A phase Ib study of combination of Avelumab and Taxane based chemotherapy in platinum refractory or ineligible metastatic urothelial cancer (AVETAX study)

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Version 1 – 3/21/2018
Version 2 – 3/19/2019
Version 3 – 10/19/2020

Sponsor: University of Iowa
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Summary of Changes
Protocol Version 3
10/19/2020

Page	***Protocol Changes:***
Cover	- Revised Version number and date
35	5.2 EXCLUSION CRITERIA- Prostate cancer with GS 6-7 allowed, changed from <7
57	6.4 CONCOMITANT THERAPY- Clarifies Long term high dose (>40 mg) glucocorticoids are excluded. Short course of glucocorticoids for the treatment of non-immune related issues such as COPD, asthma, osteoarthritis, chronic back pain etc at the discretion of investigator is allowed.-

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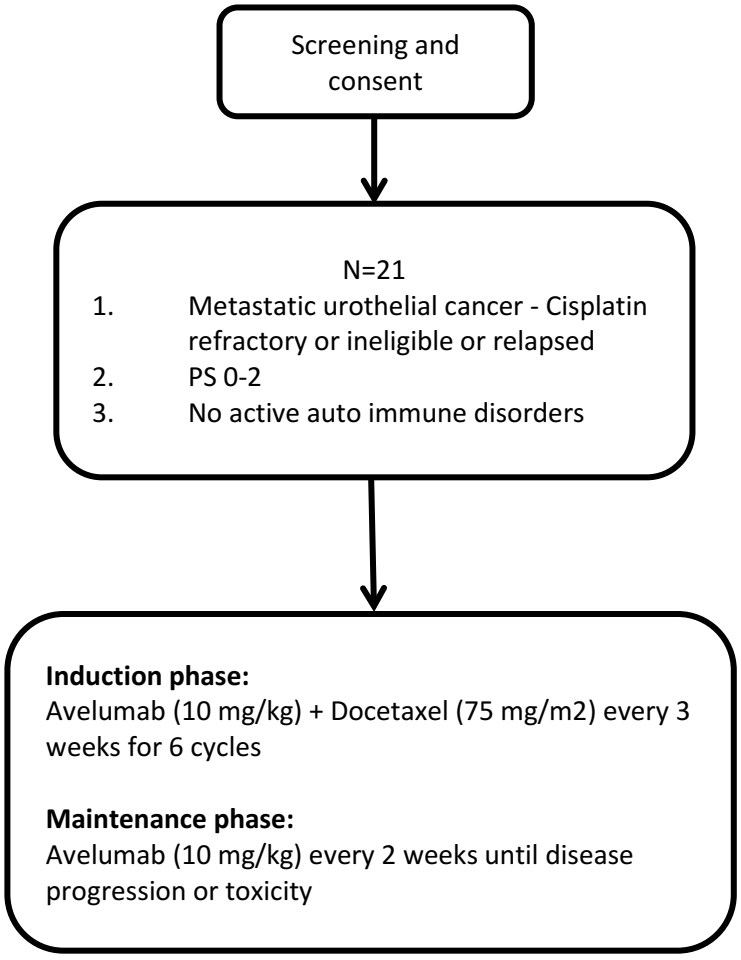
1 Protocol Summary

1.1 SYNOPSIS

Title:	A phase Ib study of combination of Avelumab and Taxane based chemotherapy in platinum ineligible or refractory metastatic urothelial cancer. (AVETAX study)
Study Description:	This study evaluates the safety and efficacy of the combination of Avelumab, (a fully human anti-programmed death ligand 1 (PD-L1) IgG1 antibody) in combination with a taxane chemotherapy (docetaxel) in patients with metastatic urothelial cancer who are either ineligible to receive cisplatin based chemotherapy, refractory to cisplatin in first line setting or have disease relapse after receiving cisplatin based chemotherapy within a year in the neoadjuvant or adjuvant setting.
Objectives:	Primary Objective: To assess the safety and efficacy of the combination therapy
Endpoints:	Primary Endpoint: To assess dose limiting toxicities and overall response rate (CR,PR) with the combination therapy in subjects with metastatic urothelial cancer Secondary Endpoints: To assess progression free survival and Overall survival
Study Population:	Adults, n=21, both male and female, Age ≥18, with cisplatin ineligible or refractory metastatic urothelial carcinoma
Phase:	Phase Ib
Description of Sites/Facilities Enrolling Participants:	University of Iowa - Holden Comprehensive Cancer Center - Iowa City, IA USA.
Description of Study Intervention:	After a screening phase of up to 28 days, eligible subjects will receive Avelumab 10 mg/kg and Taxane based chemotherapy (Docetaxel 75 mg/m2) on Day 1 of each 3-week (Q3W) cycle for a total of 6 cycles. Subsequently, the subjects will receive single agent Avelumab 10 mg/kg every 2 weeks until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with the trial treatment or procedure requirements or administrative reasons.
Study Duration:	We estimate that the study will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit

Participant Duration:	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact (up to approximately 5 years).

1.2 SCHEMA



	Screening (visit 1)	Treatment Cycles (Treatment cycles are 3 weeks for the combination therapy and 2 weeks while on Avelumab alone)[1]	End of Treatment[6]

1.3 SCHEDULE OF ACTIVITIES (SOA/ STUDY CALENDAR)

Treatment Cycle / Scheduled Time	**Screening (Visit 1)**	**Treatment Cycles (Treatment cycles are 3 weeks (21-days) for the combination therapy and 2 weeks while on Avelumab alone)**															**End of Treatment**
Scheduling Window (Days):	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35		Discontinuation Visit (30 +/- 7 days after final administration of drug)
Treatment Cycle / Scheduled Time															Subsequent cycles 35		
Scheduling Window (Days):			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		
Administrative Procedures																	
Informed Consent		X															
Inclusion/Exclusion Criteria		X															
Laboratory Procedures / Assessments:																	
Pregnancy Test - Urine or Serum β-HCG [2]	X	X			X			X			X			X		X	
Medical History and Demographics		X															
Medications (current)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Details regarding urothelial cancer – Diagnosis and prior treatment		X															
Clinical Procedures / Assessments																	
Review Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs,Weight, Height[7]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG		X															
ECOG Performance Status		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration																	
Docetaxel[a]				X	X	X	X	X	X								
Avelumab				X	X	X	X	X	X	X	X	X	X	X	X	X	X

PT/INR and aPTT [3]	X															
CBC with Differential	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic panel	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X					X				X				X	X	X
T3, FT3, FT4 and TSH	X		X			X				X				X	X[5]	X
Tumor PDL1 Expression[8]																
Efficacy Measurements																
Tumor Imaging (CT and/or MRI)[4]	X				X			X						X	Every 12 weeks	X

a Premedication with dexamethasone 20 mg po once prior to infusion of Docetaxel

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. **Treatment cycles are 3 weeks for the combination therapy (Avelumab and Docetaxel) and 2 weeks while on Avelumab alone.**
2. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Pregnancy test in woman of child bearing age will be checked every other cycle (every 6 weeks in induction and every 4 weeks in maintenance phase)
3. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
4. Brain MRI is obtained if clinically required at baseline. CT scans are performed every 3 cycles (+/- 7 days) for the first 18 weeks during the induction phase and then every 12 weeks until treatment discontinuation. After the first documentation of progression (if the subject is clinically stable) or response per RECIST 1.1, repeat imaging for confirmation is required. Confirmatory imaging should be performed 4 to 6 weeks later. Tumor assessments will be adjusted accordingly to match +/-7 days from Day 1 of each even cycle.
5. Thyroid function test will be checked every 8 weeks in the maintenance phase from Cycle 13.
6. After the End of treatment visit, patients without disease progression will be followed every 3 months (+1 month) with CT scans per physician standard of care. Patients with disease progression or who have started subsequent therapy will move to survival only data collection (passive chart review or phone calls) every 3 months(+1 month) for 2 years, then every 6 months (+1 month) until death or lost-to-follow up.
7. Height at screening only.
8. Check PDL1 status on tumor specimen using institutional standards in any timeframe, but this is not required for screening or eligibility

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-t	Area under the concentration-time curve from 0 to last quantifiable concentration
AUCtau	Average area under the concentration-time curve
BOR	Best overall response
bpm	Beats per minute
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine kinase
Cmax	Maximum concentration
Cmin	Minimum (trough) concentration
CMP	Clinical Monitoring Plan
CNS	Central nervous system
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disorder
CPK	Creatine phosphokinase
CR	Complete response
CRA	Cytokine release assays
CRF	Case Report Form
CYP	Cytochrome P
DCC	Data Coordinating Center
DDI	Drug-drug interaction
DHHS	Department of Health and Human Services
DLT	Dose-limiting toxicity
DRE	Disease-Related Event
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC50	Effective concentration exerting 50% effect
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Forms
FACS	Fluorescence-activated cell sorting
Fc	Fragment crystalline
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
FOLFOX	Combination therapy with folinic acid, 5-fluorouracil, and oxaliplatin
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
HAHA	Human anti-human antibody response
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IND	Investigational New Drug Application
ip	Intraperitoneal
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
KD	Dissociation constant
KM	Michaelis-Menten constant (concentration at the half-maximal elimination rate)
LFT	Liver function test
LLN	Lower limit of normal
mAb	Monoclonal antibody
MBC	Metastatic breast cancer
MCC	Merkel cell carcinoma
MCP-1	Monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NK	Natural killer
NOAEL	No observed adverse effect level
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OHRP	Office for Human Research Protections
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
Ph Eur	European Pharmacopeia
PHA	Phytohemagglutinin
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
QA	Quality Assurance
QC	Quality Control
QTc	Corrected QC interval
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SEA	Staphylococcal enterotoxin A
SMC	Safety Monitoring Committee
SMC	Safety Monitoring Committee
SOA	Schedule of Activities

SOC	System organ class
SOP	Standard Operating Procedure
StD	Standard deviation
t1/2	Terminal half-life
T4	Free thyroxine
TCR	Tissue cross reactivity
TEAE	Treatment-emergent adverse event
TEM	T effector memory
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TO	Target occupancy
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
Vmax	Maximal elimination
WBC	White blood cell

2 INTRODUCTION

2.1 STUDY RATIONALE

Bladder cancer is the most common malignancy of the urinary system. As per SEER database, about 76,960 new cases of bladder cancer and an estimated 16,390 bladder cancer associated deaths were estimated in 2016.

Platinum based chemotherapy was the only option until 2016, during which five checkpoint inhibitors (Nivolumab [1], Pembrolizumab [2], Avelumab [3], Atezolizumab [4] and Durvalumab) were approved for metastatic urothelial cancer. This new therapy has brought a paradigm shift in the treatment of locally advanced unresectable and metastatic urothelial cancer. Most of the patients will be able to get one of these agents. Also, the response rates have been in the range of 18-25%. These agents have broadened the options for a disease with a dismal prognosis, but eventually, most patients experience disease progression.

In addition to the immunotherapeutic agents, there are no other standard therapeutic options. Taxane based chemotherapy is the most commonly utilized with low response. Single agent Docetaxel was studied in phase II clinical of 30 patients with metastatic urothelial cancer in a second-line setting. Four out of 30 patients demonstrated partial response rate of 13.3% and a median survival of 9 months. [5] In another phase 3 study of pembrolizumab as second line therapy for metastatic urothelial cancer, the comparator chemotherapy arm (Docetaxel) had median overall survival of 7.4 months with an objective response of 11.4%. [2]

Novel and newer treatment strategies are warranted to improve the outcome of these patients further. The renaissance of Immunotherapy in the past decade has opened doors to explore its synergism with standard treatments including chemotherapy, hormonal therapy, radiation and targeted therapy, as a vital component of cancer treatment.

Among the various strategies, one unique approach would be to combine immunotherapy with chemotherapy to enhance the anti-tumor activity. Avelumab is fully human anti-programmed death ligand 1 (PD-L1) IgG1 antibody that binds PD-L1 receptors on tumor cells and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1 on T cells. This interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. Also, Avelumab has a unique feature of antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro [6] that segregates it from currently available immunotherapeutic agents. We hypothesize that combining Avelumab with chemotherapy leads to cancer cell death releasing neoantigens and potentiating an inflammatory response, which could enhance the anti-tumor activity.

To evaluate its safety and efficacy with chemotherapy, a phase 3 study of Avelumab in combination with and/or following platinum-based chemotherapy is currently on-going in ovarian malignancies (NCT02718417).

CheckMate 012, a phase I, multicohort study, was conducted to explore the safety and efficacy of the combination of nivolumab and platinum based doublet in advanced non-small cell lung cancer. Objective response rates for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus pemetrexed-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin were 33%, 47%, 47%, and 43%, respectively; 24-week progression-free survival rates were 51%, 71%, 38%, and 51%, respectively; 2-year OS rates were 25%, 33%, 27%, and 62%, respectively. Forty-five percent of patients (25 of 56 patients) reported grade 3 or 4 treatment-related adverse events (AEs); 7% of patients (n = 4) had pneumonitis. Twenty-one percent of patients (n = 12) discontinued all study therapy as a result of treatment-related AEs. Encouraging activity was observed, especially for the nivolumab 5 mg/kg plus paclitaxel-carboplatin group, with a 2-year OS rate of 62%. [7]

Another clinical trial KEYNOTE-021 reported that the addition of pembrolizumab to chemotherapy (carboplatin and pemetrexed) in patients with advanced non-small cell lung cancer (NSCLC) has significantly improved the overall response rate (ORR) from 29% to 55% (p = 0.0016). Progression-free survival (PFS) was also improved (median PFS 13.0 months vs. 8.9 months), and although toxicity was higher in the pembrolizumab arm, it did not increase the number of treatment discontinuations or treatment-related deaths. [8] Overall, from the three trials in ovarian and non-small cell lung cancers, the combination of immunotherapy with taxane, platinum-based drugs is a relatively safe option with improved overall survival compared to single therapy. Also, once a particular agent is utilized, other agents cannot be used as the efficacy in such setting is unknown.

The therapeutic armamentarium is changing in the first line therapy as well for bladder cancer. Immunotherapeutic agents are being tested in first-line therapy in combination with chemotherapy and TKIs. There are two randomized phase 3 trials evaluating the efficacy of checkpoint inhibitors in combination with platinum-based chemotherapy (NCT02853305 and NCT02807636) in first line setting for metastatic urothelial cancer. Realistically, the elderly patients (a major proportion of metastatic bladder cancer) will be Cisplatin ineligible due to renal impairment. Also, there is a concern for toxicity of combining cisplatin and immunotherapeutic agents (pending final results of these studies). Hence, it appears rationale to combine taxane based agent along with immunotherapeutic agent in second line that doesn't include cisplatin. Also, a second line option of combination therapy will be unique when compared to utilizing single agent immunotherapeutic agent for a vast proportion of patients who did not receive immunotherapeutic agent previously and were treated with either cisplatin or carboplatin based therapy. Hence, this study will aim to answer the unmet need in this patient population.

We hypothesize the combination of Avelumab and taxane based chemotherapy (Docetaxel) would be safe, synergistic in patients with metastatic urothelial cancer after progressing on cisplatin-based chemotherapy or in patients who are ineligible for cisplatin. PD-L1 is an important biomarker but we will not use it to select patients for this study. PD-L1 is a non-specific marker for response in treatment of

bladder cancer. PD-L1 low tumors had lower response with pembrolizumab and atezolizumab when compared to platinum-based chemotherapy. However, when Avelumab was evaluated in platinum ineligible patients, the responses were seen in both PDL-1 high and low tumors but responses were slightly lower in PD-L1 low patients. Currently single agent avelumab has accelerated approval by FDA irrespective of PD-L1 status.

2.2 BACKGROUND

2.2.1 PRECLINICAL EVIDENCE FOR AVELUMAB

Based on the known role of PD-L1 in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/PD-1 interaction is viewed as a highly promising strategy for cancer immunotherapy (Topalian et al 2012a). The Sponsor has developed a fully human IgG1 antibody (Avelumab) with neutralizing activity against PD-L1. The nonclinical pharmacology investigations have shown that Avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo.

To further characterize the immunological activity of Avelumab, and identify potential PD biomarkers, various immunomonitoring assays were incorporated into in vivo studies. Surface expression of PD-1 is upregulated on activated T cells; thereby conferring susceptibility to PD-L1 induced apoptosis. It is hypothesized that treatment with Avelumab effectively blocks PD-L1 induced apoptosis of activated T-cells, which then results in a measurable accumulation of CD8+PD-1+ T cells. Fluorescence activated cell-sorting (FACS) based immunophenotyping of T cells subsets consistently showed an increase in the percentage of CD8+PD-1+ T cells following treatment with Avelumab. In agreement with the hypothesis that PD-L1 neutralization acts to release anti-tumor T cells from immune suppression, the anti-tumor effects of Avelumab in vivo were found to be primarily mediated by CD8+ T cells, as highlighted by the observation that the in vivo depletion of this cell type was sufficient to completely abrogate anti-tumor activity.

Increased frequency of CD8+ TEM phenotype was another consistent effect of Avelumab treatment. Anti-tumor CD8+ T cells that become activated through blockade of inhibitory PD-1 signaling are expected to enter an effector phase characterized by an increased cytotoxic capacity. A fraction of these activated T cells will further differentiate into effector memory cells. TEM are capable of mounting a rapid and highly effective immune response upon a repeated encounter with their cognate antigen. The increases in CD8+PD-1+ T cells and CD8+ TEM cells that are consistently observed in response to treatment with Avelumab may be leveraged as PD biomarkers with translational relevance for the clinical setting.

Avelumab is also capable of stimulating ADCC activity against PD-L1+ tumor cells in vitro and elimination of ADCC potential in vivo significantly reduced anti-tumor activity. Commonly used cancer treatments, such as chemotherapy and radiation therapy, that were once thought to be purely immunosuppressive

in nature, are now known to exert positive immunomodulatory effects that can be exploited to enhance the efficacy of immunotherapy (Nowak et al 2003a, Nowak et al 2003b, Matsumara et al 2008). Of the combination approaches that have currently been explored for Avelumab, chemotherapy with FOLFOX and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination capable of causing complete regression of established tumors with the potential to generate anti-tumor immune memory. Depletion of CD8+ T cells also eliminated the synergistic efficacy of Avelumab when given in combination with radiotherapy, suggesting that this combination synergizes through cooperative immune-enhancing mechanisms.

In summary, the available preclinical data demonstrate that Avelumab is capable of inhibiting tumor growth in vivo when applied as a monotherapy and its efficacy can be further enhanced via combination with standard-of-care therapies. Avelumab has the potential to offer significant clinical benefits to cancer subjects through its ability to release anti-tumor CD8+ T cells from the suppressive effects of PD-L1 in the tumor microenvironment, increase frequency of CD8+ TEM phenotype, and improve synergistic response to conventional chemo and radiation therapy. The enzyme-linked immunosorbent spot and pentamer assays used to measure T cell responses are also commonly applied in the clinic. Therefore, it is desirable to measure immunophenotypic changes and, whenever possible, tumor-antigen-specific responses in human subjects treated with Avelumab.

2.2.1.1 PHARMACOKINETICS AND PRODUCT METABOLISM IN ANIMALS SUMMARY

The pharmacokinetics of Avelumab and precursor molecules were evaluated in mice, the primary pharmacology species, and cynomolgus monkeys, the relevant species for nonclinical safety testing. Avelumab has similar binding affinity to programmed death ligand 1 (PD-L1) from mouse, monkey, and human; therefore, these species are likely to have similar target-mediated clearance. Full PK profiles were evaluated in mice and cynomolgus monkeys. Additional TK data were obtained during the course of repeated dose toxicity studies with Avelumab in mice, rats, and cynomolgus monkeys. Molecules MSB0010294 and MSB0010682 are precursors to the final molecule Avelumab. The anti-PD-L1 antibodies from research batches and precursor molecules tested in single-dose
PK studies in mice and cynomolgus monkeys demonstrated pronounced nonlinear PK characteristics in mice and cynomolgus monkeys in single-dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Volume of distribution of Avelumab was in the range of the plasma volume in each species. Similar t1/2 ranging from 58 to 70 hours at doses between 20 and 140 mg/kg were observed in toxicity studies in mice and monkeys, indicating saturation of the target-mediated clearance. No significant gender-related differences were observed in monkeys or mice. With weekly dosing in mice and monkey, moderate accumulation was observed after 4 to 5 doses, with no additional accumulation after 13 doses in monkey. As Avelumab represents a foreign protein to the immune system of animals, anti-Avelumab antibodies in rodents and nonhuman primates were observed and have been considered in interpreting the nonclinical data. Overall, 40.5% to 100% of mice, 22.2% of rats, and 0 to 100% of monkeys treated with Avelumab developed detectable ADAs. In mouse and monkey studies,

higher doses generally resulted in lower immunogenicity incidence, potentially due to interference of Avelumab trough concentrations with the measurement of ADA. The potentially underreported incidence in higher dose cohorts did not affect exposure, and therefore did not impact the conclusions of the toxicity studies. In animals, the detected ADAs seem to have the potential to increase the clearance of the Avelumab, although the lower observed concentration may also be due either to ADA interference with detection of Avelumab at lower concentrations or coinciding with the clearance change when target-mediated disposition is no longer saturated. It should be emphasized that immunogenicity incidence against the human antibody Avelumab in animals is not deemed predictive for human subjects. For the pivotal toxicity study in cynomolgus monkeys, exposure was maintained through the duration of treatment. The clearance from the clinical population PK model is well predicted by allometric scaling from the cynomolgus monkey, confirming the suitability as the primary nonclinical PK species.

2.2.1.2 TOXICOLOGY SUMMARY

The toxicological profile of Avelumab was investigated in vivo in mice, rats, and cynomolgus monkeys. In addition, in vitro cytokine release assays in human and cynomolgus monkey whole blood and PBMCs as well as tissue cross reactivity studies in normal human and cynomolgus monkey tissues were performed. Additionally, data on the UV absorption of Avelumab were generated. Investigations on local tolerance were integrated in the repeat-dose toxicity studies as well as investigation of safety pharmacology relevant parameters which was included in the primate repeat-dose toxicity studies. On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of Avelumab. However, in the repeat dose toxicity studies in CD-1 mice with Avelumab IV bolus injection mortality occurred mainly after the 3rd administration. The second mechanistic study supported the hypothesis that the mortalities were caused by an immune-mediated anaphylactic reaction (IgG/IgE mediated) primarily driven by IgG isotype antibodies. Due to severe post-dose anaphylactic reactions after repeated administration in mice and the low binding affinity in rats, rodent species were not considered appropriate for further nonclinical safety testing of Avelumab and therefore, a single species approach (cynomolgus monkey) was followed and confirmed with Health Authorities. Accordingly, repeat-dose toxicity studies of 4 and 13 weeks duration were conducted in cynomolgus monkeys. Clinical signs of hypersensitivity or Avelumab-related infusion reactions were not observed in cynomolgus monkeys after repeated treatment with Avelumab at dose levels of 20, 60 and 140 mg/kg. Avelumab was well tolerated systemically and accordingly, the NOAEL was established at the high dose of 140 mg/kg in both, the 4-week and the pivotal 13- week, repeat-dose monkey studies. This dose was the maximum feasible dose based on administration volume and the concentration of the DP formulation. With respect to local tolerance, local inflammatory reactions at the injection site were slightly, but not dose dependently, enhanced in monkeys of the Avelumab-treated groups, compared to controls, possibly as a consequence of locally infiltrated test article. Overall, in the pivotal 13-week repeat-dose study, injection site findings were considered nonadverse up to the high dose and the changes were fully resolved during the recovery period. No reproductive toxicity studies were conducted. However, the reproductive and developmental toxicity potentially associated with Avelumab

treatment is considered adequately established based on available data, from repeat-dose studies and public sources and in view of the pursued indications and targeted indications (life threatening cancer diseases, advanced-stage cancer subjects). Considering that disruption of PD-1/PD-L1 communication has been reported to significantly increase the risk of fetal loss during pregnancy, the potential for adverse outcomes on embryofetal development cannot be excluded and adequate protections must be in place to prevent risk of pregnancies.

Systemic AUC exposures at NOAELs from monkey repeat-dose toxicity studies are well above the exposure measured in human subjects at therapeutic doses, providing a safety margin of at least 10-fold. Local tolerance was evaluated in the repeat-dose toxicity studies and only mild to moderate reactions at the injection/infusion sites which were slightly elevated in Avelumab treated animals, were observed. Injection site findings were fully resolved during recovery and overall considered nonadverse. Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed little to no release of pro-inflammatory cytokines in most samples. However, a subsequent, CRA with PHA prestimulated PBMCs from healthy human volunteers demonstrated evidence of cytokine release indicating the potential for infusion-related reactions. Evaluation of UV absorption did not show any evidence for phototoxicity. Toxicological assessment of the chemical substances potentially leaching from the CCS into Avelumab DP did not identify any risk for subjects. Overall, the nonclinical safety profile established for Avelumab is considered adequate to support the use of Avelumab in the planned therapeutic indication in humans.

2.2.2 CLINICAL EVIDENCE FOR AVELUMAB

In May 2017, the U.S Food and Drug Administration (FDA) granted accelerated approval for Avelumab for patients with locally advanced or metastatic bladder cancer whose disease has progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy. Also, in March 2017, the FDA granted accelerated approval for Avelumab for the treatment of patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

2.2.2.1 POPULATION PHARMACOKINETICS

Data from 1629 subjects from ongoing Studies EMR100070 001 (20 November 2015 cut-off date), EMR100070 002 (20 November 2015 cut-off date), and EMR100070 003 (03 March 2016 cut-off date) were used to estimate PK parameters and to evaluate the PK interindividual variability and any covariates that may be predictive of the variability using the NONMEM. A 2-compartment model with linear elimination fitted the data best. Interindividual variability on CL, V1 and V2 were modeled as a full variance-covariance block. Residual error was described by a combination additive and proportional model. Even though nonlinearity was observed at the lower doses in Studies EMR100070-001 and EMR100070-002 studies by NCA analyses, TMDD was not explicitly explored given the lack of evidence in concentration-time plots and the adequacy of the 2-compartment linear model, and the vast majority of concentrations in the linear range. Body weight was included a priori on CL and V1 before the start of

the stepwise covariate modeling process. CL in the base Pop PK model was estimated to be 0.0268 L/h, was dependent upon body weight and was associated with 30.3% IIV. Vss was calculated as the sum of V1 and V2 for each individual, and had a geometric mean of 4.72 L (44.5% CV) for subjects in the 10 mg/kg dose group. The calculated t1/2 for subjects in the 10 mg/kg dose group was 146 hours (6.1 days) (91.5 % CV). Body weight, sex, albumin, tumor burden, dose level of 3 mg/kg and tumor type (namely mMCC, NSCLC, head and neck, and ovarian) were included in the final model as statistically significant covariates. However, none of them were considered as clinically meaningful and no dose adjustment is warranted.

- **Absorption:**
  Avelumab is administered intravenously and is 100% bioavailable.

- **Distribution**

  Molecular weight is a key determinant of the distribution of therapeutic proteins. With a calculated molecular weight of 143,832 Dalton, Avelumab is expected to be distributed in the systemic circulation and to a lesser extent in the extracellular space. In vitro studies suggested that Avelumab binds to human tissues that are known for PD-L1 expression: various epithelial cell types, endothelium, mononuclear cells (including dendritic cells, lymphocytes, monocytes, and macrophages), pancreatic islets, placental trophoblasts and decidual cells, smooth muscle cells, neural cells, and mesenchymal stem cells as shown. The volumes of the central and peripheral compartments were estimated in the Pop PK analysis to be 2.84 L and 1.21 L in the typical subject, respectively. The geometric mean Vss (calculated from individual V1 and V2 parameter values) for a subject receiving 10 mg/kg was 4.72 L, which is consistent with distribution mainly restrained to the systemic circulation.

- **Metabolism**
  Avelumab is degraded by proteolytic catabolism. CYP450 does not contribute to its metabolism.

- **Elimination**
  As an antibody, the primary elimination mechanism of Avelumab is proteolytic degradation (catabolism). The geometric mean CL calculated by NCA analysis in Study EMR100070-001 was 0.362 mL/hr/kg (0.0264 L/hr for a typical subject who has a body weight of 73 kg) for the first 10 mg/kg dose. The corresponding value for the Japanese subjects in Study EMR100070-002 was calculated to be 0.471 mL/hr/kg (0.0344 L/hr for a typical subject who has a body weight of 73 kg) at the 10 mg/kg dose. The estimate of CL obtained for the typical subject in the Pop PK analysis was 0.0246 L/hr. The estimates between NCA and Pop PK analyses are comparable.

- **Influence of Hepatic Impairment**
  No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment on the PK of Avelumab. The Pop PK analysis of data from Studies EMR100070-001, EMR100070-002 and EMR100070-003 examined the potential influence of hepatic impairment on systemic

clearance. There was no influence of the composite category of hepatic impairment on Avelumab CL in the final Pop PK model.

- **Influence of Renal Impairment**
  No dedicated clinical studies were conducted to evaluate the effect of renal impairment on the PK of Avelumab. The Pop PK analysis examined the potential influence of renal impairment by evaluating the influence of baseline estimated glomerular filtration rate (eGFR) on the parameters of the Pop PK model in a wide range of renal function including none, mild, moderate and severe impairment. There was no influence of eGFR on Avelumab CL in the final Pop PK model. Even though a limited number of subjects with severe renal impairment have been studied, renal impairment including mild, moderate and severe degree is not expected to have an effect on the PK of Avelumab because the molecular weight of Avelumab is much higher than the glomerular filtration cut-off.

2.2.2.2 METASTATIC MERKEL CELL CARCINOMA

The efficacy and safety of Avelumab was demonstrated in the JAVELIN Merkel 200 trial (NCT02155647), an open-label, single-arm, multi-center study conducted in patients with histologically confirmed metastatic MCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease. The trial excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; CNS metastases; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2. Patients received Avelumab 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than 2 weeks, and no need for salvage therapy, could continue treatment. Tumor response assessments were performed every 6 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response. The efficacy analysis was conducted when the last patient enrolled had completed 12 months of follow-up. A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV. Efficacy results are presented in Table 1. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.

Table 1: Efficacy Results of the JAVELIN Merkel 200 Trial

Efficacy Endpoints	Results (N=88)
Overall Response Rate (ORR)	
Overall response rate, (95% CI)	33.0% (23.3%, 43.8%)
Complete response (CR) rate, (95% CI)	11.4% (6.6%, 19.9%)
Partial response (PR) rate, (95% CI)	21.6% (13.5%, 31.7%)
Duration of Response (DOR)	N=29
Range in months	2.8 to 23.3+
Patients with DOR ≥ 6 months, n (%)	25 (86%)
Patients with DOR ≥ 12 months, n (%)	13 (45%)

CI: Confidence interval

2.2.2.3 UROTHELIAL CARCINOMA EXPANSION COHORT

Trial EMR100070-001 enrolled 2 cohorts of subjects with locally advanced or metastatic UC who were either cisplatin ineligible or had PD after at least 1 line of platinum-based therapy. As of 19 March 2016, a combined 241 subjects had been treated in the 2 UC cohorts, of whom 153 had at least 6 months of follow-up (all 44 subjects in the secondary UC cohort and 109 of the 197 subjects in the efficacy UC cohort). Of the 241 subjects, 87 (36.1%) were still on treatment at the time of data cut-off. Table 2 presents the BOR results as assessed by the Independent Endpoint Review Committee (IERC) for the 2 UC cohorts and the pooled group of subjects with at least 6 months follow-up, together with the ORR according to RECIST 1.1 and duration of response.

In the pooled group of 153 subjects with at least 6 months of follow-up, the confirmed ORR was 17.6% (95% CI: 12.0, 24.6), consisting of 9 subjects (5.9%) with CR and 18 subjects (11.8%) with PR. Onset of response was documented at the first or second tumor assessment for 21 of the 27 confirmed responses (77.8%), with a median time to response of 11.43 weeks (range: 5.6 to
48 weeks). Median duration of response was not yet reached (95% CI: 42.14 weeks, not estimable [NE]); the Kaplan-Meier estimate of 24-week durability of response was 92.0% (95% CI: 71.6, 97.9). Of the 27 confirmed responses, 24 (88.9%) were ongoing at the time of data cutoff, with duration of response ranging from 4.7 to 65.7 weeks.

Table 2: Tumor Response Observed in Subjects with ≥ 6 Months Follow-up in Urothelial Carcinoma Cohorts in Trial EMR100070-001

Confirmed BOR by RECIST v1.1, IERC	Secondary Expansion Cohort (n=44) n (%)	Efficacy Expansion Cohort (n=109) n (%)	Pooled (n=153) n (%)
Confirmed Best Overall Response (BOR)			
Complete Response (CR) [a]	5 (11.4)	4 (3.7)	9 (5.9)
Partial Response (PR) [a]	3 (6.8)	15 (13.8)	18 (11.8)
Stable disease	15 (34.1)	21 (19.3)	36 (23.5)
NonCR / nonPR	0	1 (0.9)	1 (0.7)
Progressive disease	15 (34.1)	46 (42.2)	61 (39.9)
Nonevaluable	6 (13.6)	22 (20.2)	28 (18.3)
ORR (%, 95% CI)	8 (18.2) (8.2, 32.7)	19 (17.4) (10.8, 25.9)	27 (17.6) (12.0, 24.6)
Duration of Response [b]			
Median, weeks (95% CI)	NE (12.14, NE)	NE (NE, NE)	NE (42.14, NE)
≥ 24 weeks by K-M estimate, % (95% CI)	87.5 (38.7, 98.1)	94.1 (65.0, 99.1)	92.0 (71.6, 97.9)

BOR: Best Overall Response; CI: Confidence interval; CR: Complete Response; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; NE: not estimable; ORR: Overall Response Rate; P: Partial Response; RECIST: Response Evaluation Criteria in Solid Tumors.

[a] CR or PR was confirmed at a subsequent tumor assessment

[b] Based on number of subjects with confirmed response (CR or PR)

Objective response rate was defined as proportion of subjects with best overall response of CR or PR.

2.2.3 CLINICAL EVIDENCE FOR DOCETAXEL

In a phase II trial of docetaxel conducted in patients with advanced transitional-cell carcinoma (TCC) who had failed to respond to prior cisplatin-based therapy, 30 patients were treated with Docetaxel 100 mg/m2 over 1 hour every 21 days. To avoid allergic reactions and capillary leak, the patients were pre-treated with dexamethasone and diphenhydramine. Four of 30 patients (13.3%; 95% confidence interval [CI], 3.8% to 30.7%) demonstrated a partial response (PR), with durations of response ranging from 3 to 8 months. The estimated median survival duration for all patients is 9 months (95% CI, 6 to 12 months) with a median follow-up time of 14 months (range, 1 to 27). Hematologic toxicity included anemia, thrombocytopenia, neutropenia, and febrile neutropenia. Nonhematologic toxicity included alopecia and mucositis. Fluid retention was not observed and cutaneous toxicity was mild and infrequent. Dose reductions were necessary for adverse events in 18 patients (60%).

As per the NCCN (National Comprehensive Cancer Network) guidelines Version 5.2017, Docetaxel is a standard of care medication in second line therapy for local advanced or metastatic urothelial cancer.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 AVELUMAB:

The following adverse reactions and relative frequency were noted in the clinical studies:

Adverse reactions: >10%:

- Cardiovascular: Peripheral edema (17% to 20%), hypertension (10% to 13%)
- Central nervous system: Fatigue (41% to 50%), dizziness (14%)
- Dermatologic: Skin rash (15% to 22%)
- Endocrine & metabolic: Weight loss (15% to 19%), hyponatremia (grades 3/4: 16%), increased gamma-glutamyl transferase (grades 3/4: 12%)
- Gastrointestinal: Nausea (22% to 24%), diarrhea (18% to 23%), decreased appetite (20% to 21%), abdominal pain (16% to 19%), constipation (17% to 18%), increased serum lipase (14%), vomiting (13% to 14%)
- Genitourinary: Urinary tract infection (21%)
- Hematologic & oncologic: Lymphocytopenia (49%; grades 3/4: 11% to 19%), anemia (35%; grades 3/4: 6% to 9%), thrombocytopenia (27%; grades 3/4: 1%)
- Hepatic: Increased serum AST (34%), increased serum ALT (20%)
- Neuromuscular & skeletal: Musculoskeletal pain (25% to 32%), arthralgia (16%)
- Renal: Increased serum creatinine (≤16%), renal failure (≤16%)
- Respiratory: Cough (14% to 18%), dyspnea (11% to 17%)
- Miscellaneous: Infusion-related reaction (14% to 30%), fever (16%)

Adverse reactions: 1% to 10%:

- Central nervous system: Headache (10%)
- Dermatologic: Pruritus (10%), cellulitis (>1%)
- Endocrine & metabolic: Hyperglycemia (grades 3/4: 3% to 9%), increased amylase (8%), hypothyroidism (immune-mediated: 5%)
- Gastrointestinal: Colitis (immune-mediated: 2%), intestinal obstruction (≥2%)
- Hematologic & oncologic: Neutropenia (6%; grades 3/4: 1%)
- Hepatic: Increased serum alkaline phosphatase (grades 3/4: 7%), increased serum bilirubin (6%), increased serum bilirubin (grades 3/4: 1%)
- Immunologic: Antibody development (4%)

- Neuromuscular & skeletal: Weakness (>1%)
- Renal: Acute renal failure (>1%)
- Respiratory: Pneumonitis (immune-mediated: 1%)
- Frequency not defined: Cardiovascular: Pericardial effusion

Adverse reactions <1%, postmarketing, and/or case reports:

- Adrenocortical insufficiency (immune-mediated), arthritis (immune-mediated), erythema multiforme (immune-mediated), exfoliative dermatitis (immune-mediated), Guillain-Barré syndrome (immune-mediated), hepatitis (immune-mediated), hyperthyroidism (immune-mediated), myocarditis (immune-mediated), myositis (immune-mediated), nephritis (immune-mediated), pemphigoid (immune-mediated), pituitary insufficiency (immune-mediated), psoriasis (immune-mediated), sepsis (systemic inflammatory response; immune-mediated), thyroiditis (immune-mediated), type 1 diabetes mellitus (immune-mediated), uveitis (immune-mediated)

Contraindications

- There are no contraindications

2.3.1.2 DOCETAXEL

The percentages reported for docetaxel monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication.

Adverse Reactions >10%:

- Central nervous system: Central nervous system toxicity (20% to 58%; severe: ≤6%; including neuropathy)
- Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)
- Endocrine & metabolic: Fluid retention (includes edema and effusion; 13% to 60%; severe: 7% to 9%; dose dependent)
- Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
- Hematologic & oncologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days; dose dependent), leukopenia (84% to 99%; grade 4:

32% to 44%), anemia (65% to 97%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (≤14%; dose dependent)

- Hepatic: Increased serum transaminases (4% to 19%)
- Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)
- Infection: Infection (1% to 34%; dose dependent)
- Neuromuscular & skeletal: Weakness (53% to 66%; severe: ≤18%), myalgia (3% to 23%), neuromuscular reaction (16%)
- Respiratory: Pulmonary reaction (41%)
- Miscellaneous: Fever (31% to 35%)

Adverse Reactions 1% to 10%:

- Cardiovascular: Decreased left ventricular ejection fraction (8%), hypotension (3%)
- Central nervous system: Peripheral motor neuropathy (4%; severe; mainly distal extremity weakness)
- Gastrointestinal: Dysgeusia (6%)
- Hepatic: Increased serum bilirubin (9%), increased serum alkaline phosphatase (4% to 7%)
- Infection: Severe infection (6%)
- Local: Infusion site reactions (4%, including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein)
- Neuromuscular and skeletal: Arthralgia (3% to 9%)

Adverse Reactions<1%, postmarketing, and/or case reports:

- Abdominal pain, acute hepatic failure, acute myelocytic leukemia, acute respiratory distress, alopecia (permanent), anaphylactic shock, anorexia, ascites, atrial fibrillation, atrial flutter, back pain, bronchospasm, cardiac arrhythmia, cardiac tamponade, chest pain, chest tightness, chills, colitis, confusion, conjunctivitis, constipation, cystoid macular edema, deep vein thrombosis, dehydration, disease of the lacrimal apparatus (duct obstruction), disseminated intravascular coagulation, drug fever, duodenal ulcer, dyspnea, ECG abnormality, epiphora (more common with weekly administration [Kintzel 2006]), erythema multiforme, esophagitis, flushing, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hearing loss, hemorrhagic diathesis, hepatitis, hypertension, hyponatremia, intestinal obstruction, interstitial pulmonary disease, ischemic colitis, lacrimation, localized erythema of the extremities, loss of consciousness (transient), lymphedema (peripheral), multiorgan failure,

myelodysplastic syndrome, myocardial infarction, neutropenic enterocolitis, ototoxicity, pain, palmar-plantar erythrodysesthesia, pneumonia, pneumonitis, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall phenomenon, renal failure, renal insufficiency, respiratory failure, skin changes (scleroderma-like), seizure, sepsis, sinus tachycardia, skin rash, Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, syncope, tachycardia, thrombophlebitis, toxic epidermal necrolysis, unstable angina pectoris, visual disturbance (transient)

Contraindications

- Severe hypersensitivity to docetaxel or any component of the formulation; severe hypersensitivity to other medications containing polysorbate 80; neutrophil count <1,500/mm^3

2.3.1.3 SPECIFIC SITUATIONS FOR DOCETAXEL:

• Bone marrow suppression: Patients with an absolute neutrophil count <1,500/mm3 should not receive docetaxel. Monitor blood counts frequently to monitor for neutropenia (which may be severe and result in infection). The dose-limiting toxicity is neutropenia. Platelets should recover to >100,000/mm3 prior to treatment. Patients with increased liver function tests experienced more episodes of neutropenia with a greater number of severe infections; monitor liver function tests frequently. Hematologic toxicity may require dose reduction or therapy discontinuation.

• Cutaneous reactions: Cutaneous reactions, including erythema (with edema) and desquamation, have been reported; may require dose reduction.

• Extravasation: Docetaxel is an irritant with vesicant-like properties; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation.

• Fluid retention: Severe fluid retention, characterized by pleural effusion (requiring immediate drainage), ascites with pronounced abdominal distention, peripheral edema (poorly tolerated), dyspnea at rest, cardiac tamponade, generalized edema, and weight gain, has been reported. Fluid retention may begin as lower extremity peripheral edema and become generalized with a median weight gain of 2 kg. In patients with breast cancer, the median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m2; fluid retention resolves in a median of 16 weeks after discontinuation. Patients should be premedicated with a corticosteroid (starting 1 day prior to administration) to reduce the incidence and severity of fluid retention. Closely monitor patients with existing effusions.

• Hypersensitivity reactions: [US Boxed Warning]: Severe hypersensitivity reactions, characterized by generalized rash/erythema, hypotension, bronchospasms, or rare anaphylaxis may occur (may be fatal; has occurred in patients receiving a 3-day corticosteroid premedication). Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. Do not administer to patients with a history of severe hypersensitivity to docetaxel or polysorbate 80. Minor reactions including flushing or localized skin reactions may also occur. Observe for

hypersensitivity, especially with the first 2 infusions. Discontinue for severe reactions; do not rechallenge if severe. Patients should be premedicated with a corticosteroid (starting 1 day prior to administration) to prevent or reduce the severity of hypersensitivity reactions.

• Neurosensory symptoms: Dosage adjustment is recommended with severe neurosensory symptoms (paresthesia, dysesthesia, pain); persistent symptoms may require discontinuation. Reversal of symptoms may be delayed after discontinuation.

• Ocular adverse effects: Cystoid macular edema (CME) has been reported; if vision impairment occurs, a prompt comprehensive ophthalmic exam is recommended. If CME is diagnosed, initiate appropriate CME management and discontinue docetaxel (consider non-taxane treatments). In a study of patients receiving docetaxel for the adjuvant treatment of breast cancer, a majority of patients experienced tearing, which occurred in patients with and without lacrimal duct obstruction at baseline. Onset was generally after cycle 1, but subsided in most patients within 4 months after therapy completion (Chan 2013).

• Secondary malignancies: Treatment-related acute myeloid leukemia or myelodysplasia occurred in patients receiving docetaxel in combination with anthracyclines and/or cyclophosphamide.

• Treatment-related mortality: [US Boxed Warning]: Patients with abnormal liver function, those receiving higher doses, and patients with non–small cell lung cancer and a history of prior treatment with platinum derivatives who receive single-agent docetaxel at a dose of 100 mg/m2 are at higher risk for treatment-related mortality.

• Weakness: Fatigue and weakness (may be severe) have been reported; symptoms may last a few days up to several weeks. In patients with progressive disease, weakness may be associated with a decrease in performance status.

Disease-related concerns:

• Hepatic impairment: [US Boxed Warning]: Avoid use in patients with bilirubin exceeding upper limit of normal (ULN) or AST and/or ALT >1.5 times ULN in conjunction with alkaline phosphatase >2.5 times ULN. Patients with bilirubin elevations or abnormal transaminases (with concurrent abnormal alkaline phosphatase) are at increased risk for grade 4 neutropenia, neutropenic fever, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated transaminase elevations >1.5 times ULN also had a higher rate of grade 4 neutropenic fever, although no increased incidence of toxic death. Monitor bilirubin, AST or ALT, and alkaline phosphatase prior to each docetaxel cycle. The alcohol content of the docetaxel formulation should be taken into account when administering to patients with hepatic impairment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Premedication:

- Premedication with oral corticosteroids is recommended to decrease the incidence and severity of fluid retention and severity of hypersensitivity reactions. We will use dexamethasone 20 mg PO once prior to Docetaxel.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Phase 1b Dose De-escalation: To determine the recommended phase 2 dose (RP2D) of combination therapy with Avelumab and Docetaxel in subjects with metastatic urothelial cancer **Phase 1b Dose Expansion:** To assess the preliminary efficacy of the established dose of combination therapy with Avelumab and Docetaxel in subjects with metastatic urothelial cancer	**Phase 1b Dose De-escalation:** Incidence of dose limiting toxicities in subjects with metastatic urothelial cancer **Phase 1b Dose Expansion:** Best overall response rate (ORR) (complete response (CR) + partial response (PR)) per RECIST v1.1 with the established dose of combination therapy with Avelumab and Docetaxel in subjects with metastatic urothelial cancer	The combination of Docetaxel and Avelumab was not tested in urothelial cancer. Hence, it would be prudent to establish the safe dose of this combination to study in phase II and III clinical trials **Phase 1b Dose Expansion:** The best overall response rate is a good surrogate marker and a suitable endpoint
Secondary		
Phase 1b Dose Expansion: To evaluate the progression-free survival and overall survival of combination therapy with Avelumab and Docetaxel in subjects with metastatic urothelial cancer	**Phase 1b Dose Expansion:** Radiologic progression-free survival (PFS) per RECIST v1.1 criteria. PFS is defined as the time between the first dose of study therapy and the earliest date of progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. Overall survival defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date).	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
Biomarkers PDL-1 immunostains of the tumor specimen. Used for exploring its predictive and prognostic implications. It will not be used for response assessment or trial eligibility.		

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study is a single institution, phase 1b, single arm non-randomized, open label prospective clinical trial to evaluate the combination of Avelumab and Docetaxel in adult subjects with locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

The study has two phases:

1) A Phase 1b dose de-escalation of Docetaxel in combination with Avelumab, to establish the recommended phase 2 dose for the combination. The Dose De-escalation Phase will utilize a 3+3 design over 3 planned dose levels leading to the identification of a RP2D for the combination of Docetaxel and Avelumab. Note: Dose de-escalation is allowed only for Docetaxel and no changes will done to standard dose of Avelumab (i.e, 10 mg/kg).

2) In the dose expansion phase of the study, the fixed dose of Docetaxel in combination with Avelumab will be evaluated. The study is powered to a primary endpoint of overall response rate (ORR) with the combination of Docetaxel and Avelumab. Enrollment for Part 2 will commence only after a RP2D is identified from phase 1.

Treatment will be administered on an outpatient basis. The treatment will be given in two stages. The initial **Induction phase** of treatment will include the combination of Docetaxel and Avelumab for a total of 6 cycles (1 cycle = 21 days). The dose of Avelumab in combination with Docetaxel will be 10 mg/kg administered every 3 weeks (Q3W) to avoid dosing of avelumab during the period of maximum bone marrow suppression for patients receiving Q3W chemotherapy. This schedule of avelumab is predicted to achieve therapeutic avelumab levels based upon PK modeling and simulation, resulting in exposures of avelumab needed to achieve >95% PD-L1 target occupancy (Pfizer data on file). A similar dosing schedule is being investigated in the Arm C of Javelin ovarian 100 clinical trial (NCT02718417).

In the subsequent **Maintenance phase**, the subjects will receive Avelumab every 2 weeks (1 cycle = 2 weeks) until disease progression. Reported adverse events and potential risks are described in section 2.3. Appropriate dose modifications are described in Section 6.1.5 No other investigational or commercial cancer directed agents or therapies other than those described below may be administered.

Safety assessment will follow the guidelines provided in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Patients will be followed both clinically and radiographically. The timeline of these assessments are summarized as per the study calendar. Post-treatment scans will be compared to the baseline scan and responses will be assessed using RECIST v1.1.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

See section 9

4.3 JUSTIFICATION FOR DOSE

4.3.1 DOSE LIMITING TOXICITIES

Standard safety monitoring will be employed for DLT assessment and dose de-escalation decisions. All toxicities (AEs) that are possibly related to the Avelumab and Docetaxel will be considered in DLT assessment unless an event is clearly unrelated to trial treatment. DLTs are assessed *during the first 21 days of therapy*. All AEs, including DLTs, are to be graded using NCI CTCAE, Version 4.03. Attribution of AEs specifically to either Docetaxel or Avelumab is challenging. There are some toxicities that are clearly attributable to either docetaxel or avelumab as per section 2.3.1. The investigator will take the final decision on the attribution of AEs or DLTs if it is related to combination therapy.

The following AEs will be considered DLTs**:**:

Hematologic criteria:

- Grade 4 febrile neutropenia > 7 days
- Grade 4 or greater thrombocytopenia > 7 days
- Grade 3 or 4 thrombocytopenia with significant hemorrhage of any duration.

Non-hematologic criteria:

- Grade ≥ 3 toxicities (non-laboratory)
- Grade ≥ 3 nausea, vomiting or diarrhea despite maximal medical intervention
- Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- Other (non AST/ALT) non-hematologic Grade ≥ 3 laboratory value if the abnormality leads to overnight hospitalization.

Grade 3 or greater treatment-related clinical non-hematological toxicity excluding those listed below:

- Grade 3-4 nausea, vomiting in the absence of maximal medical therapy that resolves in 72 hours
- Grade 3-4 laboratory abnormalities that are not clinically significant and which resolve in 72 hours.
- Grade 3 hypertension that can be controlled with medical therapy.
- Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3-4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.
- Grade 3 or 4 lymphopenia
- Transient asymptomatic laboratory abnormalities that do not require hospitalization

4.4 END OF STUDY DEFINITION

The End-of-study date is defined as the date of the last visit of the last participant. However, the PI reserves the right to terminate the trial at any time. Reasons for discontinuation include but are not limited to:

- Inability to enroll a sufficient number of patients into the trial
- Good clinical practice (GCP) compliance issues that compromise the validity of the trial

Procedures for withdrawal of individual patients can be found in Section 7.2

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age ≥18 to 85 years
2. Histologically or cytologically confirmed locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra). Additional mixed histologies such as squamous, plasmacytoid, adenocarcinoma, sarcomatoid, papillary, micropapillary are permitted provided the urothelial cancer is the predominant histological component.
3. Eligible patients must have had either:
    - Progressed after treatment with at least 1 platinum-containing regimen (e.g., cisplatin or carboplatin plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence, *or*
    - Were ineligible for cisplatin-based chemotherapy, with ineligibility to cisplatin defined by impaired renal function (creatinine clearance <60 ml/min), a hearing loss of 25 decibels at 2 contiguous frequencies, or grade ≥ 2 peripheral neuropathy *or*
    - Locally advanced or metastatic bladder cancer whose disease has progressed within 12 months of neoadjuvant or adjuvant chemotherapy.
4. Biopsy material is required (archival tissue is acceptable if patient could not provide fresh or recent biopsy)
5. ECOG performance status of 0 to 1
6. Estimated life expectancy ≥3 months
7. At least one measurable lesion by RECIST version 1.1
8. Adequate hematologic function defined by white blood cell count ≥3 × 10^9/L with absolute neutrophil count ≥1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥9 g/dL (may have been transfused)
9. Adequate hepatic function defined by a total bilirubin level ≤ the upper limit of normal range (ULN), an aspartate aminotransferase (AST) level ≤1.5 × ULN, and an alanine aminotransferase (ALT) level ≤1.5 × ULN.

10. Adequate renal function defined by an calculated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula

11. Both male and female subjects must be willing to use highly effective contraception (that is, methods with a failure rate of less than 1% per year) throughout the study and for at least 30 days after last avelumab treatment administration if the risk of conception exists (see section 6.1.7). [NOTE: The effects of the study treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, as stipulated in national or local guidelines. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately.

12. Signed written informed consent

5.2 EXCLUSION CRITERIA

- Concurrent treatment with an anticancer treatment
- Prior therapy with any drug targeting T cell coregulatory proteins
- Major surgery for any reason within 4 weeks or if the patient had not fully recovered within 4 weeks
- Concurrent systemic therapy with corticosteroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting trial drug; short-term administration of systemic steroids (that is, for allergic reactions or the management of immune-mediated adverse events while on study is allowed
- Patients with active central nervous metastases will be excluded. Appropriately treated CNS metastases with either surgery or radiation therapy are permitted to participate in the study
- Previous malignant disease (other than urothelial carcinoma) within the last 5 years, with the exclusion of basal or squamous cell carcinoma of the skin, cervical carcinoma in situ and prostate adenocarcinoma with Gleason score 6-7, pT2b.
- Prior organ transplantation, including allogenic stem-cell transplantation
- Known history of testing positive for HIV/AIDS, HBV, or HCV (including acute and chronic infection)
- Active or history of any autoimmune disease or immune-deficiencies (patients with type 1 diabetes, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible)

- Known monoclonal antibody hypersensitivity, history of anaphylaxis, or uncontrolled asthma
- Persisting toxicity related to prior therapy that was > grade 1 according to NCI-CTCAE v4.0; grade ≤2 sensory neuropathy is allowed
- Pregnancy or lactation
- Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication All other significant diseases, which in the investigator's opinion may influence the patient's tolerance of trial treatment. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- Patients with symptomatic severe COPD with continuous oxygen requirement will be excluded.
- Legal incapacity or limited legal capacity, including any psychiatric condition that would prohibit the understanding or rendering of informed consent
- Vaccination within 4 weeks of the first dose of Avelumab and while on study was prohibited except for administration of inactivated vaccines (e.g., inactivated influenza vaccines)

5.3 LIFESTYLE CONSIDERATIONS

No specific restrictions

5.4 SCREEN FAILURES

The reason for screen failure will be documented clearly. If the reason for screen failure is reversible, then the patient can be considered for the re-screening if >1 month has been passed from the time of initial screening, after discussion with primary investigator and the trial sponsor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at the Holden Comprehensive Cancer Center, of the University of Iowa Hospitals and Clinics. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at HCCC/UIHC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 SCREENING AND BASELINE EVALUATION

The screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his/her participation. The investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.
Screening includes obtaining written informed consent, a physical exam, demography, medical history/current medical conditions, current concomitant medications/therapies, disease history and extent of disease, and prior anticancer therapies.

- The following patient demographic and baseline characteristics will be collected:
  · General demography
  · Medical history/current medical conditions (including prior and concomitant medications)
  · History and current disease status (including staging, diagnosis information, , and sites of disease).
  · Additionally, the following assessments will be performed:
  · Physical examination, weight and height
  · Vital signs including sitting blood pressure/pulse and heart rate, respiratory rate and temperature
  · ECOG performance status
- · ECG
- · Safety laboratory assessments: biochemistry, INR, PT, TSH,T3, FT3, FT4, hematology and urinalysis
  · Pregnancy test (if applicable)
  · Chest, abdomen and pelvis CT-scan. Consider MRI if CT scan not feasible
  · Brain MRI (if clinically indicated for assessment of neurological symptoms).

  Patients will be asked to visit the clinic as per the study calendar in section 1.3

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6.1.2 DOSING

Both the study drugs will be administered in the infusion center at Holden Comprehensive Cancer Center. In the initial induction phase, Avelumab is administered 10 mg/kg as an intravenous infusion over 60 minutes every 3 weeks followed by Docetaxel (dose level depends on the study cohort). Docetaxel is administered as per institutional guidelines, the first 2 doses over 90 minutes to decrease the risk of infusion reaction and then subsequently it can be infused over 1 hour through non-absorbing

polyethylene lined (non-DEHP) tubing. After 6 cycles of combination therapy, Avelumab will be continued at 10 mg/kg every 2 weeks.

6.1.3 PREMEDICATION FOR AVELUMAB

Premedicate patients with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of Avelumab. Premedication should be administered for subsequent Avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

6.1.4 PREMEDICATION FOR DOCETAXEL

Premedication with dexamethasone 20 mg PO once prior to docetaxel administration is recommended to reduce the incidence and severity of hypersensitivity reactions and fluid retention.

6.1.5 DOSE MODIFICATIONS AND INTERRUPTION

Subjects will be monitored for AEs from the Cycle 1 Day 1 of infusion of combination therapy until Day 30 post investigational treatment. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be graded by the investigator according to CTCAE v. 4.03. Dose escalation or reduction is not recommended for Avelumab.

The following should be taken into consideration in decisions regarding dose modifications: (reductions or interruption):

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity considered related to study treatment. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- If the etiology of AEs is unclear the first dose reduction must be made to Docetaxel.
- Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table below, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of Docetaxel or Avelumab treatment for AEs may occur at any time per investigator discretion. If treatment is interrupted due to AEs for more than 6 weeks, Docetaxel should be discontinued unless the investigator deems there to previous or ongoing clinical benefit.

- Dose interruptions for reason(s) other than AEs (e.g., surgical procedures) can be longer than 6 weeks. The acceptable length of interruption will be determined by PI.
- **Dose interruption prior to the initiation of a new cycle**: If the investigator decides on day 1 of a new cycle that dose interruption should occur, that cycle may be delayed. When the investigator decides that dosing should resume, the day that the patient restarts drug will be day 1 of that new cycle. Tumor assessments will be adjusted accordingly to match +/-7 days from Day 1 of each even cycle
- Re-escalation to any previous dose may be allowed at the discretion of the investigator no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a previous dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, renal).

Table 4: Dose Modifications of Docetaxel for Treatment Related AEs

CTCAE v4.1	**Recommended Guideline for Management**
Grade 1 AEs	Supportive care as indicated. Continue docetaxel at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue combination therapy at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be** adequately managed	At the discretion of the investigator, Docetaxel should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Docetaxel should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have Docetaxel interrupted immediately. Discontinue Docetaxel unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Management of Avelumab for Immune-Related Adverse Events (IRAEs):

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Management of specific IRAEs:

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 **Diarrhea: < 4 stools/day over Baseline** **Colitis: asymptomatic**	**Continue avelumab therapy** **Symptomatic treatment (e.g. loperamide)**	**Close monitoring for worsening symptoms** **Educate subject to report worsening immediately** **If worsens:** **Treat as Grade 2, 3 or 4.**
Grade 2 **Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL** **Colitis: abdominal pain; blood in stool**	**Withhold avelumab therapy** **Symptomatic treatment**	**If improves to Grade ≤ 1:** **Resume avelumab therapy** **If persists > 5-7 days or recurs:** **Treat as Grade 3 or 4.**
Grade 3 to 4 **Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL** **Colitis (Grade 3): severe abdominal pain, medical intervention indicated,**	**Withhold avelumab for Grade 3.** **Permanently discontinue avelumab for Grade 4 or recurrent Grade 3.** **1.0 to 2.0 mg/kg/day prednisone IV or**	**If improves:** **Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).** **If worsens, persists > 3 to 5 days, or recurs after improvement:**

peritoneal signs **Grade 4: life-threatening, perforation**	**equivalent** **Add prophylactic antibiotics for opportunistic infections** **Consider lower endoscopy**	**Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.**
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 **Covering ≤ 30% body surface area**	**Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)**	**If persists > 1 to 2 weeks or recurs:** **Withhold avelumab therapy** **Consider skin biopsy** **Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper.** **If worsens:** **Treat as Grade 3 to 4.**
Grade 3 to 4 **Grade 3: Covering > 30% body surface area;** **Grade 4: Life threatening consequences**	**Withhold avelumab for Grade 3.** **Permanently discontinue for Grade 4 or recurrent Grade 3.** **Consider skin biopsy** **Dermatology consult** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections**	**If improves to Grade ≤ 1:** **Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).**
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**

Grade 1 **Radiographic changes only**	**Consider withholding avelumab therapy** **Monitor for symptoms every 2 to 3 days** **Consider Pulmonary and Infectious Disease consults**	**Re-assess at least every 3 weeks** **If worsens:** **Treat as Grade 2 or Grade 3 to 4.**
Grade 2 **Mild to moderate new symptoms**	**Withhold avelumab therapy** **Pulmonary and Infectious Disease consults** **Monitor symptoms daily; consider hospitalization** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections** **Consider bronchoscopy, lung biopsy**	**Re-assess every 1 to 3 days** **If improves:** **When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper** **If not improving after 2 weeks or worsening:** **Treat as Grade 3 to 4.**
Grade 3 to 4 **Grade 3: Severe new symptoms; New/worsening hypoxia;** **Grade 4: Life-threatening**	**Permanently discontinue avelumab therapy.** **Hospitalize.** **Pulmonary and Infectious Disease consults.** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections** **Consider bronchoscopy, lung biopsy**	**If improves to Grade ≤ 1:** **Taper steroids over at least 1 month** **If not improving after 48 hours or worsening:** **Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)**
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 **Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin >**	**Continue avelumab therapy**	**Continue liver function monitoring** **If worsens:** **Treat as Grade 2 or 3 to 4.**

ULN to 1.5 x ULN		
Grade 2 **AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN**	**Withhold avelumab therapy** **Increase frequency of monitoring to every 3 days.**	**If returns to Grade ≤ 1:** **Resume routine monitoring; resume avelumab therapy.** **If elevation persists > 5 to 7 days or worsens:** **Treat as Grade 3 to 4.**
Grade 3 to 4 **AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN**	**Permanently discontinue avelumab therapy** **Increase frequency of monitoring to every 1 to 2 days** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections** **Consult gastroenterologist/ hepatologist** **Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted**	**If returns to Grade ≤ 1:** **Taper steroids over at least 1 month** **If does not improve in > 3 to 5 days, worsens or rebounds:** **Add mycophenolate mofetil 1 gram (g) twice daily** **If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.**
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 **Creatinine increased > ULN to 1.5 x ULN**	**Continue avelumab therapy**	**Continue renal function monitoring** **If worsens:** **Treat as Grade 2 to 3 or 4.**
Grade 2 to 3 **Creatinine increased > 1.5 and ≤ 6 x ULN**	**Withhold avelumab therapy** **Increase frequency of monitoring to every 3 days** **1.0 to 2.0 mg/kg/day prednisone or equivalent.** **Add prophylactic antibiotics for opportunistic infections**	**If returns to Grade ≤1:** **Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper.** **If worsens:** **Treat as Grade 4.**

	Consider renal biopsy	
Grade 4 **Creatinine increased > 6 x ULN**	**Permanently discontinue avelumab therapy** **Monitor creatinine daily** **1.0 to 2.0 mg/kg/day prednisone or equivalent.** **Add prophylactic antibiotics for opportunistic infections** **Consider renal biopsy** **Nephrology consult**	**If returns to Grade ≤1:** **Taper steroids over at least 1 month.**
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	**Withhold avelumab therapy.** **Hospitalize.** **In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.** **Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.** **Guideline based supportive treatment as per cardiology consult.*** **Consider myocardial biopsy if recommended per cardiology consult.**	**If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.** **If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.**
Immune-mediated myocarditis	**Permanently discontinue avelumab.** **Guideline based supportive treatment as appropriate as per cardiology consult.*** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections.**	**Once improving, taper steroids over at least 1 month.** **If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).**

***Local guidelines, or eg. ESC or AHA guidelines** **ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines** **AHA guidelines website:** **http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001**		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	**Continue avelumab therapy** **Endocrinology consult if needed** **Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate.** **Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)**	**Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.**
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	**Withhold avelumab therapy** **Consider hospitalization** **Endocrinology consult** **Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.** **Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)**	**Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).** **Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.**
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	**If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with**	**Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).**

	inappropriately low ACTH) : • **Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)** • **Hormone replacement/suppressive therapy as appropriate** • **Perform pituitary MRI and visual field examination as indicated** **If hypophysitis confirmed:** • **Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month** • **Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.** • **Add prophylactic antibiotics for opportunistic infections.**	**In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.** **Continue hormone replacement/suppression therapy as appropriate.**
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	**Withhold avelumab therapy pending clinical investigation**	**If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy** **If irAE is confirmed, treat as**

		Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	**Withhold avelumab therapy** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections** **Specialty consult as appropriate**	**If improves to Grade ≤ 1:** **Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.**
Recurrence of same Grade 3 irAEs	**Permanently discontinue avelumab therapy** **1.0 to 2.0 mg/kg/day prednisone or equivalent** **Add prophylactic antibiotics for opportunistic infections** **Specialty consult as appropriate**	**If improves to Grade ≤ 1:** **Taper steroids over at least 1 month.**
Grade 4	**Permanently discontinue avelumab therapy** **1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed** **Add prophylactic antibiotics for opportunistic infections** **Specialty consult.**	**If improves to Grade ≤ 1:** **Taper steroids over at least 1 month**
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	**Permanently discontinue avelumab therapy** **Specialty consult**	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.0).

Management of infusion - Related reactions:

In order to mitigate infusion-related reactions, subjects have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of Avelumab. Premedication should

be administered for subsequent Avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab:

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild · Mild transient reaction; infusion interruption not indicated; intervention not indicated	· Decrease the Avelumab infusion rate by 50% and monitor closely for any worsening
Grade 2 – moderate · Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for £ 24h	· Temporarily discontinue Avelumab infusion · Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening · Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae · Grade 4: Life-threatening consequences; urgent intervention indicated	· Stop the Avelumab infusion immediately and disconnect infusion tubing from the subject · Subjects have to be withdrawn immediately from Avelumab treatment and must not receive any further Avelumab treatment

IV: intravenous; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.1.6 WARNINGS AND PRECAUTIONS FOR AVELUMAB:

IMMUNE-RELATED PNEUMONITIS

Avelumab can cause immune-related pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater pneumonitis. Withhold Avelumab for moderate (Grade 2) pneumonitis, and permanently discontinue for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis.

Pneumonitis occurred in 1.2% (21/1738) of patients receiving Avelumab including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3 pneumonitis. Immune-related

pneumonitis led to permanent discontinuation of Avelumab in 0.3% (6/1738) of patients. Among the 21 patients with immune-related pneumonitis, the median time to onset was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to 4+ months). All 21 patients were treated with systemic corticosteroids; 17 (81%) of the 21 patients received high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Resolution of pneumonitis occurred in 12 (57%) of the 21 patients at the time of data cut-off.

IMMUNE-RELATED HEPATITIS

Avelumab can cause immune-related hepatitis including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater hepatitis. Withhold Avelumab for moderate (Grade 2) immune-related hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-related hepatitis.

Immune-related hepatitis occurred in 0.9% (16/1738) of patients receiving Avelumab including two (0.1%) patients with Grade 5 and 11 (0.6 %) patients with Grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of Avelumab in 0.5% (9/1738) of patients. Among the 16 patients with immune-related hepatitis, the median time to onset was 3.2 months (range: 1 week to 15 months), and the median duration of hepatitis was 2.5 months (range: 1 day to 7.4+ months). All 16 patients were treated with corticosteroids; 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Resolution of hepatitis occurred in 9 (56%) of the 16 patients at the time of data cut-off.

IMMUNE-RELATED COLITIS

Avelumab can cause immune-related colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater colitis. Withhold Avelumab for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue Avelumab for life-threatening (Grade 4) or for recurrent (Grade 3) colitis upon re-initiation of Avelumab.

Immune-related colitis occurred in 1.5% (26/1738) of patients receiving Avelumab including seven (0.4%) patients with Grade 3 colitis. Immune-related colitis led to permanent discontinuation of Avelumab in 0.5% (9/1738) of patients. Among the 26 patients with immune-related colitis, the median time to onset was 2.1 months (range: 2 days to 11 months) and the median duration of colitis was 6 weeks (range: 1 day to 14+ months). All 26 patients were treated with corticosteroids; 15 (58%) of the

26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Resolution of colitis occurred in 18 (70%) of the patients at the time of data cut-off.

IMMUNE-RELATED ENDOCRINOPATHIES

Thyroid disorders (Hypothyroidism/Hyperthyroidism)

Avelumab can cause immune-related thyroid disorders. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone-replacement therapy. Initiate medical management for control of hyperthyroidism. Withhold Avelumab for severe (Grade 3) or life threatening (Grade 4) thyroid disorders.

Immune-related thyroid disorders occurred in 6% (98/1738) of patients receiving Avelumab including 3 (0.2%) Grade 3 immune-related thyroid disorders. Immune-related thyroid disorders led to discontinuation of Avelumab in 0.1% (2/1738) of patients. Hypothyroidism occurred in 90 (5%) patients, hyperthyroidism in seven (0.4%), and thyroiditis in four (0.2%) patients treated with Avelumab. Among the 98 patients with immune-related thyroid disorders, the median time to onset was 2.8 months (range: 2 weeks to 13 months) and the median duration was not estimable (range: 6 days to more than 26 months). Immune-related thyroid disorders resolved in seven (7%) of the 98 patients.

ADRENAL INSUFFICIENCY

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids as appropriate for adrenal insufficiency. Withhold Avelumab for severe (Grade 3) or life threatening (Grade 4) adrenal insufficiency.

Adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving Avelumab including one patient (0.1%) with Grade 3 adrenal insufficiency. Immune-related adrenal insufficiency led to permanent discontinuation of Avelumab in 0.1% (2/1738) of patients. Among the 8 patients with immune-related adrenal insufficiency, the median time to onset was 2.5 months (range: 1 day to 8 months). All eight patients were treated with corticosteroids; four (50%) of the eight patients received high-dose corticosteroids for a median of 1 day (range: 1 day to 24 days).

TYPE 1 DIABETES MELLITUS

Avelumab can cause type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold Avelumab and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia. Resume treatment with Avelumab when metabolic control is achieved on insulin replacement or anti-hyperglycemics.

Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients and led to permanent discontinuation of Avelumab.

IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION

Avelumab can cause immune-related nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater nephritis. Withhold Avelumab for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to ≤ Grade 1. Permanently discontinue Avelumab for life-threatening (Grade 4) nephritis.

Immune-related nephritis occurred in 0.1% (1/1738) of patients receiving Avelumab; Avelumab was permanently discontinued in this patient.

OTHER IMMUNE-RELATED ADVERSE EVENTS

Avelumab can result in severe and fatal immune-related adverse reactions. These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during Avelumab treatment; however, immune-related adverse reactions can occur after discontinuation of Avelumab.

For suspected immune-related adverse reactions, evaluate to confirm or rule out an immune- related adverse reaction and to exclude other causes. Depending upon the severity of the adverse reaction, withhold or permanently discontinue Avelumab, administer high dose corticosteroids, and if appropriate, initiate hormone replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper. Resume Avelumab when the immune-related adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue Avelumab for any severe (Grade 3) immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

The following clinically significant, immune-related adverse reactions occurred at an incidence of less than 1% of 1738 patients treated with Avelumab for each of the following adverse reactions: immune-

related myocarditis including fatal events, immune-related myositis, hypopituitarism, uveitis, and Guillain-Barré syndrome.

INFUSION-RELATED REACTIONS

Avelumab can cause severe or life-threatening infusion-related reactions. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue Avelumab for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.

Infusion-related reactions occurred in 25% (439/1738) of patients treated with Avelumab including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent (1615/1738) of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade ≥ 3 reactions were treated with intravenous corticosteroids.

6.1.7 PREGNANCY, LACATION AND FERTILITY ISSUES WITH AVELUMAB

PREGNANCY

Based on its mechanism of action, Avelumab can cause fetal harm when administered to a pregnant woman.

In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.

Human IgG1 immunoglobulins are known to cross the placenta. Therefore, Avelumab has the potential to be transmitted from the mother to the developing fetus.

Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in fetal loss. Therefore, potential risks of administering Avelumab during pregnancy include increased rates of abortion or stillbirth.

Advise females of reproductive potential to use effective contraception during treatment with Avelumab and for at least one month after the last dose of Avelumab. Highly effective methods of contraception

are those that, alone or in combination, result in afailure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:
1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository).
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female patients of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum FSH level within the laboratory's reference range for postmenopausal women.

All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

LACTATION

There is no information regarding the presence of Avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of Avelumab due to the potential for serious adverse reactions in breastfed infants.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Drug accountability and subject compliance will be assessed with drug dispensing and return records.

Study Drug Accountability: The investigator will maintain accurate records of receipt of all Avelumab, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused Avelumab will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

DOSAGE FORMS AND STRENGTHS
Injection: 200 mg/10 mL (20 mg/mL), clear, colorless to slightly yellow solution in a single-dose vial.

6.2.3 PRODUCT STORAGE AND STABILITY

All study medications will be stored and inventoried in accordance with applicable state and federal regulations.

Avelumab Injection is a sterile, preservative-free, and clear, colorless to slightly yellow solution for intravenous infusion supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL), individually packed into a carton (NDC 44087-3535-1). Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light. Do not freeze or shake the vial. The vial stopper is not made with natural rubber latex.

Preparation of Avelumab:
• Visually inspect vial for particulate matter and discoloration. Avelumab is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter.
• Withdraw the required volume of Avelumab from the vial(s) and inject it into a 250-mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection.
• Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing.
• Inspect the solution to ensure it is clear, colorless, and free of visible particles.
• Discard any partially used or empty vials.

Storage of diluted Avelumab solution:
Protect from light
Store diluted Avelumab solution:
• At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution.
Or

• Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze or shake diluted solution.

- **Administration of Avelumab:**
  • Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron).
  • Do not co-administer other drugs through the same intravenous line.
- **Setting:** Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access
- **Observation period:** Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study is non-randomized and open label.

6.4 CONCOMITANT THERAPY

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Palliative surgery (for eg: TURBT) is allowed for symptom control (eg: bleeding or intractable pain). Procedures such as thoracentesis, paracentesis, pericardial fluid drainage etc, are also allowed for symptom management. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion.. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded. All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded.

Prohibited Concomitant Medications and/or Treatments:
Subjects are prohibited from receiving the following therapies during the Screening, Treatment Phases of this trial.

- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than Avelumab and Docetaxel
- Radiation therapy for tumor control
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu (that contain a live virus), H1N1 flu, rabies, BCG, and typhoid vaccine.
- Long term use of high dose glucocorticoids (>40mg) for any purpose other than to modulate symptoms from an event of clinical interest, use as a pre-medication for chemotherapeutic agents specified in the protocol, or for use as a pre medication in subjects with a known history of an IV contrast allergy administered as part of CT radiography. Replacement doses of steroids (for example, prednisone 5-10 mg daily) are permitted while on study. Short course of glucocorticoids for the treatment of non-immune related issues such as COPD, asthma, osteoarthritis, chronic back pain etc at the discretion of investigator is allowed.
- Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed. These therapies may be continued IF treatment with an agent from one of these two classes was initiated PRIOR to signing informed consent

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.
Subjects may receive other medications that the investigator deems to be medically necessary.

6.4.1 RESCUE MEDICINE

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Nausea/vomiting: Administration of prophylaxis for nausea and vomiting should be administered per institutional guidelines and local standard practices for the standard of care chemotherapies.For Avelumab, the therapy is considered to be of low to moderate emetogenic potential. Consideration for chemo induced nausea and vomiting prophylaxis should be given in subsequent cycles of the administration according to standard institutional practice and should not be routinely administered prior to the initial trial treatment of Avelumab. Subjects should be strongly encouraged to maintain liberal oral fluid intake

Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications. Consider a potential immunologic etiology.

Neutropenia: Use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is allowed in accordance to institutional standards or as deemed appropriate by study investigator.

Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

Events of Clinical Interest with a potential immunologic etiology (ECI): Please see the separate guidance document in the administrative binder regarding identification, evaluation and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an ECI, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Treatment with Docetaxel and Avelumab may continue until one of the following events occurs:

- Documented disease progression after confirmation with a scan as per the criteria described in section 8
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences.
- Patient withdraws consent
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient.
- Patient is lost to follow-up
- Pregnancy in patient

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients may withdraw from the study at any time. Patients who discontinue early should return within 30 days (+/- 7 days) of the last dose of the study drugs for a follow-up evaluation. Any assessments listed for the final visit in the Schedule of Activities will be performed at that time.

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The trial coordinator will attempt to contact the participant and reschedule the missed visit, at the earliest available appoint and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator and trial coordinator will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 END OF TREATMENT AND PREMATURE WITHDRAWAL VISIT

- An end of treatment visit will occur 30 days(+/- 7days) after last dose of study treatment. After the End of Treatment visit, patients without disease progression will be followed every 3 months (+1 month) with CT scans per physician standard of care. Patients with disease progression or who have started subsequent therapy will move to survival only data collection (passive chart review or phone calls) every 3 months (+1 month) for 2 years, then every 6 months (+ 1 month) until death or lost-to-follow up.
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8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Conventional response criteria may not adequately assess the activity of immunotherapy because progressive disease (by initial radiographic assessment) does not necessarily reflect therapeutic failure. The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy as:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after disease progression as defined by conventional criteria (because of potential for pseudo progression/tumor-immune infiltration)
- The appearance of new lesions may not represent PD with immunotherapy

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study will implement the following in addition to standard RECIST 1.1 criteria:

- Patients progressing by RECIST 1.1 criteria will be allowed to remain on study treatment (provided they have no significant clinical deterioration) until disease progression is confirmed in follow up scans obtained in 6 weeks. If the patients have confirmed disease progression in the follow-up scan when compared to the first assessment scan, then they will be taken off study. On the other hand, if the patients have partial response or stable disease when compared to the first assessment scan, they will continue with the study therapy.
- The study treatment will be discontinued if significant clinical deterioration occurs at any time due to disease progression. Some examples of significant clinical deterioration include – new CNS metastases, organ failure, cord compression etc.

EFFICACY ASSESSMENT SCHEDULE:

- The intention of the study design is to closely monitor patients with safety follow-up and disease assessments in the absence of study discontinuation criteria.
- For the purposes of this study, patients should be re-evaluated after Cycles 3 and 6 and then every 12 weeks during maintenance treatment. **In addition to a baseline scan, confirmatory scans will** also be obtained in 6 weeks following initial documentation of an objective response (CR, PR) or progressive disease (PD).
-

The tumor assessment (TA) performed during screening will be used as a baseline for efficacy assessments. CT/MRI imaging of the chest, abdomen and pelvis is required at screening and at each TA,

regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest, abdomen and pelvis scans in subjects where there is clinical suspicion of deep soft tissue metastases (e.g., lesions in the thigh). Such additional CT/MRIs will be required at Screening when deep soft tissue disease is known/suspected and must be consistently repeated at all TAs if a deep soft tissue lesion is identified during screening**.** The same imaging modality must be used for all TAs, unless contraindicated. Imaging-based evaluation is preferred to clinical examination. IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast maybe used. If contrast cannot be used then non-contrast scans are allowed as determined by investigator.Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g., from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

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Definition of Measurable and Non-measurable Lesions:

- **Disease measurements:**

We will use RECIST 1.1 to define measurable and non-measurable lesions.

Measurable Lymph nodes: Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring 10 mm to <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Measurable disease: (non-nodal):
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam.
Target lesions:

At screening (baseline), when more than one measurable lesion is present all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Non-Target lesions:

All other lesions (or sites of disease) including pathological lymph nodes, malignant effusions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver/lung metastases').

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Note: Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

EVALUATION OF TARGET LESIONS

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the investigator should prevail in such circumstances, and the progression status should be confirmed by scans in 6 weeks.

EVALUATION OF BEST OVERALL RESPONSE:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

DEFINITIONS FOR RESPONSE EVALUATION:

- **Objective response rate (ORR)** defined as the proportion of all treated subjects whose best response at any time during the study following initiation of therapy is confirmed CR or confirmed PR. This will be assessed according to the RECIST v1.1

- **Progression free survival (PFS)** defined as the time between the first dose of study therapy and the earliest date of confirmed progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS.

- **Disease control rate (DCR)** defined as the percentage of patients achieving CR + PR + SD at any time during the study following initiation of therapy. This will be assessed according to RECIST v1.1 criteria.

- **Overall survival (OS)** defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date), will also be analyzed.

8.2 SAFETY ASSESSMENTS

- An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03.
- Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
- All adverse events regardless of CTCAE grade must also be evaluated for seriousness.
  As the study treatment is combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign, symptoms, clinically significant laboratory abnormality,, temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event is any adverse event occurring at any dose or during any use of Investigation product/s that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

  The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the CRF.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

An investigator who is a qualified physician will evaluate all adverse events as to:

CTCAE V 4.03	
Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic

	observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The determination of the likelihood that the study treatment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

8.3.3.3 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment.

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

8.3.8 ADVERSE EVENT REPORTING

For non-serious Adverse Events, documentation must begin from the time the informed consent document is signed through the 30 day follow-up period after study drug is discontinued**.**

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)v.4.03), onset and resolved dates (if applicable), and the relationship to the study drug

should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

8.3.9 SERIOUS ADVERSE EVENT REPORTING

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Given the potential risk for delayed immune-related toxicities, SAE's that are at least possibly related to study drug will be captured for 90 days after the last dose of study drug administration.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

8.3.10 REPORTING EVENTS TO PARTICIPANTS

All grade 4 adverse events noted among other patients in this study, or other studies with this combination will be notified to other patients enrolled in the study.

8.3.11 REPORTING OF PREGNANCY

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 working days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The combination of Avelumab and Docetaxel was not tested in urothelial cancer. Hence, it would be prudent to establish the safe dose of this combination to study in phase II and III clinical trials. We hypothesize the combination of Avelumab and Docetaxel is safe and efficacious in patients with metastatic urothelial cancer.

Primary Endpoints:

Phase 1b Dose De-escalation: Incidence of dose limiting toxicities (DLTs) with combination of Avelumab and Docetaxel in subjects with metastatic urothelial cancer

Phase 1b Dose Expansion: Overall response rate (ORR) (complete response (CR) + partial response (PR)) per RECIST v1.1 with the established dose of combination therapy with Avelumab and Docetaxel in subjects with metastatic urothelial cancer

Secondary Endpoints:

Phase 1b Dose Expansion:

- Radiologic progression-free survival (PFS) per RECIST v1.1. PFS is defined as the time between the first dose of study therapy and the earliest date of confirmed progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. Efficacy assessments as per section 8.
- Overall survival (OS) defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date).

9.2 SAMPLE SIZE DETERMINATION

Phase Ib De-escalation phase:
The primary objectives of the Phase 1b portion of this study are to assess the safety of and determine the recommended dose of a combination treatment of avelumab (10 mg/kg) and docetaxel for metastatic bladder cancer. This study will utilize a standard 3+3 dose de-escalation design. The dose levels to which patients will be assigned in sequential cohorts are listed below.

	Avelumab	Docetaxel
Level 0	10 mg/kg	75 mg/m2
Level -1	10 mg/kg	60 mg/m2
Level -2	10 mg/kg	45 mg/m2

An initial cohort of three patients will be treated at dose level 0. Decision of when and how to de-escalate are described below.

Number of patients with DLT at a given dose level	Decision Rule
0 out of 3	Enter 3 additional patients at the same dose level • If 1 or fewer of these three patients experience DLT, this dose level will be declared the maximally administered dose. • If 2 or more experience a DLT, de-escalate to next dose level.
1 out of 3	Enter up to 3 additional patients at the same dose level. • If 0 of these 3 patients experience DLT, this dose level will be declared the maximally administered dose. • If 1 or more of these 3 patients experience DLT, de-escalate to the next dose level.
≥2 out of 3	De-escalate the next dose level.

Up to 6 patients will be treated at each dose level. If DLT meets the stopping boundaries set by the above dose algorithm at dose level 0 (for example, more than 1 out of 3 or more than 1 out of 6 patients), the next set of 3 patients will be entered at the dose level of -1. If dose level -1 meets the stopping boundaries, the next set of 3 patients will be entered at dose level -2. If dose level -2 meets the stopping boundaries, the trial will be stopped. The recommended Phase Ib dose for the expansion cohort will be defined as the highest dose level for which at most 1 out of 6 patients experience a DLT.

Phase Ib Expansion

The primary objective of the expansion cohort is to evaluate initial tumor response to a combination treatment of avelumab (10 mg/kg) and docetaxel at the recommended dose for metastatic bladder cancer. The overall response rate for avelumab alone in second line is approximately 18% [3]. For the combination treatment, a response rate of 33% or more is considered clinically important, whereas 18% or below is considered uninteresting. A response is defined as a complete or partial response. To obtain preliminary information regarding the response rate and evaluate futility, sample size requirements are based on the probability of stopping early for futility under the two response rates. If the true response rate is 33%, we want to probability of stopping for futility to be less than 15% and if the true response rate is 18% we want the probability of stopping for futility to be at least 65%. The table below shows the probability of stopping for futility under the two response rates when R or fewer of the N patients has a response.

Number of Patients (N)	Rejection number (R)	Probability of stopping under response rate of 33%	Probability of stopping under response rate of 18%
20	4	15.9%	71.5%
20	5	30.8%	86.4%
21	3	4.9%	46.2%
21	**4**	**12.8%**	**67.7%**

21	5	25.9%	83.8%
22	3	3.8%	42.2%
22	4	10.2%	63.8%

The bolded line in the table is the preferred combination of patients and responses. Twenty one (21) patients will be enrolled. If 4 or fewer patients have a response the trial will stop for futility. If 5 or more patients have a response, the treatment will be deemed worthy of further investigation in a Phase II Trial.

Sample Size/Accrual Rate
The Phase Ib portion of this study is expected to require a minimum of 6 and a maximum of 18 evaluable patients (if de-escalation to dose levels -1 and -2 is warranted). Patients treated in Phase Ib at the recommend dose will also be included in the Phase Ib expansion portion. Additional evaluable patients will be accrued for a total of 21 patients treated at the recommended dose. The anticipated accrual rate is 1-2 patients per month who would meet inclusion criteria.

9.3 POPULATIONS FOR ANALYSES

The safety population will include all enrolled patients who receive at least 1 dose of both Avelumab and Docetaxel. The primary analysis population for the study will include the safety population with separate analyses for Phase 1 dose escalation and Phase 1b dose expansion cohort. The efficacy population will comprise all patients who receive at least 1 dose of both Avelumab and Docetaxel and who have baseline and at least 1 post-baseline imaging assessment.

9.4 STATISTICAL ANALYSES

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, changes are made to primary or exploratory objectives and/or hypotheses, or to the statistical methods related to those objectives and/or hypotheses, then those changes, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR. No imputations will be made for missing data. Additional details of the statistical analyses to be performed will be provided in the trial Statistical Analysis Plan.

9.4.1 GENERAL APPROACH

Descriptive statistics will be employed to evaluate the endpoint and analyze the data. Summary statistics for continuous variables will include mean, standard deviation, median and range.

Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier medians and survival plots. Data listings will be created to support tables and present data. The preliminary efficacy analysis will be conducted on the efficacy evaluable population and safety analysis will be performed on the safety population. SAS 9.2 or higher

will be used for data analysis. The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline

9.4.4 SAFETY ANALYSES

All safety data will be analyzed descriptively. Absolute and relative frequencies will be used to describe the incidence of all injection-site reactions, AEs, SAEs, deaths, and laboratory values. DLTs occurring in Phase 1 will be summarized by dose level received and presented in both tables and listings

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics will be listed by patient and summarized using the all-treated population. Descriptive summary statistics (sample size, mean, median, SD, and range, when appropriate) will be provided for the continuous variables such as age, weight, and height. Count and percentage will be reported for categorical variables such as sex, race, and ethnicity.

9.4.6 PLANNED INTERIM ANALYSES

No interim efficacy analysis is planned.

9.4.7 SUB-GROUP ANALYSES

No sub-group analysis is planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

The investigator must maintain detailed records of all trial participants who are enrolled in the trial or who undergo screening. Source documents include, but are not limited to, patient medical records and investigator's patient trial files, as well as all test results.

The following minimum information should be entered into the enrolled patient's source documents:

- The date the patient entered the trial and the patient number
- The trial protocol number
- The date that informed consent was signed
- Evidence that the patient meets trial eligibility requirements (e.g., medical history, trial procedures, evaluations)
- The dates of all trial-related patient visits
- Evidence that trial-required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of trial medication accountability
- Occurrence and status of any AEs

• The date the patient exited the trial, and a notation as to whether the patient completed the trial or was discontinued early, including the reason for discontinuation
• Any deviations from the protocol

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Potential subjects will be recruited from patients seen at the Holden Comprehensive Cancer Center at University of Iowa Hospitals and Clinics who appear to be eligible for the study. A member of the research team will meet with the patient to go over the informed consent document and answer any questions they may have. Other potential treatment options, whether investigational or standard of care, will be discussed with the patient. The patient will be given the time they need to make their decision; they are encouraged to discuss it with their family and/or friends. If the patient decides to participate, they will need to sign the consent form during one of their clinic visits. No study-specific procedures will be performed before the informed consent document is signed.

To avoid coercion, potential patients will be informed that they are free to refuse to participate in the trial, and that refusing to participate will not affect the availability of future medical care at UIHC. A copy of the signed informed consent document will be given to the patient.

10.1.2 DATA MONITORING AND MANAGEMENT

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

10.1.2.1 SUBJECT DATA

For HCCC investigator initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than 14 (fourteen) business days after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than 14 (fourteen) business days following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

10.1.2.2 FORMS MONITORING

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

10.1.2.3 FINAL REPORTS

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

10.2 TRIAL-SPECIFIC DATA AND SAFETY MONITORING PLAN

10.2.1 STUDY RISK-LEVEL:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ❑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 ADvers 1% – 5%
- ☑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

10.2.2 REPORTING AND MONITORING REQUIREMENTS:

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore data export

10.2.3 SELECTED MONITORING STRATEGY BASED ON RISK-LEVEL:

10.2.3.1 RISK LEVEL 4

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

10.2.3.2 STUDY SAFETY REVIEW

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

10.2.4 ADDITIONAL REPORTING REQUIREMENTS:

- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

Monitoring will involve the following:

- review eligibility of patients accrued to the study,
- check for the presence of a signed informed consent,
- determine compliance with protocol's study plan,
- determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
- compare accuracy of data in the research record with the primary source documents,
- review investigational drug processing and documentation,
- Assess cumulative AE/SAE reports for trends and compare to study stopping rules.

FDA Reporting Requirements (for Sponsor-Investigators)

It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571. See Instructions for completing Form 3500A. Please note all instance of UIHC, location, and faculty / staff should be redacted from supporting documentation and the 3500A.

The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

For detailed explanation of the above definitions, requirements, and procedures related to IND application safety reports and the responsibilities of IND applications sponsors with regard to such reporting, refer to Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (PDF - 227KB)

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known (grading the event per CTCAE)
- Supportive laboratory results and diagnostics

- Sponsor-Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

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6. Boyerinas, B., et al., *Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti-PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells.* Cancer Immunol Res, 2015. **3**(10): p. 1148-57.

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