CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761069Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 26, 2016
From	Virginia Ellen Maher, M.D.
Subject	Durvalumab
NDA/BLA # Supplement#	761069/0
Applicant	AstraZeneca UK Limited
Date of Submission	October 13, 2016
PDUFA Goal Date	June 13, 2017
Proprietary Name / Established (USAN) names	Imfinzi/durvalumab
Dosage forms / Strength	Injection/500 mg per 10 mL vial and 120 mg per 2.4 mL vial
Proposed Indication(s)	Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)
Recommended:	Approval

1. Introduction

On October 13, 2016, the Applicant submitted a Biologics License Application for durvalumab for the following indication:

> Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

This supplement is supported by:

Safety and efficacy data in patients with urothelial cancer who have received platinum-based therapy using an October 24, 2016 cutoff from:

- **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)

Safety data based on April 29, 2016 and July 24, 2016 cutoffs from:

- **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 = 970, including urothelial cancer pts)

- **D4191C00003:** A Phase 2 Non-comparative Open-label Multi-center, International Study of MEDI4736 in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen (N = 444)

2. Background

Durvalumab

Durvalumab is a human IgG1κ monoclonal antibody that binds to programmed death ligand-1 (PD-L1). It has been engineered to have reduced antibody dependent cytotoxicity and complement fixation. In vitro studies suggest that a durvalumab concentration of 3 μg/mL is able to activate T cells.

Normally, binding of the receptor, PD-1 (programmed death protein 1) on activated T cells by PD-L1 provides a negative signal to the T cell and dampens the immune response. Cancer cells can also express PD-L1 and can evade the immune system by binding PD-1 and inhibiting the immune response. Binding of durvalumab to PD-L1 on cancer cells could prevent this negative interaction, allowing the immune system to remain active. Note in addition to cancer cells, PD-L1 is also found on resting T cells, B cells, dendritic cells, macrophages, vascular endothelial cells, pancreatic islet cells, and on respiratory epithelial cells (Sci Rep 2015 5:13110, J Infect Dis 2006 193:404).

Treatment of Urothelial Cancer

The current application is for the treatment of patients (pts) with metastatic or locally advanced urothelial cancer who have disease progression following a platinum-based regimen. The platinum-based regimen may be given for metastatic disease or in the neoadjuvant/adjuvant setting. To be eligible for Study 1108, pts must have relapsed within 1 year of completion of neoadjuvant/adjuvant therapy. The 1 year time point was chosen because pts who develop metastatic disease several years after completion of a neoadjuvant/adjuvant platinum-containing regimen often benefit from additional platinum-based therapy. Atezolizumab received accelerated approval for this indication on May 18, 2016. Approval was based on a response rate (RR) of 14.8% with a prolonged duration of response. Nivolumab also received accelerated approval for this indication on February 2, 2017. Approval was based on a RR of 19.6% with a median duration of response of 10.3 months.

In addition to these two agents, several drugs are used off-label for this indication. Single-agent chemotherapeutic agents used in this setting include docetaxel, paclitaxel, and albumin-bound paclitaxel. Response rates range from 9-28% (J Clin Oncol 2012 30:507, Clin Genitourin Cancer 2009 7:E28, Lancet Oncol 2013 14:769). In the European Union, vinflunine is approved for use in pts with 2nd-line urothelial cancer on the basis of a non-significant improvement in overall survival (OS). The RR of vinflunine was 9% (J Clin Oncol 2009 27:4454). Combination chemotherapy is also used in the treatment of pts with 2nd-line urothelial cancer. The RR is higher with combination therapy (compared to single agents), but these regimens are associated with substantial toxicity.

Regulatory History

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. (b) (4)

(b) (4)

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.

3. CMC/Device

Durvalumab Manufacture

(b) (4)

Ventana PD-L1 (SP263)

The Applicant has 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 evaluates PD-L1 staining in both tumor cells and immune cells. The Applicant states that the PD-L1 expression cutoff was defined following analysis of the first 20 urothelial cancer patients enrolled on Study 1108. The current definition of high and low PD-L1 staining (see below) was applied after Amendment 8.

4. Nonclinical Pharmacology/Toxicology

In tissue cross reactivity studies, durvalumab bound to human monocytes, trophoblastic epithelium, and the pituitary epithelium. Four and 13 week repeat dose nonclinical toxicology studies found a reversible decrease in thymic size and a decrease in lymph node cellularity. Rash, acute tubular necrosis, and intra-renal thrombi were also seen. No genotoxicity or carcinogenicity studies were conducted. Enhanced pre-and postnatal development studies in cynomolgus monkeys found increased premature delivery, fetal loss, and premature neonatal death at durvalumab levels 20 times the human AUC. No maternal toxicity, effects on embryofetal development, pregnancy, or effects on infants during the 6 month postnatal period were seen.

5. Clinical Pharmacology/Biopharmaceutics

Durvalumab has been administered at 0.1 to 20 mg/kg. The dose used in patients with urothelial cancer is 10 mg/kg intravenously every 2 weeks. Below 3 mg/kg the pharmacokinetics of durvalumab is nonlinear. It is likely that this is due to binding to PD-L1. 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 ~ 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. There was no exposure-response rate effect in the urothelial cancer cohort and no exposure-adverse event (including adverse events of special interest) effect in the safety database.

Anti-therapeutic antibodies (ATA) were found in 37/1124 (3.3%) pts who received durvalumab 10 mg/kg. Neutralizing antibodies were found in 2 pts. However, the current assay for the detection of neutralizing antibodies may not detect all of the pts who develop neutralizing antibodies and additional work on this assay will be included as a postmarketing commitment. Two AEs that were temporally associated with the development of an ATA include an infusion reaction and wheezing/fever. None of the pts with urothelial cancer who had ATAs had a response.

Changes in the QT interval were studied in 265 pts with NSCLC receiving durvalumab 10 mg/kg every 2 weeks. No relationship between durvalumab concentration and a change in QTcF was seen.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

This submission is supported by a single study of safety and efficacy and a large safety database. Safety and efficacy data for pts with urothelial cancer previously treated with a platinum-based regimen, using a data cutoff of October 24, 2016, comes from:

- **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)

Study Design

Study 1108 included a dose escalation and dose exploration phase that did not enroll pts with urothelial cancer. It included several dose expansion cohorts, one of which enrolled pts with urothelial cancer. Patient had locally advanced or metastatic transitional cell (or mixed) carcinoma of the bladder, ureter, urethra, or renal pelvis. Measurable disease was required. The protocol initially enrolled pts who had received or refused 1st-line therapy. It was later amended to enroll patients who had received 1-2 prior lines of systemic therapy, including a platinum-based regimen. Patients who received prior neoadjuvant or adjuvant therapy were eligible if they progressed within 12 months of surgery (neoadjuvant) or completion of adjuvant therapy. Requirements for PD-L1 tumor staining changed during the course of the study. Initially, pts were enrolled regardless of PD-L1 staining and their tumor specimens were used to develop the

PD-L1 assay. Later, tumor cell staining for PD-L1 ≥ 5% was required. The final group of pts, N = 128, was enrolled regardless of PD-L1 staining and the final PD-L1 assay (and final definition of PD-L1 high and low) was used.

During the course of the study, the Applicant examined data from the first 20 pts and defined PD-L1 high and low as:

- PD-L1 high: tumor or immune cell staining ≥ 25%;
- PD-L1 low: tumor or immune cell staining < 25%; and
- If immune cells infiltrate ≤ 1% of the tumor area:
  - PD-L1 high is defined as tumor cell staining ≥ 25% or immune cell staining 100%.
  - PD-L1 low is defined as tumor cell staining < 25% or immune cell staining < 100%.

Durvalumab 10 mg/kg was given intravenously over 2 hour every 2 weeks for 12 months. Durvalumab could be permanently discontinued or delayed, but the dose could not be modified. Patients with confirmed disease progression could discontinue study drug. However, pts thought to be deriving benefit could continue beyond confirmed progression. Further, pts who completed 12 months and developed disease progression off treatment could be retreated with durvalumab.

Laboratories, including CBC, chemistries, urinalysis, coagulation parameters, and thyroid function tests, were obtained at baseline and with each dose. A CBC was also obtained on Day 10. An EKG was done at baseline and every 12 weeks. Anti-therapeutic antibody levels were obtained at baseline and prior to doses 3, 7, and 13. Tumor measurements were obtained at baseline, Weeks 7, 12, and 16 and then every 8 weeks. After discontinuation of durvalumab, end of treatment assessments were to occur at 30 and 90 days. A CBC, ATA level, and AEs were assessed at 90 days.

Statistical Analysis Plan

Primary Analysis: The primary endpoint is confirmed RR, as determined by the independent review committee (IRC), using RECIST v1.1. The primary analysis population is defined as pts who meet all of the following conditions: 1) IRC-determined measurable disease at baseline, 2) ≥ 24 weeks of follow up, 3) at least 1 prior therapy, and 4) PD-L1 high tumor staining. Thus, the primary analysis of RR was to occur in PD-L1 high patients rather than in all pts regardless of PD-L1 status.

If the lower bound of the 95% confidence interval for the response rate in the PD-L1 high cohort excluded 10%, the RR was to be assessed regardless of PD-L1 staining (still meeting conditions 1-3). The analyses of IRC- and INV-determined RR rate in all treated pts were considered supportive.

Interim Analysis: An interim analysis based on IRC-determined RR in 103 treated pts who had been followed for ≥ 13 weeks was conducted. This formed the basis of the initial BLA submission. Additional efficacy data was added for a total of 182 pts.

Secondary Endpoints: Duration of response is defined as the time from first documented response until first documented disease progression (PD) or death due to any cause. Patients without PD or death will be censored at their last disease assessment. Additional secondary

endpoints include disease control at 12 and 24 weeks (stable disease or better), PFS, duration of stable disease, time to response, OS, and change in target lesion size.

The sample size was based on the expected enrollment of 100 pts with PD-L1 high tumors who had received at least 1 prior systemic therapy. With 70 PD-L1 high and 50 PD-L1 low pts, the study had 80% power to detect a 20% difference in ORR between the PD-L1 high and low groups using a 1-sided 5% alpha.

Independent Radiology Committee Charter

(b) (4) provided the independent radiology review. After January 2016, version 2 of the Charter, pt eligibility was based on the IRC-determined presence of measurable disease. To determine response, Radiologists 1 and 2 separately recorded tumor measurements at each time point. Each then conducted a Global Radiology Review that evaluated all the scans at the same time. The results of the Global Radiology Review could change pt status (response/no response). If the 2 radiologists did not agree, a 3rd radiologist could review the scans and choose one of the 2 radiologists' readings.

The Charter states that the radiologist can select a response assessment that differs from that determined by the sum of the diameters. The rationale stated in the Charter is that changes in the measurements of very small lesions and in splitting/merging lesions can drive incorrect assessments of response/progression. The rationale also states, "Inflammatory or reactive lesion swelling, for example, may increase the lesion size, but that should not trigger PD." The Charter allows a new lesion to be categorized as equivocal and not considered PD. However, an equivocal new lesion can be changed to unequivocal and the assessment updated to PD.

Amendments to the Protocol: There were 9 amendments to the protocol.
Amendment 5 added pts with bladder cancer. Patients could have had PD following a 1st-line therapy or could have refused/been ineligible for 1st-line treatment. Pts enrolled regardless of PD-L1 staining; enrolled 20 pts.
Amendments 6 and 7 required tumor cell PD-L1 expression $\geq$ 5%; enrolled 43 pts.
Amendment 8 required transitional cell (or mixed) cancer of the urothelium, a prior platinum-based regimen, and that the results of PD-L1 staining be available prior to enrollment.
Amendment 9 enrolled pts regardless of PD-L1 staining, but required assessment of a tumor specimen obtained within 6 months of entry. Amendments 8 and 9 enrolled 128 pts.

Disposition
Beginning in August 2012 and using a cutoff of October 2016, the Applicant enrolled 182 patients with urothelial cancer who had received prior platinum-based therapy. Enrollment occurred at 60 sites in 9 countries with 90 (49%) pts enrolled in the US.

Table 1: Disposition	
	2nd Line Urothelial N = 182
Treated	182
Completed 12 Months of Treatment	15
Ongoing	44
Discontinued	123
Disease Progression	93
Withdrawal of Consent	8
Death	10
Adverse Event	8
Patient Request/Investigator Decision	4

Data Cutoff: October 24, 2016

- Radiographic PD was documented in 86/93 pts who discontinued due to PD.
- Among the 12 pts who withdrew consent or discontinued due to Investigator/Patient decision, 8 appeared to have PD. One pt from South Korea developed pulmonary tuberculosis approximately 1 month prior to discontinuation and had a grade 3 ALT at the end of study visit. The pt had not received steroids and had no known liver metastases.
- Among the 10 pts who died while on durvalumab, 1 death was due to pneumonitis. Three additional deaths are of concern; 1 with increased AST (no known liver metastases) and 2 with possible adrenal insufficiency. Adrenal insufficiency was not documented and in 1 case could have been related to prior steroid use.
- The disposition dataset includes 8 pts while the adverse event dataset include 10 pts who discontinued to due to an AE. Among the 8 pts in the disposition dataset, AEs of concern included: ALT/AST elevation (2 pts) and acute kidney injury (1). The 2 additional pts in the AE dataset discontinued due to bladder cancer and back pain.

Demographics and Baseline Characteristics

Among the 182 pts, median age was 66 years (range; 34-88) and 72% of the pts were male. Patients were primarily White (64%), but the study also included pts who identified as: Black 3%, Asian 20%, and Other 3%. Race was not available in 9% of pts. Performance status was 0 in 34% and 1 in 66% of pts.

The table below provides information on baseline disease characteristics including tumor staining for PD-L1. Tumor histology was missing in 1 pt and PD-L1 status was not evaluable/missing in 14 pts. Approximately half the pts were considered to have high PD-L1 staining. This was most commonly due to immune cell infiltration and increased PD-L1 staining of these cells. Among the small number of pts who had ≤ 1% immune cell infiltration of the tumor area, 7 had tumor cell staining ≥ 25% and none had immune cell staining of 100%.

Table 2: Baseline Disease Characteristics and PD-L1 Staining	
	2nd Line Urothelial N = 182 (%)
Primary Site	
Bladder	114 (63)
Renal Pelvis/Ureter/Ureteral Orifice	48 (26)
Urethra/Bladder Neck	13 (7)
Missing	7 (4)
Cell Type	
Transitional Cell Carcinoma (TCC) Only	161 (88)
TCC with Squamous Differentiation	15 (8)
TCC with Variant Histology[1]	5 (3)
Missing	1 (5)
Stage at Study Entry per Investigator	
Metastatic Disease[2]	173 (95)
Locally Advanced	9 (5)
PD-L1	
PD-L1 High	95 (52)
Immune Cell Infiltration > 1%	88
Tumor Cells ≥ 25% Only	21
Immune Cells ≥ 25% Only	50
Both	17
Immune Cell Infiltration ≤ 1%	7
Tumor Cells ≥ 25%	7
Immune Cells 100%	0
PD-L1 Low	73 (40)
Immune Cell Infiltration > 1%	39
Immune Cell Infiltration ≤ 1%	34
Not Evaluable	14 (8)

[1]Includes variant histology NOS (N=4) and glandular differentiation (N=1) Data Cutoff: October 24, 2016
[2]Patients with metastatic disease may also have locally advanced disease.

The table below provides information on the extent of disease at baseline. In general the disease burden was low with a median sum of the diameters (SOD) of 6 cm; however, 34% of pts had liver metastases and most had 2-3 target lesions (per IRC). Five (5) pts had no target lesion per IRC. The IRC did not identify non-target lesions in 10% of pts.

Both the Bellmunt and MSKCC scoring systems have prognostic value for OS. The Bellmunt scoring system uses performance status, hemoglobin, and the presence of liver metastases (JCO 2010 38:1850). The MSKCC score uses performance status and the presence of visceral (bone, liver, and lung) metastases (JCO 1999 17:3173). The distribution of these scores, based on INV and IRC review is shown below.

Table 3: Extent of Disease at Baseline		
	Durvalumab N = 182 (%)	
	IRC-determined	INV-determined
Disease Sites		
Liver	62 (34)	60 (33)
Lymph Nodes Only	23 (13)	36 (20)
Median SOD (range)	6.0 cm (1.6, 33.3)	5.9 cm (1.0, 36.8)
Number of Target Lesions		
0	5 (3)	0
1	30 (16)	38 (21)
2-3	114 (63)	113 (62)
4-6	33 (18)	31 (17)
Number of Non-Target Lesions		
0	19 (10)	34 (19)
1	39 (21)	41 (23)
2-3	95 (52)	82 (45)
4-11	29 (16)	25 (14)
Bellmunt Score		
0	42 (23)	43 (24)
1	69 (38)	69 (38)
2	52 (29)	50 (27)
3	17 (9)	18 (10)
Missing	2 (1)	2 (1)
MSKCC Score		
0	62 (34)	64 (35)
1	120 (66)	118 (65)
2	0	0

Data Cutoff: October 24, 2016

The table below provides information on prior therapy. The Applicant recorded therapy as "neoadjuvant, adjuvant, primary, or recurrence locally advanced or metastatic disease." Twenty percent (20%) of pts received only neoadjuvant/adjuvant therapy prior to study entry. The time between completion of neoadjuvant/adjuvant therapy and disease progression was > 12 months in 1 pt. Primary chemotherapy or radiation therapy was given in 17 pts. All 17 received systemic chemotherapy as primary treatment for their urothelial cancer and 1 pt received concomitant radiation. Among the 17 pts receiving primary chemotherapy, only 9 were reported to be Stage IV at the time of administration of systemic chemotherapy.

One concern is that a substantial number of pts were reported to have a long period (> 90 days) between disease progression on prior therapy and initiation of durvalumab. Among the 145 pts with available dates of progression, 3 progressed more than 1 year prior to initiation of durvalumab with 45/145 (31%) progressing > 90 days prior to the start of durvalumab. It is unclear whether these pts had atypical presentations of urothelial cancer or whether this suggests poor record keeping. These 45 pts had a slightly lower tumor burden than the population as a

whole with a median SOD of 5.4 cm. They were also slightly more likely to have node only disease; 9/45 (20%) pts by IRC.

Table 4: Prior Therapy	
	2nd Line Urothelial N = 182 (%)
Disease Setting of Prior Therapy	
Neoadjuvant/Adjuvant Only	37 (20)
Metastatic/Locally Advanced Disease	145
Prior Platinum-based Therapy	
Any	182
Cisplatin	139
Carboplatin	70
Other Platinum[1]	2
	N = 145
> 90 Days Since Progression on Last Systemic Therapy	45 (31)

[1]Oxaliplatin (N=1), platin NOS (N=1) Data Cutoff: October 24, 2016

Primary Analysis

The table below provides the results of the primary analysis per IRC. The RR of 17.0% is consistent with the response rates seen with other PD-L1/PD-1 inhibitors in pts with urothelial cancer who have received prior platinum-based therapy. The median duration of response has not been reached and ranges from 0.92+ to 19.9+ months. This suggests that the median duration of response with durvalumab will be substantial. The Investigator-determined RR is 19.2% (35/182).

One area of concern is that the IRC charter allowed changes in response status that were not limited to equivocal/unequivocal new lesions. The IRC reassessed images in 26/152 pts and re-reviewed images in 21/152 pts. Among the 152 pts, 13 (9%) had a change in their response status. The changes in response status did not result in additional pts with a complete or partial response.

The RR for all pts and for pts with high and low PD-L1 tumor staining is shown below. The difference in RR among pts with high and low PD-L1 tumor staining is greater than that seen with atezolizumab (16.5%) and nivolumab (9.9%). This is due to the RR of 3-4% seen in pts whose tumors have low PD-L1 staining. The low RR could be due to unique properties of durvalumab or its PD-L1 assay. Alternatively, one could speculate that the low RR seen with durvalumab may be due to inaccuracy in the determination of RR in a small number of patients. Given the current data, practitioners should strongly consider the use of PD-L1 testing prior to treatment with durvalumab. However, examination of the current data shows that low PD-L1 tumor staining does not preclude a response and 1 pt with low PD-L1 staining achieved a complete response. This pt had a small disease burden, but maintained their response until Day 333.

The PD-L1 assay was developed using pts enrolled in Study 1108. Although 182 pts were included in the primary analysis (because they had received prior platinum-based therapy), the

study enrolled 191 pts with urothelial cancer. The first 20 pts were enrolled regardless of PD-L1 status and their tumor specimens used as the "training set" to develop the PD-L1 assay. Eighteen of the 20 pts had received prior platinum-based therapy and are included in the primary analysis. The "training set" was used to determine the cutoff for PD-L1 (based on response) and has a marked difference in RR: 40.0% (4/10) in pts with PD-L1 high and 0% (0/8) with PD-L1 low tumor staining. In addition to assay development, the Applicant changed the requirements for study entry during the trial. Thirty-six pts had tumor cell staining for PD-L1 > 5% at entry.

- One hundred twenty-eight (128) pts were enrolled regardless of PD-L1 status and their PD-L1 status was determined using the final assay and the final definition of PD-L1 high and low. The RR in these pts is shown in the table below.

Note that the difference in RR in pts with high and low PD-L1 staining is difference is 15.4% and is consistent with the difference seen with atezolizumab.

Table 5: Primary Analysis Based on IRC Assessment in All Treated Patients				
	All Patients N = 182	PD-L1 High N = 95	PD-L1 Low N = 73	PD-L1 NE N = 14
Response Rate (%) (95% CI)	31 (17.0) (11.9, 23.3)	25 (26.3) (17.8, 36.4)	3 (4.1) (0.9, 11.5)	3 (21.4) (4.7, 50.8)
Complete Response	5	3	1	1
Partial Response	26	22	2	2
Median Duration of Response (range)	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.3 mos (1.9+, 12.3)	NR (2.3+, 2.6+)
Primary Analysis Based on IRC Assessment in Patients Enrolled Regardless of PD-L1 Status With PD-L1 Staining Determined Using the Final PD-L1 Assay				
	All Patients N = 128	PD-L1 High N = 58	PD-L1 Low N = 56	PD-L1 NE N = 14
Response Rate (%) (95% CI)	16 (12.5) (7.3, 19.5)	11 (19.0) (9.9, 31.4)	2 (3.6) (0.4, 12.3)	3 (21.4) (4.7, 50.8)
Complete Response	3	2	0	1
Partial Response	13	9	2	2
Median Duration of Response (range)	NE (0.9+, 4.2+)	NE (0.9+, 4.2)	NR (1.9+, 4.2+)	NR (2.3+, 2.6+)

NE-not evaluable ; NR-not reached; mos-months Data Cutoff: October 24, 2016

The median time to response in all 182 pts was 43 days. Among the 31 responders, 24 (77%) responded at their 1st assessment. The first assessment was at Day 43 $\pm$ 7 days.

Subgroup Analyses

These are based on the IRC-determined RR in 182 pts.

- Among the pts with > 90 days between progression on last recorded therapy and study entry, 8/45 (17.8%) were responders. Given the atypical characteristics of urothelial cancer in these pts, a RR consistent with the population as a whole is surprising.

- Among those with minor histological variants, 1/20 (5%) responded. With conventional therapy, a lower RR is expected in pts with histological variants. Given the small number of pts, it is unclear if this also is true for immunotherapy.

- By primary site, RRs were: bladder 15%, upper tract 23%, and urethra/bladder neck 23%. With conventional therapy, a lower RR is expected in pts with upper tract disease. Given the small number of pts in each subgroup, it is unclear if this also is true for immunotherapy.

- The RR among pts who received only neoadjuvant/adjuvant therapy prior to study entry was 24% (9/37). With other immunotherapies tested in pts with urothelial cancer, a higher RR has been seen in pts who have received only neoadjuvant/adjuvant therapy.

- The median SOD by IRC among responders was 5.3 cm compared to 6.0 cm in all pts. Responders were more likely to have only 1 target lesion than the population as a whole; 26% vs. 16%, respectively. Responders were also more likely to have lymph node only disease and less likely to have liver metastases. With other immunotherapies, a higher RR has been seen in pts with a small tumor burden, node only disease, and with no liver metastases.

- The RR among pts with an irAE was 33% (7/21). A higher RR in pts with irAEs has not been consistently seen with immunotherapy.

- Further examination of the RR by PD-L1 status found the following RRs:

    - High PD-L1 staining in both the tumor and immune cells-17.6%
    - High PD-L1 staining in tumor cells only-28%
    - High PD-L1 staining in immune cells only-30%
    - Immune cells involving $\leq$ 1% the tumor area-4.9%.

    It is surprising that the RR is not greater in pts who have high PD-L1 staining in both tumor and immune cells. This may be due to the small number of pts in each subgroup.

- The RR among the 90 US pts was 16.7%. This is consistent with the study as a whole.

The table below provides information on the RR by Bellmunt and MSKCC score. Patients with low scores were more likely to respond. There was a substantial drop off from MSKCC 0 to 1 or 2. The number of pts in each of these subgroups is small and this is an exploratory analysis so these results should be viewed with caution. However, it may be that pts with a high Bellmunt or MSKCC score are less likely to develop a response, regardless of the type of therapy. Another possibility is that these pts have an extensive disease burden and cannot develop an immune response prior to disease progression.

Table 6: Response Rate by Bellmunt and MSKCC Score							
	Bellmunt Score (%)				MSKCC Score (%)		
	0 N = 42	1 N = 69	2 N = 52	3 N = 17	0 N = 62	1 N = 120	2 N = 0
Response (%)	11 (26)	11 (16)	9 (17)	0	24 (39)	7 (6)	0

Data Cutoff: October 24, 2016

Concordance between IRC and Investigator

Among the 35 responders by Investigator review and the 31 responders by IRC review, there are 28 pts who overlap. Differences in the timing of the responses were not examined. If each response category is examined individually (CR, PR, SD, PD, or NE by both Investigator and IRC), 142/182 pts had the same response by Investigator and IRC. Only 4 pts had a two-category change in response (e.g., CR by IRC and SD or PD by Investigator).

Secondary Endpoints

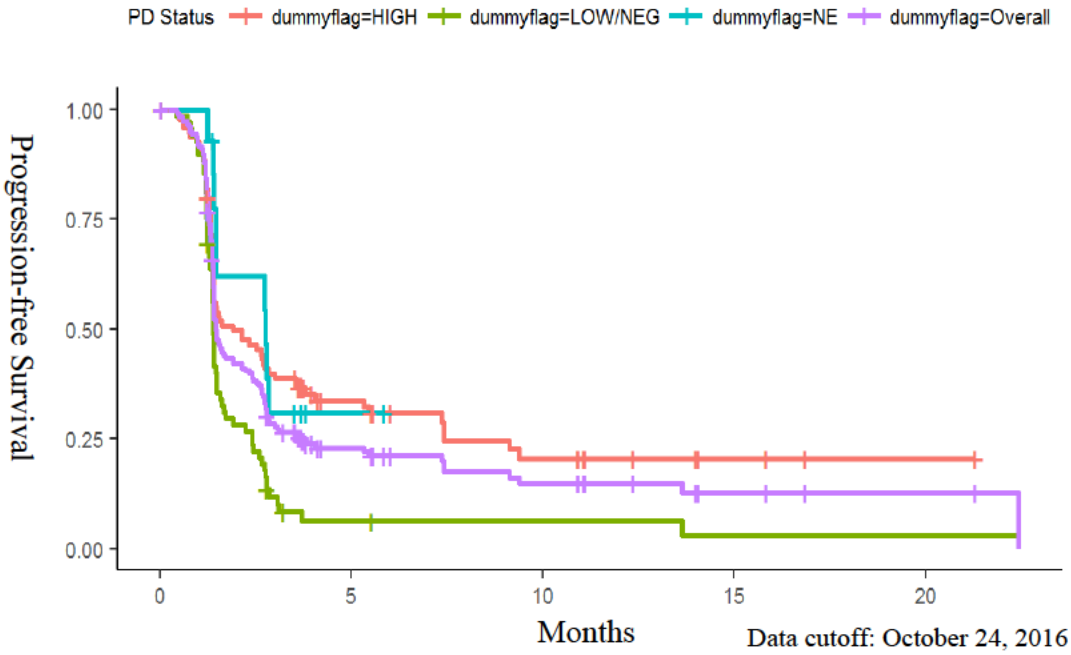
With 142 events, median PFS was 1.4 months in pts treated with durvalumab. Using cross-study comparisons, this can be compared to a median PFS of 1.6 months with docetaxel (J Clin Oncol 2012 30:507) and 6 months with nab-paclitaxel (Lancet Oncol 2013 14:769). The difference in median PFS between docetaxel and nab-paclitaxel illustrate the point that the results of these studies and any cross study comparisons should be interpreted with caution.

The curve below shows PFS in all pts (purple) and in the PD-L1 high (red) and PD-L1 low (green) groups. There was a more marked drop in PFS in the PD-L1 low group. Given the profound initial drop in the PFS curve in all pts, but particularly in the PD-L1 low group, pts with an event prior to or at the first assessment, Day 43 $\pm$ 7 days, were examined. Twenty-six (26) pts discontinued or died prior to the first assessment. This includes 15 pts who died prior to Day 50 and 5 pts who discontinued and withdrew consent for further follow up. In addition to these 26 pts, 85 pts had disease progression at their first assessment. Thus, 111/182 (61%) pts had a PFS event on or before the first assessment.

Examination of the 26 pts who discontinued or died prior to their first assessment found the following; all comparisons are the 26 pts vs. the population as a whole.

- 96% vs. 66% had a performance status of 1
- 35% vs. 52% had tumor that was PD-L1 high
- Median SOD was 9.3 cm vs. 6.0 cm
- 73% vs. 35% had a Bellmunt score of 2-3

The number of pts in this group, N = 26, is too small to draw any conclusions and these should be considered exploratory analyses. However, this suggests that some pts may not benefit from durvalumab.



A short follow up is available and, therefore, limited information exists concerning the use of subsequent therapy. Twelve percent (12%) of pts received subsequent therapy, most commonly paclitaxel or enrollment on a clinical trial.

With 64 events, median OS was 18.2 months in pts treated with durvalumab. In cross-study comparisons, which should be interpreted with caution, median OS in previous treated patients who received docetaxel was 7.0 months (J Clin Oncol 2012 30:507) and median OS with nab-paclitaxel was 10.8 months (Lancet Oncol 2013 14:769). A marked improvement in OS with little to no improvement in PFS has been seen in randomized trials of PD-1/PD-L1 inhibitors. The pattern here is consistent with that finding. However, no conclusions can be drawn concerning the benefit of durvalumab relative to taxanes from these cross-study comparisons.

There was a marked difference in median OS among pts with high PD-L1 tumor staining, 18.2 months, and low PD-L1 tumor staining, 8.1 months. With durvalumab, PD-L1 status appears to be predictive for response (26.3% vs. 4.1% RR). Although this cannot be determined from a single-arm study, it is possible that PD-L1 staining is a prognostic factor. That is, the pts with a large number of tumor infiltrating lymphocytes, a good prognostic feature (Ann Oncol 2015 26:812), may be more likely to have high PD-L1 staining and a better outcome.

8. Safety

The safety database contains N = 1414 patients from studies of durvalumab 10 mg/kg in 2nd-line urothelial cancer (N = 182), solid tumors (N = 788), and non-small cell lung cancer (N = 444). There are an additional 48 pts who received durvalumab at doses other than 10 mg/kg. The 788 pts with solid tumors includes 9 pts with 1st line urothelial cancer.

The data cutoffs for this submission are complex. The data cutoff for the study of pts with solid tumors (N = 788) was April 29, 2016 and the BLA was submitted October 13, 2016. However,

pts in the urothelial cancer cohort within this study (N = 182) had a data cutoff of July 24, 2016. The data cutoff for a separate study of pts with non-small cell lung cancer (N = 444) was June 3, 2016. The Safety Update only provided additional information on pts in the urothelial cancer cohort and used a cutoff of October 24, 2016. The datasets for the integrated summary of safety were not updated. Therefore, the tables below include:

- Safety data on 182 pts with 2nd-line urothelial cancer with a data cutoff of October 24, 2016;
- Safety data on 1414 pts with a variety of solid tumors (including urothelial cancer) with data cutoffs of April 24, June 3, and July 24, 2016.

Note that the incidence and grade of some of the adverse events may differ slightly from those in the package insert and the primary review due to different cutoff dates and some differences in preferred terms. All tables, other than the table of patient deaths, include AEs collected up to 90 days after the last dose of durvalumab. Please see Appendix for grouping of preferred terms.

Exposure

The extent of exposure in the urothelial cancer population and in the safety database is shown below. These calculations use the last day of dosing as the end of the pt's exposure to study drug. For example, if the last dose was Day 30 and the pt discontinued the treatment period on Day 40, Day 30 is used as the last day of exposure. This table also includes the number of patients who were followed for more than 6 and 12 months. In the urothelial cancer cohort, this number is very small. However, these numbers improve when the safety database is included. Finally, the values in the table are taken from the exposure dataset. When the AE datasets are examined, 66/182 (36%) pts with urothelial cancer and 435/1414 (31%) pts in the safety database had a dose delay due to an AE. This is similar to the findings in the exposure dataset.

Table 7: Exposure

	Durvalumab 10 mg/kg	
	Urothelial Cancer N = 182 (%)	Safety Database N = 1414 (%)
Median Duration (range)	2.4 months (0.03, 12.1)	2.8 months (0.03,14.7)
Dosed		
≥ 24 weeks	39 (21)	437 (31)
≥ 52 weeks	9 (5)	98 (7)
Dose Delays		
Patients with Any Dose Delay	78 (43)	537 (38)
Patients with Delay Due to AE	65 (36)	374 (26)
Data Cutoff	October 24, 2016	4-24-16, 6-3-16, 7-24-16

Safety Summary

The table below provides a safety summary for the pts in the urothelial cancer cohort and the safety database. High-dose steroids are defined as ≥ 40 mg of prednisone or its equivalent daily.

Table 8: Safety Summary		
	Urothelial Cancer N = 182 (%)	Safety Database N = 1414 (%)
All Grade 5 Adverse Events	56 (31)	264 (19)
Grade 5 AEs Excluding Disease Progression	13 (7)	81 (6)
Grade 1-4 AEs Leading to Discontinuation	9 (5)	102 (7)
Grade 3-4 Adverse Events	96 (53)	682 (48)
Grade 1-4 Serious Adverse Events	90 (49)	634 (45)
Grade 1-5 Adverse Events of Special Interest[1]	101 (55)	756 (53)
Immune-related Adverse Events Treated with Steroids	14 (8)	99 (7)
Immune-related AEs Requiring High-dose Steroids	7 (4)	61 (4)
Data Cutoff	October 24, 2016	4-24, 6-3, 7-24-16

[1]Includes colitis/diarrhea, dermatitis/rash, endocrinopathy, infusion reaction, pneumonitis, select hepatic events, select pancreatic events, select renal events, and other

Deaths

Among the 182 pts with urothelial cancer, there were 56 pts with grade 5 AEs and in the safety database there were 264 pts with grade 5 AEs. However, when AEs clearly related to the underlying malignancy (e.g., reported adverse event is bladder cancer) were removed, there were 13 deaths in 182 pts with urothelial cancer and 81 deaths in 1414 pts in the safety database. These are listed in the table below as AEs within 30 days and 90 days of study drug.

Among the 7/182 (3.8%) pts with urothelial cancer who died due to an AE within 30 days of their last dose of durvalumab, there was: 1 death due to autoimmune hepatitis (with renal failure), 1 death due to pneumonitis, and 1 death due to general physical health deterioration in a pt hospitalized with hypotension/dehydration and treated with steroids and antibiotics shortly before her death. There were 3 additional pts whose deaths were reported to be due to PD (20001672526, 20006782366, 20010902512), but who had infection at the time of death. One of these pts had radiographic PD. Among the 6 additional pts who died within 90 days of durvalumab, 1 pt was reported to have died from acute kidney injury with a creatinine of 0.9 mg/dL 2 days prior to death.

Among the 53/1414 (3.7%) pts in the safety database who died due to an AE within 30 days of durvalumab, there was: 1 death due to disseminated intravascular coagulation (DIC) and 1 due to tumor lysis. The pt with DIC had liver failure and colitis and died despite treatment with antibiotics, steroids, and infliximab. The pt with tumor lysis had an MSI-high endometrial cancer and clear tumor lysis complicated by kidney injury. She died despite treatment with steroids and rasburicase. The death reported to be due to a transient ischemic attack appeared to be due to PD. Among the pts who died 31-90 days after their last dose, 1 pt had immune thrombocytopenic purpura that began within 30 days and did not respond to steroids and IVIG. The pt death due to pneumonitis occurred on erlotinib (prior durvalumab).

Table 9: Deaths Within 30 and 90 Days of Durvalumab		
	Urothelial Cancer N = 182 (%)	Safety Database N = 1414
Deaths Within 30 Days of Study Drug	7 (3.8)	53 (3.7%)
General Physical Health Deterioration	2	4
Sepsis/Urosepsis/Pulmonary Sepsis	1	6
Autoimmune Hepatitis	1	1
Cardiorespiratory or Cardiac Arrest/Sudden Death	1	4
Pneumonitis	1	1
Ileus/Small Intestinal Obstruction	1	3
Respiratory Failure/Distress	0	11
Gastrointestinal Hemorrhage	0	4
Pneumonia/Lung Infection	0	4
Death NOS	0	3
Dyspnea	0	2
Pulmonary Embolism	0	2
Disseminated Intravascular Coagulation	0	1
Tumor Lysis Syndrome	0	1
Other[1]	0	6
Deaths Within 31-90 Days of Study Drug	6	28
General Physical Health Deterioration	2	10
Acute Kidney Injury	1	1
Cardiorespiratory Arrest	1	1
CVA	1	1
Sepsis	1	2
Immune Thrombocytopenic Purpura	0	1
Other[2]	0	12
Data Cutoff	10-24-16	4-24, 6-3, 7-24-16

[1]Includes, 1 each, bronchial obstruction, chronic hepatic failure, ischemic cardiomyopathy, pulmonary hemorrhage, transaminases increased, and TIA.
[2]Includes, 1 each, acute respiratory failure, cardiac failure, death NOS, embolism, hepatic failure, hyperbilirubinemia, MI, paraneoplastic syndrome, post-procedural complications, pneumonia, pneumonitis, and PE

Discontinuation
Causes of discontinuation in more than 1 of the 182 pts with urothelial cancer include: general physical health deterioration/failure to thrive (3) and liver injury (2). One pt discontinued due to biopsy documented immune-mediated nephritis. One pt from South Korea developed disseminated tuberculosis. The pt had not received steroids.

Immune-mediated Adverse Events
The table below provides information on the incidence of potentially immune-related AEs and on the number of patients with that event treated with systemic corticosteroids.

- In many pts, the AE (e.g., elevated liver enzymes) was not immune-related and was not treated with steroids. These AEs may have been related to PD.

- In other instances, the AE (e.g., adrenal insufficiency) included pts who did and did not have an immune-related AE. For example, while some pts had immune-mediated adrenal insufficiency, others had adrenal insufficiency after steroid use for brain metastases, etc.
- Some AEs that appear to be immune-related (e.g., diarrhea) were not treated with systemic steroids.
- Some pts who received steroids had multiple potentially immune-related AEs (e.g., hypothyroidism and low grade renal toxicity). In these pts, it is often difficult to determine which AE led to the use of steroids.

The incidence of most AEs is similar in the urothelial cancer cohort and the safety database. There are some differences in the incidence of hypothyroidism, pneumonitis, renal toxicity, and rash. Differences in the incidence of pneumonitis may be due to the presence of pts with underlying lung cancer in the safety database. Renal toxicity was higher in the urothelial cancer cohort. However, the percentage of pts receiving systemic steroids was similar in the two groups. Many of the pts in the urothelial cohort had undergone nephrectomy prior to entry.

Examining the AEs included in the table, keratitis/uveitis (Ocular Toxicity), developed in 1 pt, and was treated with steroid eye drops. Non-bacterial meningitis was also reported in 1 pt and is the only immune-related Neurological Toxicity in the safety database. This resulted in hypophysitis with adrenal insufficiency and diabetes insipidus. Three additional pts had more than 1 endocrinopathy, raising the possibility of hypophysitis. This included adrenal insufficiency/hypothyroidism in 2 pts and hypogonadism/adrenal insufficiency in 1 pt.

Musculoskeletal Toxicity included myositis and myocarditis, 1 pt each. Myositis involved edema in the psoas muscle and was treated with steroids. No information was provided on CPK levels or outcome following the use of steroids. The pt with myocarditis was found to have tumor nodules within the myocardium on autopsy. No information was provided on CPK, troponin levels, or on cardiac arrhythmias. This was considered a grade 3 AE. However, the pt received steroids prior to death.

Renal toxicity was treated with steroids in 2 pts in the urothelial cancer cohort. One pt had tubulointerstitial nephritis on biopsy (with neutrophils) and a decrease in creatinine following the administration of steroids. An additional pt in the safety database underwent renal biopsy (results not reported) and received steroids.

Pancreatitis may have been underreported with durvalumab since amylase and lipase were not routinely collected. Amylase and lipase are being collected in the confirmatory urothelial cancer trial.

Table 10: Grade 1-5 Potentially Immune-related Adverse Events Within 90 Days				
	Urothelial Cancer N = 182 (%)		Safety Database N = 1414 (%)	
	Incidence	Systemic Steroids	Incidence	Systemic Steroids
Adrenal Insufficiency	1 (0.5)	1 (0.5)	14 (0.9)	9 (0.6)
Diarrhea	31 (17)	3 (2)	244 (17)	18 (1)
Ocular Toxicity	0	0	1 (<0.1)	0
Infusion Reaction	3 (2)	0	25 (2)	7 (0.5)
Hepatic Toxicity	30 (16)	3 (2)	228 (16)	25 (2)
Hyperglycemia	7 (4)	0	50 (4)	0
Hyperthyroidism	10 (5)	2 (1)	89 (6)	4 (0.3)
Hypogonadism	1 (0.5)	0	4 (0.3)	0
Hypophysitis	0	0	1 (<0.1)	1 (< 0.1)
Hypothyroidism	13 (7)	0	137 (10)	1 (< 0.1)
Immune Thrombocytopenic Purpura	0	0	1 (<0.1)	1 (< 0.1)
Musculoskeletal Toxicity	1 (0.5)	1 (0.5)	2 (0.1)	2 (0.1)
Neurological Toxicity	0	0	1 (<0.1)	1 (< 0.1)
Pancreatitis/Inc Amylase, Lipase	0	0	14 (0.9)	1 (< 0.1)
Pneumonitis	1 (0.5)	1 (0.5)	32 (3)	15 (1)
Renal Toxicity	31 (17)	2 (1)	86 (6)	4 (0.3)
Rash[1]	30 (16)	1 (0.5)	235 (17)	10 (0.7)
Data Cutoff	October 24, 2016		4-24, 6-3, 7-24-16	

[1]4 additional pts in the safety database had vitiligo

Significant Adverse Events

Hemolysis occurred in 2 pts. One pt with an underlying non-small cell lung cancer had grade 3 hemolytic anemia and was treated with steroids. This event began 14 d after the last dose of durvalumab and resulted in admission to a hospital not involved in the study. The other pt had grade 1 hemolysis 19 days prior to his last dose of durvalumab.

Reports of intestinal obstruction were examined in the urothelial cancer cohort. This includes 1 pt whose death was reported as grade 5 ileus. The actual cause of death (infection, electrolyte imbalance, etc.) is unclear. There were 4 additional pts with grade 3-4 ileus or intestinal obstruction for an overall incidence of 2.7% (5/182). Among the 5 pts, 4 had predisposing factors for intestinal obstruction such as peritoneal/pelvis metastases at entry, prior bladder surgery, or prior pelvic radiation. The 5th pt had carcinomatosis on CT at the time of the obstruction. Any interaction between these predisposing factors and study drug cannot be determined in a single arm study.

Grade 1-4 Adverse Events

Grade 1-4 AEs in pts with urothelial cancer and in the safety database are shown below. Note that the table included in the package insert includes grade 1-5 events. There were a small number of AEs that were not mapped to a preferred term (n = 9) or graded (N = 7). These were mapped to a preferred term during review.

The incidence of AEs is surprisingly similar in the 2 groups given the size of the urothelial cancer cohort. The following AEs differed in incidence by at least 5% in the urothelial cancer cohort and the safety database: constipation, urinary tract infection, headache, renal toxicity, dyspnea, cough, and pruritus. An increased incidence of urine infections and renal toxicity in the urothelial cancer cohort may be related to the pt's underlying cancer. Events such as headache, dyspnea, and cough may be related to an increase in the number of pts with brain metastases (or primary brain tumors) and underlying lung cancer in the safety database. The reasons for the difference in constipation and pruritus are unclear.

Table 11: Grade 1-4 Adverse Events in > 10% of Patients in Either Population				
	Durvalumab N = 182 (%)		Safety Database N = 1414 (%)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any	180 (99)	96 (53)	1367 (97)	682 (48)
Blood Disorders				
Anemia	35 (19)	20 (11)	224 (16)	86 (6)
Gastrointestinal Disorders				
Constipation/Fecaloma	48 (26)	2 (1)	271 (19)	9 (0.6)
Nausea	39 (21)	3 (2)	306 (22)	13 (0.9)
Diarrhea	31 (17)	2 (1)	244 (17)	18 (1)
Abdominal Pain/Discomfort	23 (13)	4 (2)	242 (17)	40 (3)
Vomiting/Retching	21 (12)	2 (1)	203 (14)	18 (1)
General Disorders				
Asthenic Conditions/Lethargy	79 (43)	10 (5)	612 (43)	60 (4)
Peripheral Edema	30 (16)	3 (2)	176 (12)	10 (0.7)
Pyrexia	29 (16)	0	215 (15)	3 (0.2)
Infections				
Urinary Tract Infection	36 (20)	9 (5)	121 (9)	20 (1)
Investigations				
Hepatic Toxicity	30 (16)	12 (7)	228 (16)	103 (7)
Metabolism and Nutrition Disorders				
Decreased Appetite/Hypophagia	42 (23)	1 (0.5)	334 (24)	23 (2)
Musculoskeletal Disorders				
Musculoskeletal Pain	51 (28)	10 (5)	396 (28)	44 (3)
Arthralgia	18 (10)	1 (0.5)	159 (11)	4 (0.3)
Headache	7 (4)	0	157 (11)	7 (0.5)
Renal and Urinary Disorders				
Renal Toxicity	31 (17)	11 (6)	86 (6)	18 (1)
Respiratory Disorders				
Dyspnea/Exertional Dyspnea	24 (13)	4 (2)	316 (22)	83 (6)
Cough/Productive Cough	24 (12)	0	301 (21)	6 (0.4)
Skin Disorders				
Rash	30 (16)	1 (0.5)	235 (17)	10 (0.7)
Pruritus	12 (7)	0	163 (12)	1 (0.1)
Data Cutoff	October 24, 2016		4-29-2016, 6-3-2016, 7-24-2016	

Laboratories
Laboratories, including CBC, chemistries, urinalysis, coagulation parameters, and thyroid function tests, were obtained at baseline and with each dose. Note that amylase and lipase levels were not obtained. The laboratories below exclude values obtained at baseline, Day 1, Week 0, and > 30 days after the last dose. Grade 3-4 laboratory abnormalities that occurred in > 5% of pts in either group are shown below.

The percentage of pts with grade 3-4 anemia differs between the urothelial cancer cohort and the safety database while the incidence of the remainder of the laboratories is similar. The reason for this is unknown, but the incidence of grade 3-4 anemia in pts with urothelial cancer receiving atezolizumab was 8% and the incidence with nivolumab was 7%. Thus, the incidence with durvalumab was higher than anticipated and will be examined in future studies.

Table 12: Grade 3-4 Laboratory Abnormalities in > 5% of Urothelial Cancer Patients		
	N = 182 (%)	N = 1414
Lymphocytopenia	29 (16)	222 (16)
Anemia	21 (12)	67 (4.7)
AST	10 (5)	61 (4.3)
Hyponatremia	26 (14)	153 (11)
Data Cutoff	October 24, 2016	4-29, 6-3, 7-24-2016

Among the 182 pts with urothelial cancer, 9 pts had a TSH > 10xULN on study.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held. It was thought that a meeting was not needed since similar products had received accelerated approval based on similar data.

10. Pediatrics

A pediatric waiver has been granted.

11. Other Relevant Regulatory Issues

Inspection of the manufacturing facilities for durvalumab found that all facilities were acceptable except (b) (4) site for durvalumab. Since each (b) (4) cannot be tested, to ensure product sterility, media-fill programs are conducted to ensure that sterility is maintained (b) (4) and observed for microbacterial growth. (b) (4) (b) (4) (b) (4) Further, for BLA approval, the entire facility must pass inspection. Additional issues found at (b) (4) during inspection. Please see Office of Pharmaceutical Quality Review.

To address this issue, [redacted] quickly completed two media-fill runs [redacted] with durvalumab. These vials showed no growth [redacted] also committed to correcting the other deficiencies on the Form 483 and will be asked, as a postmarketing commitment, to conduct an additional media fill run over a [redacted] period.

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.

12. Labeling

See final package insert.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
  - Approval was recommended by all disciplines.
  - The inspection findings from [redacted] were adequately addressed.

- Risk Benefit Assessment

Benefit: Durvalumab demonstrated a 17.0% RR. The median duration of response has not been reached. While this RR is comparable to that seen with cytotoxic chemotherapy, the duration of response is likely to be much longer with durvalumab. Further, this RR is consistent with the RRs seen with atezolizumab and nivolumab. Both of these agents recently obtained accelerated approval for the same indication. Progression-free survival with durvalumab appeared, in cross-study comparisons, to be similar or shorter than PFS with cytotoxic chemotherapy while OS appeared to be longer. Cross-study comparisons of small trials should be viewed with caution.

With durvalumab, the difference in RR between pts whose tumors have high and low PD-L1 staining was substantial with a RR of only 3.6% (95% CI: 0.4, 12.3) seen in pts whose tumors have low PD-L1 staining. The RR in pts with low PD-L1 tumor staining was 9.5% with atezolizumab and 15.1% with nivolumab. It may be that the actual RR with durvalumab in pts with high and low PD-L1 tumor staining is more in line with other drugs in this class and that these results are due to the small number of pts. Alternatively, these results may be correct and may represent a unique property of durvalumab or its assay for PD-L1 staining. Given the current data, practitioners should strongly consider the use of PD-L1 testing prior to treatment with durvalumab. Note, however, that low PD-L1 tumor staining does not preclude a response with durvalumab and that 1 pt with low PD-L1 staining achieved a complete response.

Durvalumab will be approved with a complementary diagnostic for PD-L1 staining of tumor specimens. Atezolizumab was approved for use with a complementary diagnostic and nivolumab has a post-marketing commitment to develop a complementary diagnostic.

Risk: The AE profile of durvalumab in urothelial cancer is consistent with the AE profile seen with other PD-1/PD-L1 inhibitors. In the absence of a randomized trial, it is difficult to state how this AE profile compares to cytotoxic chemotherapy and to other PD-1/PD-L1 inhibitors. However, in cross-study comparisons, the AE profile of durvalumab appears favorable when compared to cytotoxic chemotherapy. In the urothelial cancer cohort, deaths due an AE within 30 days of durvalumab occurred in 3.8% of pts and Grade 3-4 events in 52.7% of pts. Grade 1-4 AEs in > 15% of pts in the urothelial cohort included: fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, urinary tract infection, diarrhea, renal toxicity, hepatic toxicity, peripheral edema, rash, and fever. Immune-related adverse events resulted in the use of high-dose corticosteroids in 5.5% of pts in the urothelial cancer cohort and in 7.5% in the safety database.

- Recommendation for Postmarketing Risk Management Activities: None

- Recommendation for other Postmarketing Study Requirements

    - 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."

- Recommendation for other Postmarketing Study Commitments

    - Reevaluate the and-drug antibody (ADA) confirmatory and triple mutation assay cut points using a 1.0% false positive rate.

    - Conduct drug tolerance studies for the screening, confirmatory, titering, and triple mutation assays that are in the range of the C_{trough} of 182 μg/mL to better demonstrate that the assay can detect ADA in the presence of drug.

    - 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.

    - 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.

- Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the media fill.

- Recommended Comments to Applicant: Please see final letter to Applicant.

APPEARS THIS WAY ON ORIGINAL

Appendix: Grouping of Preferred Terms

Anemia	Anemia Anemia of Chronic Disease Hemoglobin Decreased Hemolysis Hemolytic Anemia Iron Deficiency Anemia
Diarrhea	Colitis Diarrhea Enteritis Enterocolitis Proctitis
Eye Toxicity	Keratitis Uveitis
Gastrointestinal Hemorrhage	Gastric Hemorrhage Gastrointestinal Hemorrhage Hematemesis Intra-abdominal Hemorrhage
Infusion Reaction	Drug Hypersensitivity (not due to other drugs) Hypersensitivity (not environmental allergens) Infusion-related Reactions Pyrexia (AE term infusion reaction) Systemic Inflammatory Response Syndrome
Headache	Headache Migraine Sinus Headache Tension Headache
Hyperglycemia	Blood Glucose Increased Diabetes Mellitus (not Type 2 Diabetes Mellitus) Glycosylated Hemoglobin Increased Hyperglycemia
Hyperthyroidism	Autoimmune Thyroiditis Blood TSH Decreased Hyperthyroidism Thyroiditis Thyroiditis Chronic Thyroiditis Subacute Thyroxine and Free Thyroxine Increased Triiodothyronine Increased
Hypogonadism	Blood Testosterone Decreased Primary Hypogonadism
Hypothyroidism	Autoimmune Hypothryoidism Blood TSH Increased Hypothyroidism Thyroxine and Free Thyroxine Decreased

	Triiodothyronine and Free Triiodothyronine Decreased (Goiter was not included)
Hepatic Toxicity	ALT Increased AST Increased Autoimmune Hepatitis Blood Bilirubin Increased GGT Increased Hepatic Enzymes Abnormal Hepatic Enzymes Increased Hepatic Failure Hepatic Function Abnormal Hepatitis Toxic Hepatocellular Injury Hepatotoxicity Hyperbilirubinemia Jaundice Transaminases Increased
Neurological Toxicity	Non-bacterial Meningitis
Musculoskeletal Pain	Back Pain Musculoskeletal Chest Pain Musculoskeletal Discomfort Musculoskeletal Pain Myalgia Neck Pain
Musculoskeletal Toxicity	Myocarditis Myositis
Pancreatitis	Amylase Increased Hyperlipasemia Lipase Increase Pancreatitis Pancreatitis Acute
Peripheral Edema	Edema Localized Edema Lymphedema Peripheral Edema Scrotal Edema Scrotal Swelling
Pneumonitis	Interstitial Lung Disease Pneumonitis Pulmonary Fibrosis
Rash	Acne Dermatitis Dermatitis Acneiform Dermatitis Psoriasiform Eczema Erythema

	Erythema Multiforme Lichen Planus Psoriasis Rash Erythematous Rash Generalized Rash Macular Rash Maculopapular Rash Pruritic Rash Papular Seborrheic Dermatitis Seborrhea Did not include Dermatitis Bullous, Dermatitis Exfoliative, Rash Pustular, or Skin Exfoliation
Renal Toxicity	Acute Kidney Injury Anuria Autoimmune Nephritis Blood Creatinine Increased Blood Urea Increased Glomerular Filtration Rate Decreased Glomerulonephritis Hypercreatinemia Nephritis Oliguria Renal Failure Tubulointerstitial Nephritis
Urinary Tract Infection	Cystitis Leukocyturia Pyuria Urinary Tract Infection Urinary Tract Infection Fungal

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

/s/

VIRGINIA E MAHER
04/27/2017