

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761069Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	BLA
<b>Application Number</b>	761069
<b>PDUFA Goal Date</b>	June 13, 2017
<b>OSE RCM #</b>	2016-2456, 2016-2537
<b>Reviewer Name(s)</b>	Mei-Yean Chen, Pharm.D.
<b>Acting Team Leader</b>	Doris Auth, Pharm.D., Associate Director (Acting)
<b>Division Director</b>	Cynthia LaCivita, Pharm.D.
<b>Review Completion Date</b>	March 7, 2017
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Durvalumab
<b>Trade Name</b>	Imfinzi
<b>Name of Applicant</b>	AstraZeneca
<b>Therapeutic Class</b>	Programmed Death Ligand-1 (PD L-1) blocking antibody
<b>Formulation(s)</b>	500 mg and 120 mg vials
<b>Dosing Regimen</b>	10 mg/kg given as an intravenous infusion every 2 weeks

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## EXECUTIVE SUMMARY

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Imfinzi (durvalumab) is necessary to ensure the benefits of this product outweigh its risks. AstraZeneca submitted a Biologic Licensing Application (BLA) 761069 for durvalumab with the proposed indication 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 will be 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 serious risks associated with the use of durvalumab include immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated colitis, immune-mediated endocrinopathies, immune-mediated nephritis, and infection. The applicant did not submit a proposed REMS or risk management plan with this application.

Platinum-based combination chemotherapy is the standard approach for the initial treatment of patients with locally advanced or metastatic urothelial cancer. Although initial response rates are around 46-49%, the median survival with multi-agent chemotherapy is approximately 15 months. The 5 year survival rate of stage IV bladder cancer is about 15% which demonstrates that metastatic bladder cancer remains an area of unmet need. Second-line chemotherapy has a limited role in the treatment due to low response rate and considerable toxicities. Checkpoint inhibitor immunotherapy offers an additional option for patients progressing after the initial chemotherapy.

Two other Programmed Death-Ligand 1 (PD-L1) inhibitors with similar risks, atezolizumab (approved May 2016) and nivolumab (approved February 2017) are approved 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

Similar to atezolizumab and nivolumab the risks of severe immune-mediated adverse events including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated colitis and immune-mediated endocrinopathies will be communicated through labeling

DRISK and the Division of Oncology Products 1 (DOP1) agree that a REMS is not needed to ensure the benefits of durvalumab outweigh its risks.

## 1. Introduction

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Imfinzi (durvalumab) is necessary to ensure the benefits of this product outweigh its risks. AstraZeneca submitted a Biologic Licensing

Application (BLA 761069) for durvalumab with the proposed indication 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 application is under review in the Division of Oncology Products 1 (DOP1). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

### 2.1 PRODUCT INFORMATION

Imfinzi (durvalumab BLA 761069), a new molecular entity (NME)<sup>a</sup>, is a human Programmed Death-Ligand 1 (PD-L1) blocking antibody. The applicant proposed the following indication: treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

(b) (4) DOP1 revised the indication to 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.

PD-L1 can be expressed by tumors to evade detection by the immune system through binding to PD-1 on cytotoxic T lymphocytes. Durvalumab blocks the PD-L1 interaction with PD-1,<sup>1</sup> countering the tumor's immune-evading tactics. The proposed dose of durvalumab is 10 mg/kg given as an intravenous (IV) infusion over 60 minutes every 2 weeks until confirmed disease progression or unacceptable toxicity.<sup>b</sup> Durvalumab is not currently approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for durvalumab (BLA 761069) relevant to this review:

- February 16, 2016: Breakthrough designation granted (IND (b) (4))
- July 29, 2016: Rolling review granted (IND (b) (4))
- July 29, 2016: BLA 761069, Rolling Submission First Wave submitted
- October 13, 2016: BLA 761069, Rolling Submission Final Wave submitted
- December 8, 2016: Priority Review granted
- January 23, 2016: A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for durvalumab. There are no plans for an Advisory Committee meeting at this time.

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<sup>a</sup> Section 505-1 (a) of the FD&C Act FDAAA factor (F): Whether the drug is a new molecular entity.

<sup>b</sup> Section 505-1 (b) of the FD&C Act FDAAA factor (D): The expected or actual duration of treatment with the drug

### 3. Therapeutic Context and Treatment Options

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#### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

The most common type of bladder cancer or urothelial carcinoma, is transitional cell carcinoma, which begins in urothelial cells that line the inside of the bladder. Urothelial cells are transitional cells, which are able to change shape and stretch when the bladder is full. In the United States, transitional cell carcinoma represents the vast majority (over 90%) of bladder cancers. Other types of bladder cancer include squamous cell carcinoma (about 2-7%) and adenocarcinoma (about 2%).

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 the time of diagnosis.<sup>b</sup>

Bladder cancer is the sixth most common cancer in the United States after lung cancer, prostate cancer, breast cancer, colon cancer, and lymphoma. It is the third most common cancer in men and the eleventh most common cancer in women. Bladder cancer is typically diagnosed in older individuals, with a median age at diagnosis of 69 years in men and 71 in women. The estimated number of new cases and deaths from bladder cancer in the United States in 2017 are 79,030 and 16,870, respectively.<sup>2,c</sup>

#### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Platinum-based combination chemotherapy is the standard approach for the initial treatment of patients with locally advanced or metastatic urothelial cancer. Although initial response rates are 49% for gemcitabine plus cisplatin (GC) and 46% for methotrexate/vinblastine/oxorubicin/cisplatin (MVAC) respectively,<sup>3</sup> the median survival with multi-agent chemotherapy is approximately 15 months. The 5 year survival rate of stage IV bladder cancer is about 15% which demonstrates that metastatic bladder cancer remains an area of great unmet need.

Second-line conventional chemotherapy has had only a limited role in treatment due to low response rate (around 14-32%)<sup>4</sup> and considerable toxicities. However, checkpoint inhibitor immunotherapy offers an additional option for patients progressing after the initial chemotherapy. The indication, dosing, safety and risk management for the two FDA approved PD-L1 inhibitors are described in Table 1:

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<sup>b</sup> Section 505-1 (a) of the FD&C Act FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

<sup>c</sup> Section 505-1 (a) of the FD&C Act FDAAA factor (A): The estimated size of the population likely to use the drug involved.

**Table 1: Summary of FDA-Approved PD-L1 inhibitors Relevant to Proposed Indication**

Product Generic name Year of Approval	Indication for the treatment of patients with	Dosing and Administration	Important Safety and Tolerability Issues Warnings & Precautions	Risk Management Approaches/Boxed Warning, Medication Guide
Tecentriq (atezolizumab) 2016 <sup>5</sup>	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	1200 mg intravenously every 3 weeks	Severe immune-mediated adverse events  <ul style="list-style-type: none"> <li>• pneumonitis</li> <li>• Hepatitis</li> <li>• Colitis</li> <li>• Endocrinopathies</li> <li>• Myasthenic Syndrome/Myasthenia Gravis</li> <li>• Pancreatitis</li> </ul> Ocular Inflammatory toxicity, Infection, Infusion reaction, and embryo-fetal toxicity	No boxed warning Medication Guide
Opdivo (nivolumab) Feb. 2017 <sup>6</sup>	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	240 mg intravenously every 2 weeks	Severe immune-mediated adverse events  <ul style="list-style-type: none"> <li>• Pneumonitis</li> <li>• Colitis</li> <li>• Hepatitis</li> <li>• Endocrinopathies</li> <li>• Nephritis and renal dysfunction</li> <li>• Skin adverse reactions</li> <li>• Encephalitis</li> </ul> Infusion reaction, Complication of allogeneic hematopoietic stem cell transplantation and embryo-fetal toxicity	No boxed warning Medication Guide

## 4. Benefit Assessment<sup>1</sup>

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The Study 1 is the pivotal trial supporting this application, consisted of a multicenter, multi-cohort, open-label clinical trial. Enrolled in Study 1 were 182 patients with locally advanced or metastatic urothelial carcinoma that 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. All patients received durvalumab 10 mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. The primary efficacy endpoint was Objective Response Rate (ORR) according to Response Evaluation Criteria In Solid Tumor (RECIST) as assessed by Blinded Independent Central Review. An additional efficacy endpoint included Duration of Response (DoR). The ORR was 17%<sup>4</sup> and the median DoR was not reached. The median follow-up time was 5.6 months. The ORR of durvalumab is consistent with the ORR of atezolizumab (14.8%) and the ORR of nivolumab (19.6%). The clinical reviewer concluded that the Applicant provided evidence of effectiveness based ORR.<sup>d</sup>

## 5. Risk Assessment<sup>e</sup>

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### 5.1 SERIOUS ADVERSE REACTIONS<sup>1</sup>

The serious adverse reactions that are associated with durvalumab therapy are:

- Immune-mediated pneumonitis: In Study 1 (n=182), one patient (0.5%) died from immune-mediated pneumonitis. In the combined safety database (n=1414), in patients treated with durvalumab monotherapy, immune-mediated pneumonitis occurred in 32 (2.3%) patients, including Grade 3-4 in 6 patients, and fatal pneumonitis in one patient. Seventeen patients received high-dose corticosteroid treatment. Durvalumab was interrupted in 12 patients and discontinued in 5 patients. Resolution occurred in 18 patients.
- Immune-mediated hepatitis: In study 1 (n=182), 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%) patients. In the combined safety database (n=1414), immune-mediated hepatitis was fatal in one (<0.1%) patient and occurred in an additional 16 (1.1%) patients, including Grade 3 in 9 (0.6%) patients. Twelve (0.8%) of the 16 patients received high-dose corticosteroid treatment. One patient also received mycophenolate treatment. Durvalumab was interrupted in 5 (0.3%) patients and discontinued in 3 (0.2%) patients. Resolution occurred in 9 patients. In the combined safety database, Grade 3 or 4 elevations in ALT occurred in 3.1% of patients, AST in 4.3%, and total bilirubin in 2.8% of patients.

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<sup>d</sup> Section 505-1 (a) of the FD&C Act FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

<sup>e</sup> Section 505-1 (a) of the FD&C Act FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

- Immune-mediated colitis: In Study 1 (n=182), colitis or diarrhea occurred in 23 (13%) patients. Two (1.1%) patients developed Grade 3 or 4 diarrhea. No patients in Study 1 received systemic corticosteroids or immune-suppressants for diarrhea or colitis. In the combined safety database (n=1414), immune-mediated colitis or diarrhea occurred in 18 (1.3%) patients. Of these patients, one (0.1%) had Grade 4 and four (0.3%) had Grade 3 immune-mediated colitis or diarrhea. Ten of the 18 patients received high-dose corticosteroid treatment. Two patients received non-steroidal immune-suppressants.
- Immune-mediated endocrinopathies:
  - Thyroid disorders: In the Study 1 (n=182), hypothyroidism or thyroiditis occurred in 10 (5.5%) patients. All patients had Grade 1-2 hypothyroidism. Hyperthyroidism or thyroiditis occurred in 9 (4.9%) patients. All patients had Grade 1-2 hyperthyroidism. In the combined safety database (n=1414), hypothyroidism or thyroiditis occurred in 128 (9.1%) patients, while hyperthyroidism or thyroiditis occurred in 82 (5.8%) patients.
  - Adrenal insufficiency : In Study 1 (n=182), immune-mediated adrenal insufficiency occurred in 1 (0.5%) patient (Grade 1). In the combined safety database (n=1414), adrenal insufficiency occurred in 13 (0.9%) patients, including 2 (0.1%) patients with Grade 3 adrenal insufficiency. Seven (0.5%) of these patients were treated with corticosteroids.
  - Diabetes Mellitus: New onset diabetes mellitus without an alternative etiology occurred in one patient (<0.1%) in the combined safety database.
  - Hypophysitis: Hypophysitis leading to diabetes insipidus occurred in 1 patient (<0.1%) in the combined safety database.
- Other Immune-mediated adverse reactions including rash, aseptic meningitis, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in less than 1% of patients treated with durvalumab. In the combined safety database, immune thrombocytopenic purpura led to death in one (<0.1%) patient despite the patient having received high-dose corticosteroids, human immunoglobulin, and rituximab. In study 1, one patient received systemic corticosteroids for immune-mediated nephritis. In the combined safety database, immune-mediated nephritis occurred in two (0.1%) patients including Grade 3 in one (<0.1%) patient. Both patients received high-dose corticosteroids treatment. Durvalumab was discontinued in 2 patients. Resolution occurred in 2 patients.

Infections: In Study 1, infections occurred in 54 (30%) patients. Grade 3 or 4 infection occurred in 11 (6%) patients, while 5 (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 8 (4.4%) patients. In the combined safety database, infections occurred in 531 (38%) patients.

Infusion Related Reactions: In Study 1, Infusion related reactions occurred in 2 (1.1%) patients. In the combined safety database, Infusion related reactions occurred in 26 (1.8%) patients. Of 26 patients, there were 5 (0.4%) Grade 3 and no Grade 4 or 5 reactions. Four (0.3%) patients developed urticaria within 48 hours of dosing.

Embryofetal Toxicity: Based on its mechanism of action, durvalumab may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with durvalumab and at least 4 months after the last dose of durvalumab.

## **6. Expected Postmarket Use**

Durvalumab will be administered in the inpatient and outpatient infusion settings and the likely prescribers will be oncologists. Durvalumab therapy will be under the supervision of healthcare providers.

## **7. Risk Management Activities Proposed by the Applicant**

The Applicant did not propose any risk management activities for durvalumab beyond routine pharmacovigilance and labeling. The proposed labeling communicates the adverse reactions (ARs) of immune-mediated reactions, infection, infusion-related reactions and embryo-fetal toxicity in section 5 Warnings and Precautions. In addition, Section 2.2 “Dose Modifications” “Recommended Treatment Modifications for durvalumab” illustrates how to use dose interruption and/or discontinue for immune-mediated reactions, infection, and infusion-related reactions.

## **8. Discussion of Need for a REMS**

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The Clinical Reviewers recommend approval of durvalumab on the basis of the efficacy and safety information currently available.<sup>4</sup>

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for durvalumab, DRISK considers patient population size, seriousness of the disease, expected benefit of the drug, the expected duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity.

Locally advanced or metastatic urothelial carcinoma is a serious disease. Platinum-based regimens are first line treatment. Although initial response rates are 46-49%,<sup>1</sup> the median survival with multi-agent chemotherapy is approximately 15 months, and the 5 year survival rate for metastatic disease is only about 15% with more than 15,000 deaths per year in the United States. These data demonstrates that the treatment of metastatic bladder cancer remains an area of unmet need.

Second-line conventional chemotherapy has had only a limited role in treatment, but checkpoint inhibitor immunotherapy offers an additional option for patients progressing after the initial chemotherapy. The FDA approved the PD-L1 checkpoint inhibitors atezolizumab in May 2016 and nivolumab (new indication to treat urothelial carcinoma) in February 2017.

The medical reviewer concluded the Objective Response Rate (ORR), the primary efficacy endpoint, of durvalumab treatment is 17%. This ORR is consistent with the ORRs of atezolizumab and nivolumab. The anticipated duration of use for durvalumab is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

The serious adverse reactions (ARs) of durvalumab are immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, and nephritis. Additional serious risks include infection, infusion related reactions, and embryo-fetal toxicity. The most concerning ARs associated with durvalumab therapy are the immune-mediated, though these ARs are consistent with the AR profile seen in other PD-L1 agents, such as atezolizumab and nivolumab. The monitoring, evaluation, and management of ARs are communicated in proposed labeling in Section 2.2 Dose Modifications and Section 5 Warnings and Precautions. Immune-mediated ARs are managed by administering corticosteroid and/or immune-suppressants, withholding treatment, or discontinuing therapy.

Durvalumab will likely be provided in treatment centers and its use will be under the supervision of healthcare providers who are expected to be familiar with the risks and management ARs of PD-L1 inhibitors.

## 9. Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for durvalumab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10. References

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3. Von der Maase H, Hansen SW, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large randomized, multinational, multicenter, phase III study. *J Clin Oncol.* 2000; 18(17): 3068
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8. Astra-Zeneca. BLA 761069, Clinical Overview for durvalumab, October 12, 2016.

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MEI-YEAN T CHEN  
03/07/2017

CYNTHIA L LACIVITA  
03/07/2017  
Concur