/Durvalumab</td>
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<tr>
<td>Dosage Form(s) / Strength(s)</td>
<td>Injection/500 mg per 10 mL vial and 120 mg per 2.4 mL vial</td>
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<tr>
<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>Treatment of patients with locally advanced or metastatic urothelial carcinoma</td>
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<td>Action/Recommended Action for NME:</td>
<td>Approval</td>
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| Approved/Recommended Indication/Population(s) (if applicable) | 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. |
## Material Reviewed/Consulted

<table>
<thead>
<tr>
<th>OND Action Package, including:</th>
<th>Names of discipline reviewers</th>
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</thead>
<tbody>
<tr>
<td><strong>Medical Officer Review</strong></td>
<td>Daniel Suzman/ V. Ellen Maher</td>
</tr>
<tr>
<td><strong>Statistical Review</strong></td>
<td>Laura Fernandes/ Shenghui Tang</td>
</tr>
<tr>
<td><strong>Pharmacology Toxicology Review</strong></td>
<td>Eias Zahalka/ Todd Palmby</td>
</tr>
<tr>
<td><strong>OPQ Review</strong></td>
<td>Zhong Li/ Zhihao Peter Qui/ Xu (Michael) Di/ Howard Anderson/ Davina Ligons/Maria Jose Lopez Barragan</td>
</tr>
<tr>
<td><strong>Microbiology Review</strong></td>
<td>Monica Commerford/ Patricia Hughes</td>
</tr>
<tr>
<td><strong>Clinical Pharmacology Review</strong></td>
<td>Yuhong Chen/ Stacy Shord/ Xiaofeng Wang / Jingyu (Jerry Yu)</td>
</tr>
<tr>
<td><strong>OPDP</strong></td>
<td>Nazia Fatima</td>
</tr>
<tr>
<td><strong>OSI</strong></td>
<td>Lauren Iacono-Connors</td>
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<td><strong>CDTL Review</strong></td>
<td>V. Ellen Maher</td>
</tr>
<tr>
<td><strong>OSE/DMEPA</strong></td>
<td>Tingting Gao/Alice (Chi-Ming) Tu</td>
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<tr>
<td><strong>Patient Labeling</strong></td>
<td>Rowell Medina/Barbra Fuller</td>
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OND=Office of New Drugs  
OPQ=Office of Pharmaceutical Quality  
OPDP=Office of Prescription Drug Promotion  
OSI=Office of Scientific Investigations  
CDTL=Cross-Discipline Team Leader  
OSE=Office of Surveillance and Epidemiology  
DEPI=Division of Epidemiology  
DMEPA=Division of Medication Error Prevention and Analysis  
DRISK=Division of Risk Management
1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment that was made by the clinical and statistical teams. All members of the review team recommended approval of this application or reported that there were no findings that would preclude approval. Based on the results of Study CD-ON-MEDI4736-1108: A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors (N = 182 with urothelial cancer and prior platinum-based therapy), durvalumab has demonstrated a favorable benefit-risk profile for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy with enough evidence to recommend accelerated approval.

In the United States, there are no approved second-line therapies for patients with locally advanced or metastatic urothelial carcinoma. Standard of care for patients with locally advanced or metastatic urothelial carcinoma, prior to the accelerated approvals of two other checkpoint inhibitor immunotherapies, 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 was demonstrated in 182 patients with locally advanced or metastatic urothelial carcinoma who had disease progression while on or after a platinum-containing chemotherapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. All patients received durvalumab 10mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. The major efficacy outcomes were Objective Response Rate (ORR) according to RECIST v 1.1 as assessed by Blinded Independent Central Review (BICR), and Duration of Response (DoR). Confirmed ORR was 17.0% (95% CI: 11.9, 23.3) and median DOR in responders was not reached (range: 0.9 to 19.9 months). Of the 31 responders, 14 patients (45%) had ongoing responses of 6 months or longer and five patients (16%) had ongoing responses of 12 months or longer. 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 95 patients with PD-L1 High status, ORR was 26.3% (17.8, 36.4), in the 73 patients with PD-L1 low/negative ORR was 4.1% (0.9%, 11.5%). Response durations in the PD-L1 subgroups were similar regardless of PD-L1 status. Although the point estimate for the response rate is not clearly greater than what is reported in single-arm studies involving chemotherapy or combination chemotherapy regimens in this disease setting, the durability of the responses observed with durvalumab appear to be better than available therapy and the toxicity profile offers an alternative to toxic chemotherapy. At the time of this recommendation, the data regarding the durability of response is not yet mature as there continues to be patients with ongoing responses to

Reference ID: 4091548
durvalumab, with some responses lasting for more than a year. In addition, although ORR was low in the PD-L1 low/negative population, some of these patients did respond and have long durations of response, therefore, I agree with the recommendation that the information regarding the VENTANA PD-L1 (SP263) Assay be included in the durvalumab package insert section 14 as complementary information that can better inform prescribers of the risk/benefit analysis of 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, durvalumab demonstrated an ORR with supportive DOR reasonably likely to predict clinical benefit in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, a population with an advanced, life-threatening, and substantial unmet medical need. The safety profile is acceptable in the intended population and provides an alternative toxicity profile to other chemotherapies used off-label. The benefit-risk profile is favorable to support accelerated approval of durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. I recommend accelerated approval under the provisions of 21CFR601 Subpart E. Continued approval for the indication may be contingent upon verification and description of clinical benefit in the randomized confirmatory trial DANUBE. The applicant agreed to the conduct and submit results from this trial as a post-marketing requirement as per accelerated approval requirements.

The following table is excerpted and edited from the clinical and CDTL reviews:

<table>
<thead>
<tr>
<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. |
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<th>Conclusions and Reasons</th>
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| Current Treatment Options | - There are no products in the USA with regular 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. | Patients receiving conventional chemotherapy generally have a short response duration and substantial toxicity. Atezolizumab and nivolumab may have an improved duration of response compared to historical chemotherapy but are not considered available therapy as are approved under accelerated approval. |
| 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 26.3% in the PD-L1 high group and 4.1% 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 ongoing responses of ≥6 months and 16% (5/31) had ongoing responses of ≥12 months. | ORRs and durable responses are reasonably likely to predict clinical benefit. Patients positive for PD-L1 expression appear to have a higher response rate relative to patients negative for PD-L1 expression and so a complementary diagnostic will be approved at the same time as durvalumab to inform the risk/benefit assessment. Durable responses are observed in both PD-L1 high and low responders. |
| Risk                    | - Tolerated in most study patients  
- Important risks include hepatitis, pneumonitis, endocrine disorders, colitis, infection, and neurological disorders | The profile of adverse reactions associated with durvalumab is similar to that observed in other PD-1 targeted products. Durvalumab offers an alternative toxicity profile to chemotherapies. |
| Risk Management         | - There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.  
- Confirmatory Study DANUBE ongoing | The PI and medication guide will adequately address safety concerns. Durvalumab will be prescribed by oncologists with knowledge of checkpoint inhibitor toxicity. Accelerated approval addresses uncertainty regarding clinical benefit. |
1. Background

Summary of Presubmission/Submission Regulatory Activity
From the CDTL Review:
Study 1108, the key trial supporting this application, was conducted under IND 112249. The urothelial cancer cohort was added in May 2014 and the size of the cohort was increased in November 2015.

Breakthrough Designation was granted in February 2016 for the treatment of pts with PD-L1 positive metastatic or locally advanced urothelial bladder cancer whose tumor has progressed during or after 1 platinum-based regimen. Pre-BLA meetings were held in July 2016 and September 2016. BLA submission was completed October 13, 2016; however, an efficacy update was submitted January 30, 2017.

Intended Population
Excerpted from the clinical and statistical review:

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. 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. In addition, approximately 10% of patients have regionally advanced or metastatic disease at diagnosis.

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 under accelerated approval 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 under accelerated approval 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. The reported median survival of patients after platinum-containing therapy ranges from 5 to 10 months. Clearly, there is an unmet need for patients with this serious and life-threatening disease.

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.
Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma

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<tr>
<th>Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma</th>
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<tr>
<td><strong>Trial Phase</strong></td>
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<td>N</td>
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<tr>
<td>III</td>
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<tr>
<td><strong>Patient Population Regarding Prior Platinum Use Requirement</strong></td>
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<tr>
<td><strong>Objective Response (#Evaluable Patients)</strong></td>
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<td><strong>Overall Response Rate</strong></td>
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<td><strong>Response Duration (mos), median</strong></td>
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<td><em><em>Overall Survival</em>, median</em>*</td>
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<tr>
<td><em><em>Key Safety Issues (Grade 3 or 4 Toxicity)</em> (%)</em>*</td>
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*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.

- e) Per FDA review of BLA 761034
- f) Per FDA review of BLA 125554, Supplement 24

Reference ID: 4091548
2. Product Quality

The following is excerpted and edited from the Product Quality Reviews, and Amendments to the Product Quality Reviews:

The Drug Substance (DS) manufacturer AstraZeneca Pharmaceutical LP underwent pre-license inspection and a 5-item FDA-483 was issued at the conclusion of the inspection, citing inadequate performance qualification of the durvalumab DS container closure; inadequate justification of media hold time; inadequate microbial control during storage; inadequate qualification of QC control growth promotion and sterility testing. The inspection was initially classified VAI; and approval of BLA 761069 was recommended by the inspection team. The firm’s responses to FDA-483 observations have been reviewed by OPF/DIA and deemed adequate. OPF/DIA concurs with the VAI recommendation and recommends approval for BLA 761069.

The Drug Product (DP) manufacture, underwent pre-license inspection that is not the same used during manufacturing of drug products. A four-item FDA Form 483 was issued for: 1) inadequate studies; 2) inadequate QC sample controls; 3) inadequate investigation; and 4) inadequate validation. The findings of the 2/17/17 inspection raised concerns about the adequacy of the firm’s process simulations (media fill program) performed As such, an Official Action Indicated (OAI) recommendation was given and the BLA was initially not recommended for approval. Acceptable resolution of facility inspection observations were deemed necessary for the recommendation of approval. A post-inspection OPF/DMA correspondence with the firm has identified a lack of sterility assurance of the Imfinzi (durvalumab) drug product manufactured at the facility in that the set of product contact equipment used in the production of durvalumab was NOT used during the media fills for lots 019H16, 006E15, and 002M14. Satisfactory resolution of the deficiency was required by product quality before this BLA would be recommended for approval. The firm and Agency communicated multiple times and submitted an updated written RAI response on 4/2/2017.

After review of this response, the deficiencies that lead to the initial withhold recommendation were resolved by the following:

1. OPF/DIA has conducted a PAI review of the 483 observations, EIR/exhibits, firm’s written responses to the FDA-483 and a RAI letter dated 3/23/2017. The firm’s responses and corrective actions to the 483 observations are considered adequate as they have corrected or committed to correct all observed deficiencies. With regards to the deficiency in the media fill program, the firm has committed to performing routine media fill runs with the product contact change parts used in product manufacturing through a rotational program. The worst-case product contact change parts, which are identified through a risk assessment, will be
challenged annually, in addition to their routine media fill runs. The firm also committed to perform one media fill run per product in 2017 for all products that have completed PPQ to date. The first (2) media fill runs were performed for durvalumab\[\textit{(3)}\] The media fill summary report provided by the firm was reviewed by OPF/DIA and deemed acceptable. The \[\textit{(4)}\] facility is now recommended for approval.

The OPF/DIA review is now complete for the PLI at AstraZeneca Pharmaceutical LP (FEI 3002617771) and the facility is recommended for approval. BLA761069 is recommended for approval from a facilities assessment standpoint. The amended DIA facility technical review is located in Panorama.

2. \[\textit{(5)}\] (the DMF No. \[\textit{(6)}\] holder) has provided media fill data conducted over a period of nine hours to support the durvalumab fill process. The durvalumab fill process may occur over a period \[\textit{(5)}\] The DMF holder has provided data from other media fills. However, these media fills do not use durvalumab product contact parts. Thus, the DMF holder has committed to performing a third media fill simulating worst case conditions for the durvalumab aseptic fill process that includes durvalumab product contact parts as an additional PMC. The growth promotion studies and results of this lot will be provided.

\textit{In conclusion, CDER/OPQ now recommends approval of BLA 761069 as noted in the amendment to the OPQ Integrated Review.}

\textit{Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable from the Product Quality Review and Amendment:}

1. Reevaluate the ADA confirmatory and triple mutation assay cut points using a 1.0% false positive rate.

2. Conduct drug tolerance studies for the screening, confirmatory, titering, triple mutation assays that are in the range of the Ct\text{rough} of 182 ng/ml to better demonstrate that the assay can detect ADA in the presence of drug.

3. 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 \textit{E. coli} and/or \textit{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.

4. (additional PMC added by DMA at time of review of additional information) Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies \[\textit{(8)}\] of the media fill. (Note that this post-marketing commitment was communicated to the holder of DMF No. \[\textit{(8)}\])
3. Nonclinical Pharmacology/Toxicology

I agree with the nonclinical pharmacology/toxicology reviewer, Eias Zahalka Ph.D., and the team leader, Todd Palmby, Ph.D., who state “there are no outstanding non-clinical issues that would preclude the approval of Imfinzi for the proposed indication recommend approval for the proposed indication.”

Excerpted from the TL pharmacology/toxicology review:

“Durvalumab is a human IgG1 monoclonal antibody that binds to human PD-L1, thereby inhibiting the interaction of PD-L1 with PD-1 and B7-1 receptors. In order to decrease antibody-dependent cell-mediated cytotoxicity (ADCC), the Applicant modified the heavy chain to eliminate binding to Fc receptors. Based on the submitted pharmacology data, the Established Pharmacologic Class (EPC) of “programmed death-ligand 1 (PD-L1) blocking antibody” was determined to be both clinically meaningful and scientifically valid for durvalumab. Durvalumab is not the first product in this class to be approved in the US.

“General toxicology studies included evaluation of durvalumab in Cynomolgus monkeys for up to 13 weeks. Intravenous (IV) administration of durvalumab caused multi-organ arteritis/periarteritis and inflammatory cell infiltration. The immune-mediated findings were consistent with the role of PD-L1 in regulating and maintaining peripheral tolerance. No effects were observed on the cardiovascular system. Since it is a monoclonal antibody and is not expected to interact with DNA, genetic toxicology studies were not conducted with durvalumab.

“The Applicant submitted a report from an enhanced pre- and postnatal developmental (ePPND) toxicology study with durvalumab in Cynomolgus monkeys conducted to characterize the potential risk of reproductive and developmental toxicity. Durvalumab administration once weekly by IV infusion from gestation to parturition resulted in decreases in the percent of females with normal delivery at ≥ 60/30 mg/kg (approximately 6 times the AUC0-14day at the recommended dose) and an increase in the percent of females with premature delivery (with live offspring) at 200/100 mg/kg (approximately 20 times the AUC0-14 days at the recommended dose). There was also a non-dose related decrease in live birth index, and an increase in the percent of neonatal deaths at 200/100 mg/kg. These data indicate a risk of adverse effects on pregnancy maintenance in animals receiving durvalumab when compared to the concurrent control group. Therefore, the findings in the ePPND study were consistent with the mechanism of action of durvalumab and with the role of the PD-1/PD-L1 pathway in preserving pregnancy by maintaining maternal immune tolerance to the fetus as reported in published literature.

“Durvalumab maintains binding to the FcRn receptor, so fetal exposure may occur if a patient is treated during pregnancy, although it is not recommended. Durvalumab was present in infant monkey serum in the ePPND study indicating the presence of placental transfer. It is unclear whether fetal exposure to durvalumab would occur at levels sufficient to cause adverse effects on the developing immune system. Nevertheless, if a pregnant patient receives treatment with durvalumab that does not result in loss of the fetus, there is a potential risk of developing immune-mediated disorders or altering the normal immune response in the offspring due to the mechanism of action. Based on its mechanism of action, durvalumab
treatment may increase the inflammatory response and enhance the severity of some infections in patients.”

4. Clinical Pharmacology

I agree with the clinical pharmacology team, who state that the BLA is recommended for approval from a clinical pharmacology perspective.

Excerpted from the clinical pharmacology review:

“Mechanism of Action: Durvalumab is a monoclonal antibody (mAb) that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity.

Pharmacokinetics: Durvalumab demonstrated linear PK at dose greater than or equal to 3 mg/kg. Based on data from 1418 patients who received doses of 0.1 mg/kg to 10 mg/kg of durvalumab Q2W, 15 mg/kg of durvalumab for every 3 weeks or 20 mg/kg of durvalumab for every 4 weeks, the population PK analyses show that durvalumab clearance (CL) decreases over time, with a mean maximal reduction (coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%). The following are the geometric mean (CV%) steady-state PK parameter estimates to be included in the labeling.
- Clearance of 8.2 mL/h (37.3%).
- Volume of distribution at steady-state (Vss) of 5.6 L (17.1%).
- Half-life of 17 days (23.2%).
- Time to reach steady-state concentrations was 16 weeks after a dose of 10 mg/kg Q2W and the systemic accumulation based on area under the curve (AUC), was approximately 4.3-fold.

Population Pharmacokinetic Analysis: Population PK analyses showed that the following factors have no clinically significant effects on the PK parameters of durvalumab administrated at the proposed dose: body weight, serum albumin, sex, post-baseline antidrug antibody (ADA), performance status, sPD-L1 level at baseline, creatinine clearance (CLcr), lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, tumor type, age, race, mild and moderate renal impairment (defined as CLcr 30 mL/min to 89 mL/min), and mild hepatic impairment (defined as total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN) and aspartate transaminase ≤ 2.5 × ULN). No dose individualization is recommended for these covariates.

Exposure or Dose-Response Relationship for Efficacy and Safety at 10 mg/kg Q2W: There appears to be no evident E-R relationships identified for safety (such as Grade 3 or greater adverse events (AEs), adverse events of special interest, and AEs leading to discontinuation); however, the event rate for safety was relatively low. The ER analysis is not conclusive for efficacy (i.e., ORR), because the expansion cohort included only one dose level without a comparator.

Immunogenicity: The percentages of evaluable patients who tested positive for ADA were 3.3% (37 of 1124) in Study 1108, and 4.3% (16 of 373) in Study ATLANTIC. The presence of
ADAs did not have a clinically significant impact on PK based on population PK analysis, but their impact on safety or efficacy was not evaluable due to the small number of patient samples testing positive for treatment-emergent ADA and relatively low ORR.

**Drug interaction potential:** No drug interaction studies were conducted. No cytochrome P450 based drug interactions are anticipated as durvalumab is a mAb.

**QT prolongation:** There is no evidence from nonclinical or clinical data to suggest that durvalumab has the potential to delay ventricular repolarization.

**PD-L1 status:** PD-L1 expression was classified as high (45.3%), low (43.8%), or unknown (10.9%) in tumor tissue from patients enrolled in Study 1108 using the finalized assay (N = 128). Although clinical activity was observed across PD-L1 expression subgroups, a higher ORR was observed in the subgroup of patients with high PD-L1 expression (19.0% vs. 3.6% in the low subgroup).

### 5. Clinical Microbiology

See above Product Quality Section for discussion on DP microbiology assessment.

### 6. Clinical/Statistical-Efficacy

*This application is primarily supported by a single-arm, multicenter, open-label, study (CD-ON-MEDI4736-1108) in 182 patients with locally advanced or metastatic urothelial carcinoma. The following is excerpted from the clinical studies section (14) of the agreed upon text in the durvalumab (Imfinzi) package insert regarding the design and efficacy results:*

The efficacy of IMFINZI was evaluated in Study 1, the urothelial cancer cohort of a multicenter, multi-cohort, open-label clinical trial. In Study 1, 182 patients with locally advanced or metastatic urothelial carcinoma were enrolled. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. These patients had initiated durvalumab therapy at least 13 weeks prior to the data cut-off date. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg/day of prednisone or equivalent); history of severe autoimmune disease; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection. All patients received IMFINZI 10 mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. Tumor assessments were performed at Weeks 6, 12 and 16, then every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), and duration of response (DoR).

In Study 1, the median age was 67 years (range: 34 to 88), 72% were male, 64% were Caucasian. Sixty-six percent (66%) of patients had visceral metastasis (bone, liver, or lung), including 34% with liver metastasis. Lymph node only metastasis were present in 13% of patients. Sixty-six percent (66%) of patients had ECOG score of 1 and 41% of patients had a baseline creatinine clearance of <60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in
9% of patients. Twenty percent (20%) of patients had disease progression following platinum-containing neo-adjuvant or adjuvant chemotherapy as their only prior line of therapy. Seventy percent (70%) of patients received prior cisplatin, 30% prior carboplatin and 35% received ≥2 prior lines of systemic therapy.

Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and immune cells (IC) at a central laboratory using the VENTANA PD-L1 (SP263) Assay. Of the 182 patients, 95 were classified as PD-L1 high (if ICs involve >1% of the tumor area, TC ≥25% or IC ≥25%; if ICs involve ≤1% of the tumor area, TC ≥25% or IC=100%), 73 as PD-L1 low/negative (did not meet criterion for PD-L1 high), and samples for 14 patients were not evaluable.

Table 4 summarizes the results in Study 1. The median follow-up time was 5.6 months. In 37 patients who had received only neoadjuvant or adjuvant therapy prior to study entry, nine patients (24%) responded. Among the total 31 responding patients, 14 patients (45%) had ongoing responses of 6 months or longer and five patients (16%) had ongoing responses of 12 months or longer.

### Table 4. Efficacy Results for Study 1

<table>
<thead>
<tr>
<th></th>
<th>All Patients 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>
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<tr>
<td><strong>Objective Response Rate</strong></td>
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<tr>
<td>BICR n (%) (95% CI)</td>
<td>31 (17.0%) (11.9, 23.3)</td>
<td>25 (26.3%) (17.8, 36.4)</td>
<td>3 (4.1%) (0.9, 11.5)</td>
<td>3 (21.4%) (4.7, 50.8)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response</td>
<td>26</td>
<td>22</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Median Duration of Response</strong></td>
<td>NR (0.9+, 19.9+)</td>
<td>NR (0.9+, 19.9+)</td>
<td>12.3 (1.9+, 12.3)</td>
<td>NR (2.3+, 2.6+)</td>
</tr>
</tbody>
</table>

**BICR = Blinded Independent Central Review; NE = Not Evaluable; NR = Not Reached, + denotes a censored value**

### 7. Safety

*The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert:*

The safety data described in Table 2 reflect exposure to IMFINZI in 182 patients with locally advanced or metastatic urothelial carcinoma in Study 1 whose disease has progressed during or after one standard platinum-based regimen. Patients received 10 mg/kg IMFINZI via intravenous infusion every 2 weeks. The median duration of exposure was 10.2 weeks (range: 0.14, 52.4). Thirty-one percent (31%) of patients had a drug delay or interruption for an adverse reaction. The most common (>2%) were liver injury (4.9%), urinary tract infection (3.3%), acute kidney injury (3.3%), and musculoskeletal pain (2.7%). The most common adverse reactions (≥15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%) and...
urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

Eight patients (4.4%) who were treated with IMFINZI experienced Grade 5 adverse events of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. IMFINZI was discontinued for adverse reactions in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (>2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, pyrexia/tumor associated fever (2.7% each).

Immune-mediated adverse reactions requiring systemic corticosteroids or hormone replacement therapy occurred in 8.2% (15/182) patients, including 5.5% (10/182) patients who required systemic corticosteroid therapy and 2.7% (5/182) patients who required only hormone replacement therapy. Seven patients (3.8%) received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients, while Table 3 summarizes the Grade 3 - 4 selected laboratory abnormalities that occurred in ≥1% of patients treated with IMFINZI in Study 1.
Table 2. Adverse Reactions in ≥10% of Patients in UC Cohort Study 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3 - 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Reactions</td>
<td>96</td>
<td>43</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain(^1)</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td><strong>General Disorders and Administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue(^2)</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral edema(^3)</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia/Tumor associated fever</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection(^4)</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite/Hypophagia</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain(^5)</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/Exertional Dyspnea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Cough/Productive 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(^6)</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\) Includes abdominal pain upper, abdominal pain lower and flank pain  
\(^2\) Includes asthenia, lethargy, and malaise  
\(^3\) Includes edema, localized edema, edema peripheral, lymphedema, peripheral swelling, scrotal edema, and scrotal swelling  
\(^4\) Includes cystitis, candiduria and urosepsis  
\(^5\) Includes back pain, musculoskeletal chest pain, musculoskeletal pain and discomfort, myalgia, and neck pain  
\(^6\) Includes dermatitis, dermatitis aciform, dermatitis psoriasiform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus
Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in
≥1% Patients in UC Cohort Study 1

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grade 3 - 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>12</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>4</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1</td>
</tr>
</tbody>
</table>

The following Warnings and Precautions were included in the Package Insert:

5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids.

In Study 1 (n=182), one patient (0.5%) died from immune-mediated pneumonitis. In the combined safety database (n=1414), of patients treated with IMFINZI 10 mg/kg every 2 weeks, immune-mediated pneumonitis occurred in 32 (2.3%) patients including fatal pneumonitis in one (0.1%) patient and Grade 3-4 in six (0.4%) patients. The median time to onset was 55.5 days (range: 24-423 days). Seventeen (1.2%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was interrupted in 12 patients and discontinued in five (0.4%) patients. Resolution occurred in 18 (1.3%) patients.

5.2 Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in patients receiving IMFINZI. Monitor patients for abnormal liver tests each cycle during treatment with IMFINZI. Manage immune-mediated hepatitis with treatment modifications and corticosteroids.

In Study 1, one (0.5%) patient died from immune-mediated hepatitis. An additional two (1.1%) patients experienced immune-mediated hepatitis, including Grade 3 in one (0.5%) patient. In the combined safety database, immune-mediated hepatitis occurred in 16 (1.1%) patients including fatal hepatitis in one (<0.1%) patient and Grade 3 in nine (0.6%) patients.
The median time to onset was 51.5 days (range: 15-312 days). Twelve (0.8%) of the 16 patients received high-dose corticosteroid treatment. One patient also received mycophenolate treatment. IMFINZI was interrupted in five (0.3%) patients and discontinued in three (0.2%) patients. Resolution occurred in nine (0.6%) patients. In the combined safety database, Grade 3 or 4 elevations in ALT occurred in 40/1342 (3.0%) of patients, AST in 58/1336 (4.3%), and total bilirubin in 37/1341 (2.8%) of patients.

5.3 Immune-Mediated Colitis
Immune-mediated colitis or diarrhea occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of colitis or diarrhea and manage with treatment modifications, anti-diarrheal agents, and corticosteroids.
In Study 1, colitis or diarrhea occurred in 23 (12.6%) patients including Grade 3 or 4 diarrhea in two (1.1%) patients. No patients in Study 1 received systemic corticosteroids or immunosuppressants for diarrhea or colitis. In the combined safety database, immune-mediated colitis or diarrhea occurred in 18 (1.3%) patients including Grade 4 in one (<0.1%) and Grade 3 in four (0.3%) patients. The median time to onset was 73 days (range: 13-345 days). Of these patients, one (<0.1%) had Grade 4 and four (0.3%) had Grade 3 immune-mediated colitis or diarrhea. Ten (0.7%) of the 18 patients received high-dose corticosteroid treatment. Two (0.1%) patients received non-steroidal immunosuppressants. IMFINZI was interrupted in five (0.4%) patients and discontinued in six (0.4%) patients. Resolution occurred in 11 (0.8%) patients.

5.4 Immune-Mediated Endocrinopathies
Immune-related thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism have occurred in patients receiving IMFINZI. Monitor patients for clinical signs and symptoms of endocrinopathies.

Thyroid Disorders
Monitor thyroid function prior to and periodically during treatment with IMFINZI. Asymptomatic patients with abnormal thyroid function tests can receive IMFINZI. Manage patients with abnormal thyroid function tests with hormone replacement (if indicated) and treatment modifications.
In the Study 1, hypothyroidism or thyroiditis leading to hypothyroidism occurred in ten (5.5%) patients. All patients had Grade 1-2 hypothyroidism. The median time to first onset was 42 days (range: 15-239). Thyroid stimulating hormone (TSH) was elevated and above the patient’s baseline in 25 (15.3%) of 163 patients with a follow-up measurement.
In Study 1, hyperthyroidism or thyroiditis leading to hyperthyroidism occurred in nine (4.9%) patients. All patients had Grade 1-2 hyperthyroidism. The median time to first onset was 43 days (range: 14-71). Thyroid stimulating hormone (TSH) was decreased and below the patient’s baseline in 26 (16%) of 163 patients with a follow-up measurement.
In the combined safety database, hypothyroidism occurred in 136 (9.6%) patients, while hyperthyroidism occurred in 81 (5.7%) patients. Thyroiditis occurred in ten patients, including Grade 3 in one patient who had a myocardial infarction. In nine patients with thyroiditis, transient hyperthyroidism preceded hypothyroidism. Treatment with a beta-blocker and/or thioamide was administered for hyperthyroidism in five of these patients.
Adrenal Insufficiency
Monitor patients for clinical signs and symptoms of adrenal insufficiency. Administer corticosteroids and hormone replacement as clinically indicated. In Study 1, adrenal insufficiency occurred in one (0.5%) patient (Grade 1). In the combined safety database, adrenal insufficiency occurred in 13 (0.9%) patients, including Grade 3 in two (0.1%) patients. Seven (0.5%) of these patients were treated with systemic corticosteroids.

Type 1 Diabetes Mellitus
Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate insulin for type 1 diabetes mellitus and manage patients with treatment modifications. New onset type 1 diabetes mellitus without an alternative etiology occurred in one patient (<0.1%) in the combined safety database.

Hypophysitis
Monitor for signs and symptoms of hypophysitis or hypopituitarism. Administer corticosteroids and hormone replacement as clinically indicated. Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in one patient (<0.1%) in the combined safety database.

5.5 Other Immune-Mediated Adverse Reactions
IMFINZI has caused immune-mediated rash. Other immune-related adverse reactions, including aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in ≤1.0% of patients treated with IMFINZI.

Immune-mediated Rash
Monitor for signs and symptoms of rash. In Study 1, 20 (11.0%) of patients developed rash including Grade 3 rash in one (0.5%) patient. In the combined safety database, 220 (15.6%) patients developed rash and four (0.3%) patients developed vitiligo. Systemic corticosteroids were administered in 17 (1.2%) patients. The rash resolved in 133 (9.4%) patients.

Immune Thrombocytopenic Purpura
Monitor patients for signs and symptoms of immune thrombocytopenic purpura. In the combined safety database, immune thrombocytopenic purpura led to death in one (<0.1%) patient. The patient received high-dose corticosteroids, human immunoglobulin, and rituximab.

Nephritis
Monitor patients for abnormal renal function tests prior to and each cycle during treatment with IMFINZI and manage with treatment modifications and corticosteroids. In Study 1, one patient received systemic corticosteroids for immune-mediated nephritis. In the combined safety database, immune-mediated nephritis occurred in three (0.2%) patients including Grade 3 in two (0.1%) patients. All three patients received high-dose corticosteroids treatment. IMFINZI was discontinued in all three patients. Resolution occurred in all three patients.

5.6 Infection
Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of infection and treat with anti-infectives for suspected or confirmed infections. Withhold IMFINZI for ≥Grade 3 infection.
In Study 1, infections occurred in 54 (29.7%) patients. Grade 3 or 4 infection occurred in eleven (6.0%) patients, while five (2.7%) patients were experiencing infection at the time of death. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in eight (4.4%) patients. In the combined safety database, infections occurred in 531 (37.6%) patients.

5.7 Infusion-Related Reactions

Severe infusion-related reactions have been reported in patients receiving IMFINZI. Monitor for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue IMFINZI in patients with Grade 3 or 4 infusion reactions.

Infusion related reactions occurred in three (1.6%) patients in Study 1 and 26 (1.8%) patients in the combined safety database. There were five (0.4%) Grade 3 and no Grade 4 or 5 reactions. Four (0.3%) patients developed urticaria within 48 hours of dosing.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI.

8. Advisory Committee Meeting

This application was not referred to a meeting of the Oncologic Drugs Advisory Committee as the application did not raise significant safety or efficacy issues that required the advice of the ODAC to make a risk-benefit assessment of durvalumab in this patient population.

9. Pediatrics

A pediatric waiver was granted by the PeRC.

10. Other Relevant Regulatory Issues

See Product Quality Section above for full discussion of regulatory issues surrounding the facilities assessments and inspections and media fill issues.

The Applicant and 3 clinical sites were inspected. Significant issues were found at Dr. O’Donnell’s site at the University of Chicago; the final classification of the inspection was voluntary action indicated. On inspection, it was found that some AEs in the source documents
were not reported on the CRFs and that several pts withdrew consent after study drug discontinuation. This limited follow up of late AEs and deaths. If the 8 pts with urothelial cancer enrolled at this site are not included in the analysis of AEs, the incidence of grade 1-4 AEs becomes 172/174 (99%) and grade 3-4 AEs becomes 92/174 (53%). These are identical to the incidence of grade 1-4 and grade 3-4 in all 182 pts. And therefore it is not thought the clinical site inspection issues impacted the overall results or interpretation of the study.

**Device:**
The Applicant partnered with Ventana to develop an assay to detect PD-L1 staining in formalin-fixed paraffin embedded tumor samples by immunohistochemical staining and assessment. This assay, VENTANA PD-L1 (SP263), evaluates PD-L1 staining in both tumor cells and immune cells. The Applicant states that the PD-L1 expression cutoff 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. Durvalumab will be approved with a complementary diagnostic for PD-L1 staining of tumor specimens given that the response rate differs between patients with high and low/negative PD-L1 status, however as described above in the efficacy section, patients with low/negative status still have responses, some durable. Therefore it is not thought that the device is essential for the safe and effective use of the product but rather that is informs the risk/benefit analysis.

**11. Labeling**

Agreement has been reached on the labeling.

The proposed indication was as follows:

```
Treatment of patients with locally advanced or metastatic urothelial carcinoma
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The final indication is as follows:

```
IMFINZI is 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.
```

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
The efficacy (14) and safety (5, 6.1) sections of the package insert are discussed in prior sections of this review.

12. Postmarketing

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.

The following postmarketing requirement is as follows:

3205-1 Submit the final report with datasets and labeling for the clinical trial entitled “A Phase III, Randomized, Open-label, Controlled, Multi-center, Global Study of First-line MEDI4736 Monotherapy and MEDI4735 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer.”

Trial Completion: 09/2019
Final Report Submission: 03/2020

The following postmarketing commitments are as follows:

3205-2 Conduct updated analyses of the duration of response for the patients with urothelial cancer who had received prior platinum-based therapy (N = 182) in the clinical trial entitled “A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors.” Present the median and updated information on the range of the duration of response for all patients, patients whose tumor have high PD-L1 staining, and patients whose tumors have low PD-L1 staining. Submit the final report with datasets and labeling.

Trial Completion: 12/2017
Final Report Submission: 06/2018

3205-3 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.

Study Completion: 07/2017
Final Report Submission: 01/2018
Other: Study results will be submitted as a CBE-0 01/2018
3205-4  Reevaluate the anti-drug antibody confirmatory and triple mutation assay cut points using a 1.0% false positive rate.

Study Completion: 10/2017
Final Report Submission: 04/2018

3205-5  Conduct drug tolerance studies for the screening, confirmatory, titering, and triple mutation assays that are in the range of the trough concentration of 182 μg/ml to better demonstrate that the assay can detect anti-drug antibodies in the presence of drug.

Study Completion: 12/2017
Final Report Submission: 06/2018

3205-6  Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies of the media fill.

Final Report Submission: 09/2017
Other: Study results will be submitted as a DMF update

13. Office Director Conclusion

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Beaver, Maher, and Suzman, who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

My signature below also represents the approval decision of this application under CDER.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-------------------------------
JULIA A BEAVER
05/01/2017

RICHARD PAZDUR
05/01/2017