Clinical Study Protocol
BTCRC-GU15-023

Phase Ib/II Study of Concurrent Durvalumab And Radiation Therapy (DUART) Followed by Adjuvant Durvalumab in Patients with Urothelial Cancer (T2-4 N0-2 M0) of the Bladder: Big Ten Cancer Research Consortium BTCRC-GU15-023

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PROTOCOL SIGNATURE PAGE

Phase Ib/II Study of Concurrent Durvalumab And Radiation Therapy (DUART) Followed by Adjuvant Durvalumab in Patients with Urothelial Cancer (T2-4 N0-2 M0) of the Bladder: Big Ten Cancer Research Consortium BTCRC-GU15-023

VERSION DATE: 18MAY2020

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

PLASE EMAIL COMPLETED FORM TO BTCRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	Phase Ib/II Study of Concurrent Durvalumab And Radiation Therapy (DUART) Followed by Adjuvant Durvalumab in Patients with Urothelial Cancer (T2-4 N0-2 M0) of the Bladder
SHORT TITLE	Durvalumab and Radiation Therapy (DUART)
PHASE	Ib and II
OBJECTIVES	**Primary Objectives:** Phase Ib: • To assess the safety of combining durvalumab with RT. Phase II: • To estimate the progression free survival (PFS) rate at 1 year. • To estimate the disease control rate (DCR) (DCR=complete response [CR] +partial response [PR] +stable disease [SD]) to concurrent durvaRT followed by durvalumab. **Secondary Objectives:** Phase Ib: • To estimate the DCR post completion of concurrent durvaRT. • To correlate the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR Phase II: • To estimate the median progression free survival (PFS) time. • To estimate the rate of complete remission (CR) post durvaRT by modified RECIST 1.1. • Estimate the overall survival (OS) **Exploratory Objectives:** • To explore the correlation between the PD-1, PD-L1 and FOXP3 (T-regulatory cells) expression on immunohistochemistry pre-treatment (TURBT specimen) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR, PFS and OS • We will also explore if the combination of RT with durvalumab increases the PD-L1+ status in tumor specimen when compared to baseline. We will compare the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) • To explore the correlation of PD-1 expression on T cells from peripheral blood with clinical outcomes. Peripheral blood will be collected at pretreatment, post durvaRT, and post completion of treatment with adjuvant durvalumab. • To explore correlation of next generation sequencing (NGS) of tumors and blood at pretreatment and at post durvaRT with response rate for durvaRT +adjuvant durvalumab. As part of NGS, RNA-seq would be performed and and we would attempt to perform immunosubtyping based on expression data, as well as perform deconvolution analysis in an effort to understand changes in tumor immune cell inflammation. In addition, we will do next generation

	sequencing of urine cell free DNA at pretreatment and will correlate with tumor sequencing at pretreatment stage. * • To explore the correlation of plasma cytokines such as IFN-γ level with clinical outcomes. Peripheral blood will be collected prior to durvaRT, post completion of durvaRT and post treatment of adjuvant durvalumab. Inflammatory cytokines such as IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular cytokine release by CD4 and CD8 T cells, and their phenotypic subsets, will be assessed by flow cytometry. Correlation between the level of cytokine production and clinical outcomes (RR, PFS, OS) will be analyzed.* * Contingent upon available funding.
STUDY DESIGN	Single arm study to assess the safety of combining durvalumab with RT in phase Ib cohort followed by expansion to phase II cohort. The patients from Phase Ib will be rolled over and combined with patients in Phase II in the analysis.
KEY ELIGIBILITY CRITERIA	**Phase Ib subjects:** • Locally advanced urothelial cancer of bladder who have any of the following: o T3-4, N0-2 M0, **OR** Tx N1-2 M0 **OR** T2 N1-2 M0 treatment naïve who are either unresectable, **OR** medically unfit for surgery* **OR** cisplatin ineligible**. Please note that T3 N0 M0 patients can be included if they are cisplatin ineligible**. o Patients who have T3-4, N0-2 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0 post-neoadjuvant chemotherapy who become unresectable **OR** are medically unfit for surgery* **Phase II subjects:** • Locally advanced urothelial cancer of bladder with any of the following: o T3-4, N0-2 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0: Treatment naïve, unresectable, **OR** medically unfit for surgery* **OR** cisplatin ineligible**. Please note that T3 N0 M0 patients can be included if they are cisplatin ineligible**. o T3-4, N0-1 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0 patients post-neoadjuvant chemotherapy who become unresectable **OR** unfit for surgery* (Please note: the stage of tumor is based on prechemotherapy status at the time of diagnosis) • T2, N0, M0 patients, treatment naïve, who are cisplatin ineligible** can be included in the study. • T2 N0 M0 patients who are treatment naïve or post neoadjuvant chemotherapy but are unfit for surgery* may also be enrolled. *Unfit for surgery is based on patient's cardiac status or pulmonary status or any co-morbidity that can put patients at high risk for complications during or after surgery. "Unfit for surgery" status has to be determined by treating surgeon. **Cisplatin ineligiblity is defined by the presence of one or more of the following: • Impaired renal function (GFR ≥ 30 but ≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-

acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation.

- Grade ≥ 2 Hearing Loss (hearing loss measured by audiometry of 25 dB at two contiguous frequencies)
- Grade ≥ 2 peripheral neuropathy
- ECOG Performance Status of 2
- Solitary Kidney
- Any other medical condition that makes patient cisplatin ineligible based on assessment by treating Oncologist, such as severe coronary artery disease (CAD), congestive heart failure, etc.

All subjects:

- Written informed consent and HIPPA authorization obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Age ≥ 18 years at time of informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
- Life expectancy of >6 months per treating physician
- Histologically proven pure or mixed urothelial carcinoma of bladder. Small cell histology would be excluded
- Subjects must have archival tissue available from previous TURBT (preferred) or lymph node core biopsy within 8 weeks of treatment or be assessed by the treating urologist to undergo maximal TURBT. The extent of TURBT may vary for each patient and will be determined by the treating urologist. Further, the treating urologist will decide if performing the TURBT is clinically appropriate. If the potential subject does not have tumor amenable to biopsy, there is insufficient tissue for PD-L1 testing or is not clinically appropriate for TURBT, enrollment must be discussed with the sponsor-investigator on a case-by-case basis.
- Adequate normal organ and marrow function as defined below:
  - Hemoglobin ≥ 9.0 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
  - Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
  - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
  - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal
  - Serum creatinine CL>30 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

    Males:

    $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

    Females:

	Creatinine CL (mL/min) = $\frac{\text{Weight (kg) x (140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$ x 0.85 • Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry. • Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. • No previous systemic immunotherapy. Previous use of intravesical BCG is acceptable • No previous radiation therapy to the pelvic area.
STATISTICAL CONSIDERATIONS	**Statistical Methods and Data Analysis:** Descriptive statistics will be used in the study to analyze patient's characteristics and demographics. In particular, patient age, race, weight, ECOG performance status will be described. For phase Ib, the incidence and type of DLTs will be tabulated and reported at the dose level. Other toxicity information will be summarized via frequency tables by type and grade of toxicity. The combined treatment will be considered safe to continue to phase II part of the study if 0 or 1 patient (out of 6) experiences DLT. For phase II, the primary endpoints are the progression free survival (PFS) status at 1 year, and the disease control status (CR+PR+SD) post completion of durvaRT followed by adjuvant durvalumab. The PFS will be analyzed using the Kaplan–Meier estimator with particular emphasis for one-year survival rate. Progression free survival rate at one year is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 and cystoscopy at 1 year from the start of durvalumab treatment, D1 of durvaRT. The disease control status will be summarized using point estimate values of the relative frequency and their 95% confidence intervals. Appropriate statistical tests will be used to compare the PFS rate and the disease control rate from the study sample to the existing values from historical cohorts. The secondary endpoints include the progression-free survival (PFS) time, overall survival (OS) time, and the rate of complete remission (CR) post durvaRT by RECIST/cystoscopy. The survival (PFS and OS) time will be graphical displayed by the Kaplan-Meier survival curve. The median survival time and its 95% CI will be reported. The statistical methods use for analyzing the CR rate and relapse rate will be similar to that for the disease control rate. The bi-variate relationship between the outcome variables and some key some key clinical and demographic variables, such as tumor stage, ECOG status, smoking status, and gender, etc. will be examined by Fisher's exact test or Kaplan-Meier test when appropriate. For the factors that show marginally significant relationship (for example, $p<0.1$), their relationship with the outcome variable will be reexamined by using some multiple regression methods, such as multiple logistic regression or multiple Cox proportional hazard regression. All analyses will be performed using statistical software SAS version 9.4 or higher

	(SAS Institute, Cary, NC, USA). The statistical significance level to be used is 0.05. **Sample Size Determination:** Statistical Power and Sample Size Considerations: The Phase Ib component consists of one dose level only so it requires a maximum of 6 patients. **Given the safety is not dose dependent; no dose de-escalation will be allowed.** For the Phase II component, we hope our therapy will increase the rate of PFS at 12 months from 50% to 75%. There is paucity of literature to support the exact PFS rate for this subgroup of patients. As this study is expected to enroll higher stage patients with T4 or node positive disease, it is assumed that the historic PFS rate is around 50% at 1-year (PFS rate for stage IV patients who achieve CR is around 80% but those who do not achieve CR it falls between 0-40%). To reach a statistical power of at least 80% at one-sided alpha level of 5% and to allow for 10% drop out rate, a total of 26 patients are needed for this part which allows for 10% dropout. The second primary objective of Phase II is to estimate the disease control rate (DCR), which we assume to be about 75%. With 26 combined patients in Phase Ib and Phase 2, we can, with 90% confidence, estimate DCR within 14% error. 6 patients from the Phase Ib will be included in the analysis with patients from the Phase II portion for a total number of patients of 26.
TOTAL NUMBER OF SUBJECTS	N = 26
ESTIMATED ENROLLMENT PERIOD	Estimated 36 months
ESTIMATED STUDY DURATION	Estimated 48 months

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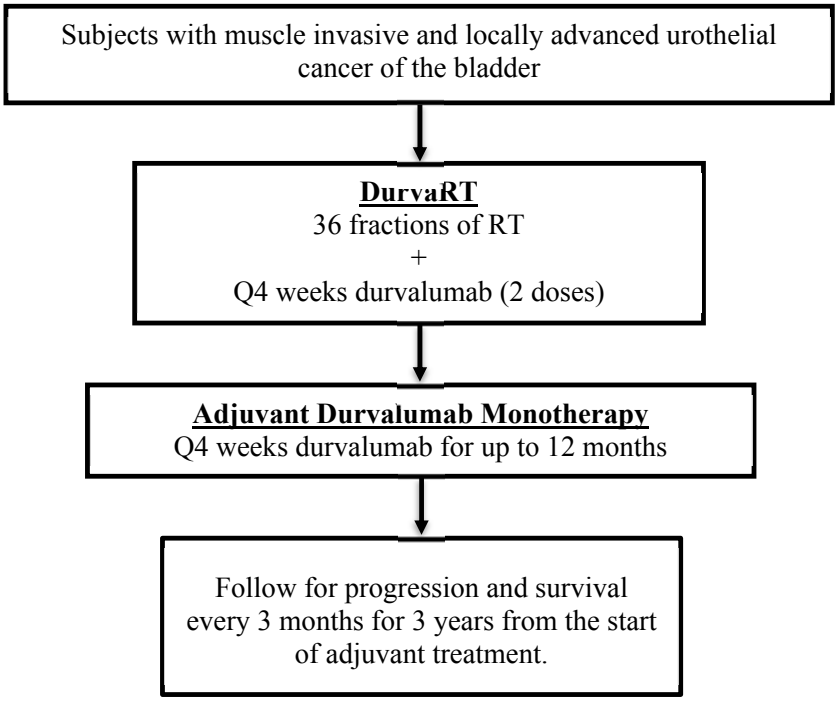
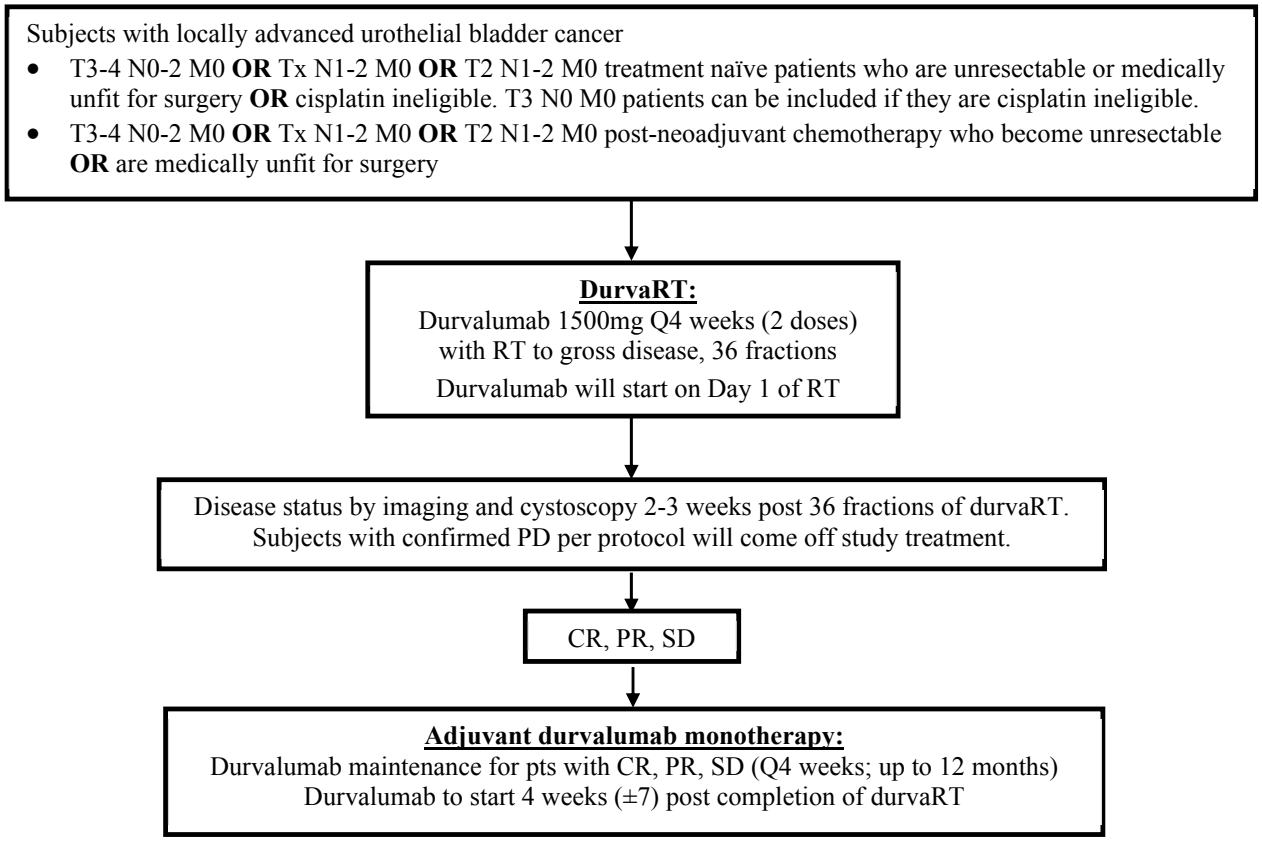
OVERALL STUDY SCHEMA

N=26 patients



PHASE IB SCHEMA

N=up to 6 patients



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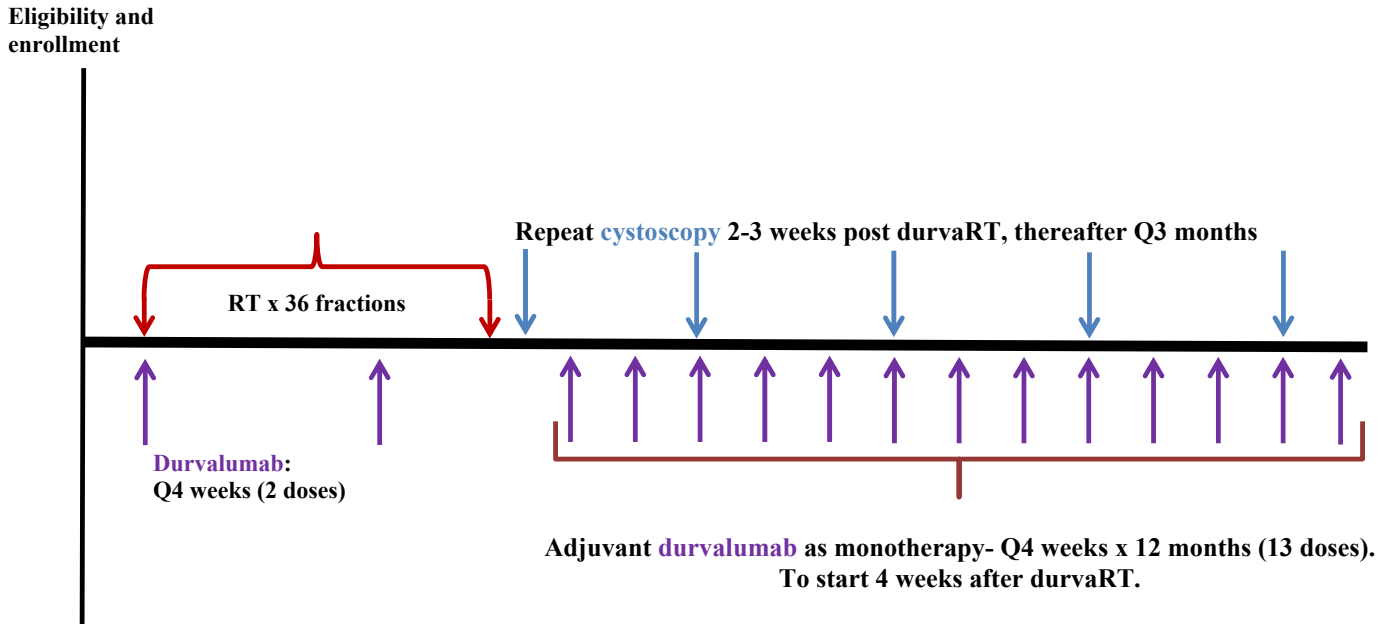
PHASE IB TREATMENT SCHEMA



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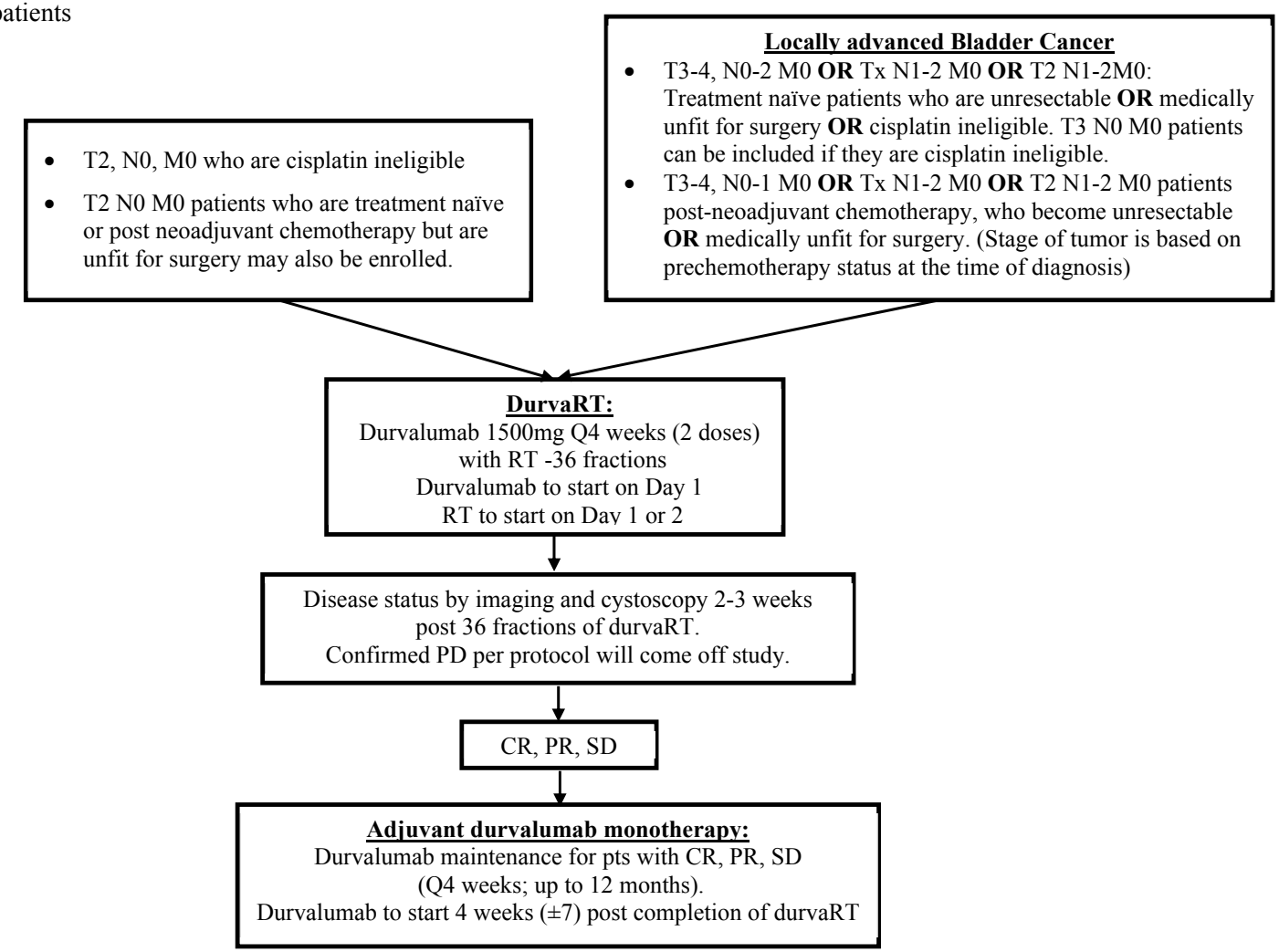
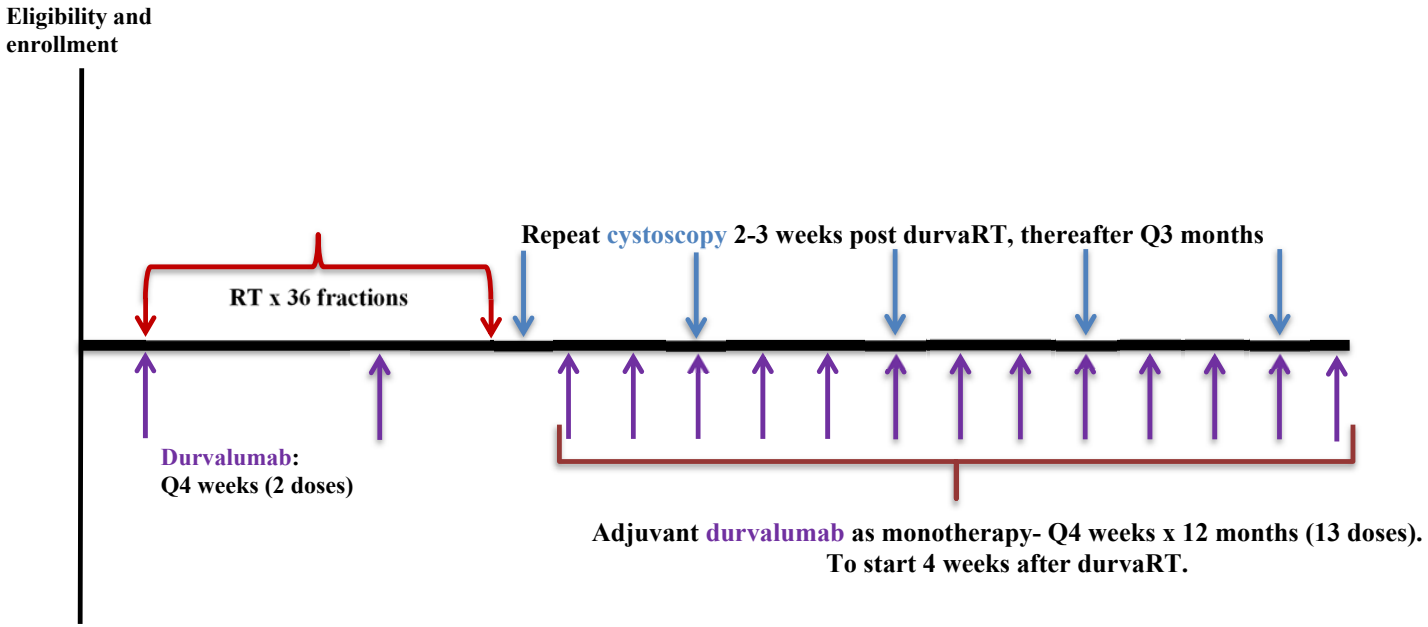
PHASE II SCHEMA

N=26 patients



PHASE II TREATMENT SCHEMA



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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
C_{max}	peak concentration
$C_{max,ss}$	peak concentration at steady state
C_{min}	trough concentration
$C_{min,ss}$	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CXCL 9	The chemokine (C-X-C motif) ligand 9
CXCL 10	The chemokine (C-X-C motif) ligand 10
CXCL 16	The chemokine (C-X-C motif) ligand 16
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
durvaRT	Durvalumab+radiation

Abbreviation or special term	Explanation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry
IL	interleukin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle-invasive bladder cancer
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging

Abbreviation or special term	Explanation
mRNA	messenger ribonucleic acid
MVAC	Methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RC	Radical cystectomy
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	**Explanation**
RNA	ribonucleic acid
RT	Radiation therapy
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
T_{max}	time to peak concentration
$T_{max,ss}$	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
TURBT	Transurethral resection of bladder tumor
UC	Urothelial cancer
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Bladder cancer is the 4th most common cancer amongst men and in 2016, it is estimated that approximately 76,960 new cases of bladder cancer will be diagnosed in the United States, with approximately 16,390 deaths from this malignancy [1]. Tumors invading the deep muscle of the bladder wall are staged as T2, while T3 and T4 lesions invade the perivesical tissue and local structures respectively. Transurethral resection of bladder tumor (TURBT) is considered standard of care for non-muscle invasive cancers of bladder but 2/3rd of patients experience recurrences, with approximately 1/3rd of those eventually requiring radical cystectomy due to progression of their disease to muscle invasive bladder cancer. Cisplatin-based chemotherapy forms the mainstay of systemic treatment for bladder cancer patients who have locally advanced (chemotherapy in neoadjuvant setting) or metastatic disease.

Over the last decade, there has been a tremendous increase in FDA approved therapeutic options for various malignancies but choices for bladder cancer have mostly remained unchanged. Historically, surgical resection via radical cystectomy, has achieved approximate 5-year recurrence-free survival rates of 81%, 68%, 47%, and 44% for pathologic T2, T3a, T3b, and T4a tumors, respectively [2]. The 5-year overall survival (OS) rate is 78% for organ-confined, node-negative disease but this declines to 45% when lymph nodes are involved, though an extended lymphadenectomy for node-positive disease may achieve a slight survival advantage [3].The 5-year OS rate for node-negative patients with extravesical extension is 47% but again falls to 25% in node-positive disease.

Neoadjuvant chemotherapy was introduced to treat micrometastatic disease in patients with T2b-T4a at the time of diagnosis as approximately half of these patients would develop metastatic disease within 2 years from surgery [4]. Neoadjuvant chemotherapy followed by radical cystectomy (RC) is the gold standard for treatment of patients with T2-4 N0-1 M0 bladder cancers. The SWOG (Southwest Oncology Group) trial is one of the most referenced clinical trials that support the benefit with neoadjuvant chemotherapy [5]. The patients with node-negative MIBC (cT2-T4N0M0) were randomized to receive either three cycles of MVAC followed by RC (n=153) or to undergo immediate RC (n=154). There was no statistically significant difference in 5-yr OS at two-sided testing but the results were promising (MVAC plus RC: 57%; RC alone: 43%; two-sided p=0.06). Patients in the neoadjuvant chemotherapy cohort were more likely to achieve a pT0 status at the time of RC (48% vs. 15%; p<0.001). Large meta-analyses showed that cisplatin-based neoadjuvant chemotherapy adds about a 5% 5-year OS benefit over cystectomy alone for T2-T4a Nx M0 bladder cancer patients [6]. Most recently two prospective clinical trials have shown benefit with accelerated or dose dense neoadjuvant 3-4 cycles of MVAC chemotherapy followed by RC in patients with T2-4 N1 M0 bladder cancer patients [7] [8]. However, both these studies included patients with N1 positive disease with nodes <2cm, but N1 positive disease is truly classified as stage IV with high risk for recurrence and poor survival so the role of this approach of neoadjuvant chemotherapy in N+ disease is still questionable. Despite the advancement in surgical techniques and addition of neoadjuvant platinum-based chemotherapy about 50% of these patients will relapse with the development of distant metastases and will subsequently die from the disease [2] [5].

In the setting of operable muscle invasive urinary bladder cancer, selective bladder preservation utilizing maximum TURBT, chemotherapy, and radiation therapy results in 5-year disease-specific survival rates of 60 – 70% [9] [10] [11] [12]. The BC2001 trial which randomized 360 patients with muscle invasive bladder cancer to radiation therapy with or without chemotherapy demonstrated improved outcomes with chemoradiotherapy over radiotherapy alone including 2-year locoregional disease-free survival of 67% versus 54% and 5-year overall survival of 48% versus 35% [13]. Multiple selective bladder preservation Radiation Therapy Oncology Group (RTOG) trials incorporated an induction phase of chemotherapy and radiation therapy with a planned break of 2 – 4 weeks for repeat cystoscopy to identify non-responders with the anticipation for early cystectomy in the event of local progression [Table]. Complete response (CR) was seen in about 70% of patients. Recognizing the favorable outcomes with bladder preservation, this approach has been evaluated in poor-risk, non-cystectomy candidates in an effort to improve disease control. One pilot study evaluating paclitaxel with concurrent radiation therapy resulted in 27 of 28 evaluable patients achieving a complete or partial remission with a 3-year OS of 40% [14]. RTOG 0524 was a phase I/II trial evaluating paclitaxel alone with daily radiation therapy and the combination of paclitaxel and trastuzumab for HER2/neu overexpression with daily radiation therapy following TURBT for non-cystectomy candidates with muscle invasive bladder cancer [15]. The radiation therapy dose and fractionation in RTOG 0524 was prescribed to deliver 39.6 Gy in 22 daily fractions to a small pelvic field followed by a field reduction to treat the whole bladder for an additional 14.4 Gy in 8 daily fractions followed by a final boost to the bladder tumor bed for 10.8 Gy in 6 daily (total dose to bladder tumor bed was 64.8 Gy in 36 daily fractions). Complete response rates at 12 weeks following treatment were 58% in the paclitaxel group and 69% in the paclitaxel with trastuzumab group but acute toxicity was observed in about 30% of patients. Most common grade greater than 3 adverse events were marrow suppression, diarrhea, and hyponatremia. While the response rates were encouraging, adverse events limit applicability in this poor-risk population.

Selected Radiation Therapy Oncology Group (RTOG) Bladder Preservation Trials									
Trial	**Stage**	**Induction RT (Gy/Fx)**	**Induction CT**	**Planned Break (weeks)**	**CR**	**Consolidative RT (Gy/Fx)**	**Consolidative CT**	**Total RT Dose (Gy/Fx)**	**OS**
RTOG 99-06	cT2 – T4a, N0	40.3/26	Cisplatin/ paclitaxel	3	81%	24/16	Cisplatin/Taxol, Cisplatin/Gemcitabine	64.3/42	56% 5 yr
RTOG 97-06	cT2 – T4a, N0	40.8/24	Cisplatin	3	74%	24/16	Cisplatin	64.8/40	61% 3 yr
RTOG 95-06	cT2 – T4a, N0	24/8	Cisplatin/5-FU	3 – 4	67%	20/8	Cisplatin/5-FU	44/16	83% 3 yr
RTOG 89-03	cT2 – T4a, N0	39.6/22	± MCV, Cisplatin	4	61%	25.2/14	Cisplatin	64.8/36	49% 5 yr
RTOG 88-02	cT2 – T4a N0	39.6/22	MCV, Cisplatin	2	80%	25.2/14	Cisplatin	64.8/36	62% 4 yr
RTOG 85-12	cT2 – T4, N0 – N2	40/20	Cisplatin	2	66%	24/12	Cisplatin	64/32	64% 3 yr

To date radical cystectomy with bilateral pelvic lymphadenectomy remains the standard of care therapy for patients with muscle invasive urothelial cancer (UC) of the bladder. But there are significant numbers of patients who are either not able to undergo surgery or are deemed unresectable due to locally advanced disease and for this select group of patients the options are limited. It is also important to note that most of these studies where neoadjuvant chemotherapy

followed by RC or chemoradiation approach were found to be effective were not done on node positive disease where current standard of care is systemic chemotherapy followed by salvage surgery. This currently represents an unmet need in the management of bladder cancer. We propose to study the effect of combining immunotherapy with radiation followed by adjuvant immunotherapy in T2-4 N0-2 M0, bladder cancer patients. For both phase Ib and phase II part we will include T3-4, N0-1 M0 **or** Tx N1-2 M0 **or** T2 N1-2 M0 patients who are either treatment naïve but unresectable or unfit for surgery **or** cisplatin ineligible **or** become unresectable **or** unfit for surgery post-neoadjuvant chemotherapy. However, T3N0 treatment naïve patients can only be included if they are ineligible for cisplatin-based chemotherapy. Please see the eligibility criteria for details. In addition, for the phase II part we will also include T2, N0, M0 who are ineligible to get cisplatin based chemotherapy.

1.2 Immunotherapy Treatment in UC

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung [16], renal [17] [18] [19], pancreatic [20] [21] [22], and hematologic malignancies [23] tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell [24] [25]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination [26].

The advances in immunotherapy with the development of immune checkpoint inhibitors have revolutionized the care in metastatic melanoma, non-small cell lung cancers [27] [28] [29]. Agents targeting PD-1 pathway, such as anti-PD-1, anti-PD-L1 monoclonal antibodies (MAb), have also shown promising results in the early phase I clinical studies in patients with UC [30] [31]. Powles et al., showed an overall 27% response rate in patients with cisplatin refractory advanced UC with the use of anti-PD-L1 MAb, atezolizumab. On May 18, 2016, atezolizumab received FDA approval for the treatment of locally advanced or metastatic urothelial cancer who have disease progression during or follow platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before or after surgery. The use of the anti-PD-1 agent, pembrolizumab has also shown comparable efficacy in metastatic UC [31]. The FDA approval for atezolizumab was based on results of IMvigor210 trial that demonstrated that atezolizumab, has around 15% overall response in refractory UC patients with a median OS of 7.9 months [32]. This affirms the effectiveness of PD-1 directed

blockade in UC and paves the way to test the efficacy of these immune checkpoint inhibitors in the earlier stages on UC. There are several other studies investigating the role of immunotherapy in early stage bladder cancer with muscle invasive node negative disease as well as upfront treatment for metastatic UC. However despite these advances, patients are not cured of their disease, hence development of further therapeutic regimens is required to improve survival in bladder cancer.

The response of the body's immune system to an external pathogen or tumor is initiated by antigen recognition, differentiation and expansion of activated T-cells followed by immune attack. There are two major pathways that play a key role in downregulating the immune attack and those include CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 checkpoints. Radiotherapy (RT) is known to cause local tumor control and is used in patients with localized disease. RT damages tumor DNA leading to tumor cells apoptosis and necrosis and these dying tumor cells release tumor antigens that induces anti-tumor specific immune response [33]. This promotes immune responses through stimulation of IFN-gamma and enhances T-cell infiltration. RT also causes abscopal effect, where by, in addition to controlling tumor growth at the site it is being delivered, it also minimizes, or eradicates cancer at distant sites [33]. The combination of an immune check point inhibitor, CTLA-4 and fractionated RT resulted in abscopal effects in xenograft models of breast and colon cancer [34]. Preclinical studies have shown that RT can enhance the therapeutic efficacy of PD-1/PD-L1 MAbs in triple negative xenograft model [35]. There are a few ongoing clinical trials evaluating the role of RT in combination with immune checkpoint inhibitors in metastatic solid malignancies (such as NCT02318771), but there are no clinical trials evaluating the role of concurrent immunotherapy with RT followed by adjuvant immunotherapy in bladder cancer.

1.3 Durvalumab Treatment

1.3.1 Durvalumab Background

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD] 274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.3.2 Summary of non-clinical experience with durvalumab

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-**γ**). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as

monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab -related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA: durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab.

Finally, data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the *in vivo* toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.3.3 Summary of clinical experience with durvalumab

As of the DCO dates (15Apr2015 to 18Sep2015, Durvalumab IB Version 9.0), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

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1.3.4 Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09 Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 μg/mL throughout the dosing interval.

As of 09 Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

1.3.5 Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-mediated AEs (imAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

1.3.6 Adverse Event Profile of Durvalumab Monotherapy

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue

(17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

The results from this phase I study has led FDA to grant breakthrough therapy designation to durvalumab in February 2016, for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen. Durvalumab is currently FDA approved for metastatic patients post cisplatin.

Encouraging results from this study has led to the design of a phase III study in bladder cancer. DANUBE is a phase III study that is evaluating the efficacy of durvalumab alone vs. durvalumab plus anti-CTLA4 Mab, tremelimumab vs. standard of care in 1st line setting for metatstatic chemo naïve cisplatin eligible and cisplatin ineligible patients. The results are expected by 2018.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were

dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

1.3.7 Efficacy

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease [5] in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

1.3.8 Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens for monotherapy. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommend only for subjects with > 30kg total body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (see Documents/Info tab of the EDC for dose calculations on subjects less than or equal to 30 kg).

1.4 Rationale for combining durvalumab with RT

Despite advances in immunotherapeutic options for cancer patients, only a select group of patients benefit from this strategy. Hence trials of combinational approaches are needed to enhance the efficacy of these immunotherapeutic agents. Radiation induces immunogenic cell death comprising of 3 main steps- cell surface transfer of calreticulin, extracellular release of high mobility group protein-B1 and release of ATP [36] [37] [38]. Immunogenic cell death causes production of neo-antigens that causes activation of tumor-specific T-cell activation and in addition ionizing radiation causes upregulation of various pro-inflammatory signals (CXCL9, CXCL10, CXCL16, IFN, interleukin 1β, MHC-1) that play a key role in immune-regulatory pathway, leading to improved anti-tumor immunity. Verbrugge *et.al*. demonstrated in animal model that combination of RT with concominant and adjuvant anti PD-1 agent can enhance the release of tumor antigens thus synergistically improving the anti-tumor immunity [35]. RT is known to cause local control of tumor but it also causes abscopal effect, where by, in addition to controlling tumor growth at the site it is being delivered, it minimizes, or eradicates cancer at distant sites [33]. The combination of an immune check point inhibitor, CTLA-4 and fractionated RT resulted in abscopal effects in xenograft models of breast and colon cancer [34]. There are various clinical trials evaluating the efficacy of combining radiation therapy with checkpoint inhibitors. Koller *et.al*. (personal communication with the author) retrospectively compared 70 patients with melanoma who had ipilimumab and concurrent radiation therapy vs 31 who had ipilimumab alone and found a higher CR rate (25.7& vs 6.45% p=0.04 and an improved OS (21 vs 10 months p=0.025) in the concurrent group suggesting that concurrent radiotherapy can improve the outcomes of check-point inhibitor therapy. The combination was well tolerated with no grade 3 or more side effects. The preliminary evidence suggests that combining radiation

therapy with immune-checkpoint inhibitor could enhance the efficacy of immunotherapeutic agents in cancer.

Our study is combining anti-PD-L1 agent, durvalumab with radiation therapy followed by 12 months of adjuvant durvalumab for patients with UC of bladder who have locally advanced disease with no distant metastases. The current standard of care for locally advanced node negative UC of bladder is neoadjuvant chemotherapy followed by surgery whereas chemoradiation remains the second best option for these patients. Despite the advancement in surgical techniques and addition of neoadjuvant platinum-based chemotherapy about 50% of these patients will relapse with the development of distant metastases and will subsequently die from the disease. It is well-recognized that improved survival is associated with absence of residual disease in the surgical specimen after neoadjuvant chemotherapy but at best approximately 30-35% of patients achieve pathological remission with these strategies [5] [13]. The 5-year OS is approximately 82-85% in those who achieve a pT0 stage as opposed to 40-45% in those who have residual disease at the time of cystectomy [2]. Given the high rate of recurrences and poor survival associated with patients who do not achieve pathological complete response, there is an urgent need to develop a treatment strategy to prevent the development of metastases.

Patients who have node positive disease are truly stage IV per American Joint Committee of Cancer (AJCC) 6th and 7th edition guidelines. These patients are very high risk for recurrence and have worse overall survival [2]. Earlier studies have demonstrated that node positive locally advanced UC of bladder patients, who got RC after achieving PR post 6 cycles of systemic chemotherapy, lived longer when compared to those who did not get surgery [39]. But the role of neoadjuvant chemotherapy and surgery in stage IV disease is poorly defined and until more definitive data from well-designed phase 3 study shows similar outcomes when compared to node negative disease, the standard of care should be systemic treatment. Systemic chemotherapy in stage IV disease gives a median OS of 13-15 months at best and for patients who progress on or after platinum based therapy, treatment options are limited. Hence more research for better therapeutic approach is needed in this select group of patients to devise better therapeutic options.

1.5 Hypothesis:

We propose a phase I/II clinical trial of concurrent and adjuvant anti-PD-L1 antibody, durvalumab in combination with radiation therapy in patients who have UC of bladder (T2-4, N0-2, M0) treatment naïve or post neoadjuvant chemotherapy who are either unresectable OR unfit for surgery or have refused surgery (post neoadjuvant chemo).

We hypothesize that RT will enhance the therapeutic efficacy of immunotherapy. Since the current standard of care for patients who are locally advanced and are not candidates for surgery is chemotherapy or chemoradiation, we plan to combine radiation with anti-PD-L1 antibody. We postulate that this combination of durvalumab, an anti-PD-L1 antibody with radiation will result in better progression free survival and disease control rate.

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1.5.1 Rationale for Objectives:

Primary Objectives:

Phase Ib:

- *To assess the safety of combining durvalumab with RT:* The phase Ib part of the study will help us determine the safety of combining the standard dose of RT with durvalumab. There is evidence from our retrospective study that the combination of RT plus immune checkpoint inhibitor is safe and is better when compared to immune checkpoint inhibitor alone (Koller et.al.- personal communication). There are ongoing studies in various solid tumor types evaluating this similar concept but there are no studies currently evaluating the efficacy of combining standard RT with PD-L1 MAb in bladder cancer. Thus, our phase Ib part will help us determine the safety for this unique combination.

Phase II:

- *To estimate the progression free survival (PFS) rate at 1 year:* We will be evaluating the efficacy of treating patients with locally advanced UC of bladder (T2-4, N0-2, M0) with concurrent durvalumab and RT to bladder and involved lymph node followed by adjuvant durvalumab. We believe that PFS rate at 1 year will be the surrogate end point for PFS and OS and will help us evaluate efficacy with this treatment strategy.
- *To estimate the disease control rate (DCR) (DCR=complete response [CR]+partial response [PR] +stable disease [SD]) to concurrent durvaRT followed by durvalumab by modified RECIST 1.1*: We will be determining the DCR, defined for this study as rates of patients achieving CR, PR or SD, post completion of concurrent durvaRT+ adjuvant durvalumab per modified RECIST 1.1 criteria.

Secondary Objective(s):

Phase Ib:

- *Estimate the DCR post completion of concurrent durvaRT by modified RECIST 1.1*: We will be determining the disease control rate, defined as percentage of patients achieving CR, PR, SD post completion of concurrent durvaRT in the phase I part of the study. This will give us some preliminary evidence for efficacy of durvaRT combination.
- *To correlate the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR*: We will be determining the correlation between PD-L1 expression on tumor and tumor infiltrating cells when compared to clinical outcome (DCR). Previous study by a PD-L1 MAb has suggested PD-L1 expression playing a potential role as a predictive biomarker for response in metastatic setting in bladder cancer to immune checkpoint blockade [30]. This is an important end-point to determine the role of PD-L1 status as an effective predictive biomarker for response to durvalumab.

Phase II:

- *Estimate the median progression free survival (PFS) time:* We will be determining the median PFS for our cohort and will compare it to the available median PFS from historical controls. Since this is a single arm phase II study with an innovative approach

for patients with locally advanced UC of bladder, who are not fit for surgery, there is limitation in having an active comparator arm.

- *Estimate the rate of complete remission (CR) post durvaRT by modified RECIST 1.1:* Rate of CR is one of the secondary objectives for phase II part of this study. This will help us determine the actual effectiveness of durvaRT approach. CR will be determined with the help of imaging and cystoscopy post completion of durvaRT per modified RECIST 1.1.
- *Estimate the overall survival (OS)*: OS is defined, as time from start of treatment to the date of death due to any cause, or to the date of censoring at the last time the subject was known to be alive in intention-to-treat population. OS is one of the secondary objectives of this study. This is an immunotherapy based clinical trial and it is prudent to determine the OS to reflect the long-term benefit from this therapeutic approach.

Exploratory Objective(s):

- *To explore the correlation between the PD-1, PD-L1 and FOXP3 (T-regulatory cells) expression on immunohistochemistry at pre-treatment (TURBT specimen) and post-durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR, PFS and OS:* We will explore the correlation between PD-L1 expression on tumor and tumor infiltrating cells when compared to clinical outcome (DCR, PFS, OS). Previous study by a PD-L1 MAb has hinted towards PD-L1 playing a potential role as a predictive biomarker for response in metastatic setting in bladder cancer to immune checkpoint blockade [30]. This is an important end-point to determine the role of PD-L1 status as an effective predictive biomarker for response to durvalumab. In addition, we will perform IHC scores for PD-1, FOXP3 to determine its correlation with tumor stage and clinical outcome.
- *We will also explore if the combination of RT with durvalumab increases the PD-L1+ status in tumor specimen when compared to baseline*. We will compare the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT). There is preliminary evidence from pre-clinical data and retrospective study that radiation will enhance the efficacy of PD-1 MAb therapy. We will explore if radiation will upregulate the PD-L1 expression.
- *Explore the correlation of PD-1 expression on T cells from peripheral blood with clinical outcomes*: Peripheral blood will be collected at baseline, post completion of durvaRT and post completion of adjuvant durvalumab. Expression of PD-1 on CD4+ and CD8+ T cells will be assessed by flow cytometry. Correlation between the level of PD-1 expression and clinical outcomes (DCR, PFS, OS) will be analyzed.
- *To explore correlation of next generation sequencing (NGS) of tumors and blood at pretreatment and at post durvaRT with response rate for durvaRT +adjuvant durvalumab. As part of NGS, RNA-seq would be performed and we would attempt to perform immunosubtyping based on expression data, as well as perform deconvolution analysis in an effort to understand changes in tumor immune cell inflammation. In addition, we will do next generation sequencing of urine cell free DNA at pretreatment and will correlate with tumor sequencing at pretreatment stage[##]:* We will explore the correlation between mutational statuses- upregulation of specific mutation/pathway, mutational burden with clinical outcome. We will also do NGS at baseline on ucfDNA

and compare it to the tumor NGS for specificity and sensitivity. This will help us determine the role of circulating DNA in urine as a non-invasive surrogate marker for tumor biopsies.

- *To explore the correlation of plasma cytokines such as IFN-γ level with clinical outcomes*[##]. Peripheral blood will be collected prior to durvaRT, post completion of durvaRT and post treatment of adjuvant durvalumab. Inflammatory cytokines such as IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular cytokine release by CD4 and CD8 T cells, and their phenotypic subsets, will be assessed by flow cytometry. Correlation between the level of cytokine production and clinical outcomes (RR, PFS, OS) will be analyzed.

##: Contingent upon available funding.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

Phase Ib:

1. To assess the safety of combining durvalumab with RT.

Phase II:

1. To estimate the progression free survival (PFS) rate at 1 year
2. To estimate the DCR to concurrent durvaRT followed by durvalumab.

2.1.2 Secondary Objectives

Phase Ib:

1. Estimate the DCR post completion of concurrent durvaRT
2. To correlate the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR.

Phase II:

1. Estimate the median progression free survival (PFS) time.
2. Estimate the rate of complete remission (CR) post durvaRT by modified RECIST 1.1
3. Estimate the overall survival (OS)

2.1.3 Correlative/Exploratory Objectives

1. To explore the correlation between the PD-1, PD-L1 and FOXP3 (T-regulatory cells) expression on immunohistochemistry pre-treatment (TURBT specimen) and post-durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR, PFS and OS.
2. We will also explore if the combination of RT with durvalumab increases the PD-L1+ status in tumor specimen when compared to baseline. We will compare the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT).

3. To explore the correlation of PD-1 expression on T cells from peripheral blood with clinical outcomes. Peripheral blood will be collected at pretreatment, post durvaRT, and post completion of treatment with adjuvant durvalumab.
4. To explore correlation of next generation sequencing (NGS) of tumors and blood at pretreatment and at post durvaRT with response rate for durvaRT +adjuvant durvalumab. As part of NGS, RNA-seq would be performed and and we would attempt to perform immunosubtyping based on expression data, as well as perform deconvolution analysis in an effort to understand changes in tumor immune cell inflammation. In addition, we will do next generation sequencing of urine cell free DNA at pretreatment and will correlate with tumor sequencing at pretreatment stage.
5. To explore the correlation of plasma cytokines such as IFN-γ level with clinical outcomes. Peripheral blood will be collected prior to durvaRT, post completion of durvaRT and post treatment of adjuvant durvalumab. Inflammatory cytokines such as IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular cytokine release by CD4 and CD8 T cells, and their phenotypic subsets, will be assessed by flow cytometry. Correlation between the level of cytokine production and clinical outcomes (RR, PFS, OS) will be analyzed.

2.2 Endpoints

2.2.1 Primary Endpoint

Phase Ib:

1. *To assess the safety of combining durvalumab with RT in that DLT rate is lower than than 33%.*

Phase II:

1. *Estimate the progression free survival (PFS) rate at 1 year.* Progression free survival rate at one year is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 and cystoscopy at 1 year from the start of durvalumab treatment, D1 of durvaRT.
2. *To estimate the DCR to concurrent durvaRT followed by durvalumab.* DCR will be defined for this study as rates of patients achieving CR, PR or SD post completion of concurrent durvaRT and adjuvant durvalumab. Response will be determined by modified RECIST 1.1.

2.2.2 Secondary Endpoints

Phase Ib:

1. Estimate the DCR post completion of concurrent durvaRT.
2. To correlate the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR

Phase II:

1. Estimate the median progression free survival (PFS) time. Median PFS for this cohort will be calculated.
2. Estimate the rate of complete remission (CR) post durvaRT by modified RECIST 1.1

3. Estimate the overall survival (OS) defined as time from start of treatment, D1, to the date of death due to any cause,

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Phase Ib subjects must meet the following inclusion criteria:

- Locally advanced urothelial cancer of bladder with any of the following:
  a) T3-4, N0-2 M0, **OR** Tx N1-2 M0 **OR** T2 N1-2 M0: Treatment naïve, unresectable, **OR** medically unfit for surgery* **OR** cisplatin ineligible**. T3 N0 M0 patients can be included if they are cisplatin ineligible**.
  b) Patients who have T3-4, N0-2 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0 post-neoadjuvant chemotherapy who become unresectable **OR** are medically unfit for surgery*

Phase II subjects must meet the following inclusion criteria:

- Locally advanced urothelial cancer of bladder with any of the following:
  a) T3-4, N0-2 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0: Treatment naïve, unresectable, **OR** medically unfit for surgery* **OR** cisplatin ineligible**. T3 N0 M0 patients can be be included if they are cisplatin ineligible**.
  b) T3-4, N0-1 M0 **OR** Tx N1-2 M0 **OR** T2 N1-2 M0 patients post-neoadjuvant chemotherapy who become unresectable **OR** medically unfit for surgery*. (Please note: the stage of tumor is based on prechemotherapy status at the time of diagnosis)
- T2, N0, M0 who are ineligible to get cisplatin based chemotherapy**
- T2 N0 M0 patients who are treatment naïve or post neoadjuvant chemotherapy but are unfit for surgery* may also be enrolled.

*Unfit for surgery is based on patient's cardiac status or pulmonary status or any co-morbidity that can put patients at high risk for complications during or after surgery. "Unfit for surgery" status has to be determined by treating surgeon.

**Cisplatin ineligibility is defined by the presence of one or more of the following:

- Impaired renal function (GFR ≥ 30 but ≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation.
- Grade ≥ 2 Hearing Loss (hearing loss measured by audiometry of 25 dB at two contiguous frequencies)
- Grade ≥ 2 peripheral neuropathy
- ECOG Performance Status of 2
- Solitary Kidney
- Any other medical condition that makes patient cisplatin ineligible based on assessment by treating Oncologist, such as severe CAD, congestive heart failure, etc.

In addition to the criteria above, **all subjects** must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for personal health information, obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of informed consent.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
4. Life expectancy of >6 months per treating physician.
5. Subjects must have archival tissue available from previous TURBT (preferred) or lymph node core biopsy within 8 weeks of treatment or be assessed by the treating urologist to undergo maximal TURBT. The extent of TURBT may vary for each patient and will be determined by the treating urologist. Further, the treating urologist will decide if performing the TURBT is clinically appropriate. If the potential subject does not have tumor amenable to biopsy, there is insufficient tissue for PD-L1 testing or is not clinically appropriate for TURBT, enrollment must be discussed with the sponsor-investigator on a case by case basis.
6. Histologically proven pure or mixed urothelial carcinoma of bladder. Small cell histology would be excluded
7. Adequate organ and marrow function as defined below:
   a) Hemoglobin ≥ 9.0 g/dL
   b) Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
   c) Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
   d) Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
   e) AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal.
   f) Serum creatinine CL>30 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

   Males:

   $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

   Females:

   $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

8. Females of childbearing potential must have a negative urine and serum pregnancy test within 3 days of study registration.
   NOTE: Female subjects are considered of child bearing potential unless they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are ≥60 years old and naturally postmenopausal for at least 12 consecutive months.
9. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

Exclusion criteria for both phase Ib and phase II subjects

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Participation in another clinical study with an investigational product within 2 weeks prior to registration.
3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.
4. Previous systemic immunotherapy. Previous use of intravesical BCG is acceptable.
5. History of another primary malignancy except for:
   a) Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study drug and of low potential risk for recurrence. However adequately treated prostate cancer >2 years ago with no significant change in PSA for past 6 months can be included. Patients with a history of prostate cancer must not have any definitive radiation therapy to prostate area.
   b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   c) Adequately treated carcinoma in situ without evidence of disease e.g., cervical cancer *in situ*.
   d) Previously adequately treated urothelial cancer of upper urinary tract T1 or CIS with no muscle invasion
6. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within 14 days prior to the first dose of study drug (14 days prior to the first dose of study drug for subjects who have received prior TKIs [e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C).
7. Mean QT interval corrected for heart rate (QTc) ≥470 ms on electrocardiogram (ECG) using Fredericia's Correction.
8. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
9. Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy. (Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripheral neuropathy).
10. Any prior Grade ≥3 immune-mediated adverse event (imAE) while receiving any previous immunotherapy agent, or any unresolved imAE >Grade 1.
11. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded. Patients with h/o completely resolved childhood asthma or atopy will not be excluded. Patients with well-controlled hypothyroidism on thyroxine replacement will be eligible as well.
12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
13. History of and/or confirmed pneumonitis.
14. History of primary immunodeficiency.
15. History of allogeneic organ transplant.
16. History of hypersensitivity to durvalumab or any excipient.
17. History of hypersensitivity to the combination or radiation therapy.

18. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
19. Known history of previous clinical diagnosis of tuberculosis.
20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of starting treatment with durvalumab.
    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
21. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control. For this study male or female patients of reproductive potential need to employ two highly effective and acceptable forms of contraception throughout their participation in the study and for 90 days after last dose of study drug
22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
23. Brain metastases or history of leptomeningeal carcinomatosis.
24. Subjects with uncontrolled seizures.
25. Previous definitive radiation to pelvic area.

4. SUBJECT REGISTRATION

All subjects must be registered through BTCRC Administrative Headquarters' electronic data capture (EDC) system OnCore. A subject is considered registered when an 'On Study' date is entered into OnCore.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within 14 days of registration.

Subjects who do not begin study treatment: If a subject signs consent, is registered to the study, and later is not able to begin the planned study treatment, for whatever reason, the subject will be considered a screen failure and will be replaced. The reason for removal from study will be clearly indicated in EDC system. The subject will then be treated off study, per physician's discretion.

Subjects who are incorrectly enrolled but have not initiated treatment should be withdrawn from the study and will be labeled as screen failure.

Subjects who have been enrolled in error and have initiated treatment should be discussed with the sponsor-investigator. It will be at the discretion of sponsor-investigator to decide about the safety of continuing treatment for that patient. If the sponsor-investigator decides to exclude the patient from the study, that subject will not be counted for any statistical analyses. Please note

that these subjects must be excluded from the phase I study analyses and treatment on the clinical trial should be discontinued.

5. TREATMENT PLAN

5.1 Overview of Study Design

This is a single arm, open-label phase Ib/II study of durvaRT followed by adjuvant durvalumab. Phase Ib will be conducted to determine the safety of durvalumab in combination with RT. Phase II will estimate the 1-year PFS and DCR.

5.2 Number of Subjects

A total of 26 subjects will be enrolled on both phases.

Phase Ib: Up to 6 subjects
Phase II: 26 subjects (including 6 rolled over from Phase Ib).

The 6 patients in Phase Ib will be rolled over and be combined with patients in Phase II in the analysis.

5.3 Durvalumab Phase Ib Study

5.3.1 DurvaRT

- Each cycle of concurrent durvalumab with RT will be Q28 days (Q4 weeks) for a maximum of 2 doses during concurrent radiation therapy. Durvalumab will be started on day 1 of RT. The dose of durvalumab may be given either before (preferred) or after the dose of RT.
- Day 1 of concurrent durvaRT treatment should start on a Monday, Tuesday or Wednesday.

Phase Ib Cohort	# of Subjects	Durvalumab IV	RT
1	Up to 6	2 doses Q4 weeks; 1500mg if >30kg OR 20mg/kg if ≤ 30kg	64.8 Gy, 36 daily fractions on weekdays over about 7 weeks

DOSE: DurvaRT – concurrent durvalumab and RT

- Durvalumab: 1500mg q 4 weeks if patients are >30kg OR 20mg/kg q 4 weeks if ≤ 30kg total body weight intravenously for 2 doses.
- RT: RTOG dose fractionation and field design will be 64.8 Gy in 36 daily fractions using a sequential field reduction technique as described below.
- Number of patients: up to 6

Given the safety is not dose dependent; no dose de-escalation will be allowed

5.3.2 Dose and Safety Definition

Patients enrolled in phase Ib during durvaRT will be managed with the rules as listed below.

Three patients will be enrolled initially. If 2 or more patients (out of 3) experience dose-limiting toxicity (DLT), the combined treatment will be considered unsafe. Otherwise, an additional 3 patients will be treated at the same dose. If 0 or 1 patient experience DLT, the dose of durvalumab in section 5.3 above will be deemed safe for phase 2 part of the study. If, however, 2

or more patients (out of 6) experience DLT, the combined treatment will be considerd unsafe. In this case, durvalumab will be permanently discontinued and the subjects followed up per protocol.

5.3.3 Definition of Dose Limiting Toxicity

Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level.

A DLT will be defined as any treatment-related toxicity described below that occurs during the durvaRT phase (7 weeks). The following will be DLTs:

- Any Grade 4 imAE*
- Any ≥ Grade 3 colitis
- Any grade of immune-mediated neurotoxicity.
- Any Grade 3 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Grade 3 liver transaminase elevation with concurrent total bilirubin > 2 × ULN
- Any grade of febrile neutropenia regardless of duration or reversibility
- Any ≥ Grade 3 non-imAE, except for the exclusions listed below

The following conditions are **excluded** from the DLT definition:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- 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 or 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
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Transient asymptomatic laboratory abnormalities that do not require hospitalization

* Immune-related AEs (imAE) are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology.

In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

DLTs will be counted based on the number of subjects with DLT, not the absolute number of DLTs. No single subject can trigger more than one DLT event. Additional subjects will not be enrolled until the initial subjects complete all planned treatment for durvaRT (defined as 2 doses of Q4 week durvalumab, along with radiation=7 weeks) and are able to start cycle 2 of durvalumab during combined durvaRT therapy with no more than a 3-week delay. Grade 3 or 4 adverse events that persist for more than 7 days should result in discontinuation from study treatment.

5.3.4 Adjuvant durvalumab

- Post-concurrent durvaRT, single agent durvalumab will be given every 4 weeks for a total period of up to 12 months (1500 mg Q 4 weeks if patients are >30kg OR 20mg/kg Q 4 weeks if ≤ 30kg total body weight).
- Adjuvant durvalumab treatment will be started 3-4 weeks post completion of durvaRT.
- Subjects who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume treatment but the 12-month treatment period may not be extended.
- **Please note** that we already have the safety data for using durvalumab as monotherapy in metastatic bladder cancer. Subjects will receive a maximum of 13 doses (or a 12-month treatment period, whichever occurs first) of Q4 week durvalumab during the entire course of adjuvant treatment.

5.4 Durvalumab Phase II Study

Once the safety of durvalumab with RT has been established, we will open the phase II part of this study.

5.4.1 DurvaRT

Patients will receive durvalumab Q4 weeks (2 doses) during RT (about 7 weeks).

- Each cycle of concurrent durvalumab with RT will be Q28 days (Q4 weeks) for a maximum of 2 doses during the entire concurrent radiation therapy. Durvalumab will be started on day 1; RT will be started on day 1 or 2. The dose of durvalumab may be given either before (preferred) or after the dose of RT.
- Phase II durvalumab dose: 1500mg q 4 weeks if patients are >30kg OR 20mg/kg q 4 weeks if ≤ 30kg total body weight.
- Day 1 of concurrent durvaRT treatment should start on a Monday, Tuesday or Wednesday.

5.4.2 Adjuvant durvalumab

- Post-concurrent durvaRT, single agent durvalumab, will be delivered every 4 weeks for a total period of up to 12 months (1500 mg Q 4 weeks if patients are >30kg OR 20mg/kg Q 4 weeks if ≤ 30kg total body weight).
- Adjuvant durvalumab treatment will be started 3-4 weeks post completion of durvaRT treatment.

- Subjects who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume treatment but the 12-month treatment period may not be extended.
- Subjects will receive a maximum of 13 doses (or a 12-month treatment period, whichever occurs first) of Q4 week durvalumab during the entire course of adjuvant treatment.

5.5 Radiation Therapy

Note: Intensity Modulated Radiation Therapy (IMRT) is required on this study. Central review of radiation therapy plans will not be prospectively performed.
IMRT may be performed at the research institution or performed locally for patient convenience. Regardless, all facilities must deliver IMRT according to the specifications below.

5.5.1 Dose Specifications:

Radiotherapy will be started within 8 weeks of maximal TURBT on a Monday, Tuesday, or Wednesday. The overall schema is for whole bladder and involved lymph node treatment for 28 daily fractions of 1.8 Gy per fraction (5 days per week) to 50.4 Gy, followed by a boost to the bladder tumor area with margin (partial sparing of bladder) using 1.8 Gy per fraction for an additional 8 daily fractions to a total dose of 64.8 Gy. During the bladder tumor area boost phase, involved lymph nodes may be treated to 54 Gy – 64.8 Gy at the discretion of the treating radiation oncologist if able to achieve acceptable normal tissue dose constraints.

5.5.2 Technical factors:

Photon IMRT with megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation using a multileaf collimator or tomotherapy is required. 6 – 10 MV energy photon beams should be used. VMAT is allowed. Protons are not allowed.

5.5.3 Immobilization and Simulation:

Immobilization
Proper immobilization is required for this protocol but the specific method of immobilization is up to the discretion of the treating institution. Patient setup reproducibility must be achieved using appropriate clinical devices that might include customized torso cradles and/or leg immobilizers.

Simulation Imaging
Patients must be immobilized in the supine position. IV and/or PO contrast may be used to help delineate anatomy but are not required. The patient should void to empty the bladder immediately prior to simulation.

CT scan thickness should be ≤ 3 mm through the region that contains the target volumes and the critical structures evaluated in Dose-Volume Histogram analysis. The CT scan should extend at least 4 cm above and below target volumes. Superior limit of the scan may be at the L1/2 interspace and the inferior limit below the perineum.

5.5.4 Definition of Target Volumes and Margins:

GTVp: The GTVp will include the bladder tumor bed as defined by imaging, cystoscopy, or fiducials if placed.

CTVp: The CTVp will be a 10 mm expansion of GTVp.

GTVn: The GTVn will include clinically involved regional lymph nodes.

CTVn: The CTVn will be a 5 mm expansion of GTVn.

CTV_5040: The CTV_5040 will represent the (whole empty bladder including GTVp) + 10 mm expansion and the CTVn if applicable.

PTV_5040: The PTV_5040 will be a direct expansion of 7 mm beyond the CTV_5040.
CTVp_6480: The CTVp_6480 represents the bladder tumor bed boost volume.

PTVp_6480: The PTV_6480 will be a direct expansion of 7 mm beyond the CTV_6480.

CTVn_boost: The CTVn_boost represents the CTVn, which will receive dose escalation beyond the initial 50.4 Gy at the discretion of the treating radiation oncologist (i.e. range between 54 – 64.8 Gy).

PTVn_boost: The PTVn_boost will be a direct expansion of 7 mm beyond the CTVn_boost.

5.5.5 Critical Structures

Bowel Space: Superiorly, the bowel space contour will start 3 cm above the superior extent of the CTV5040. Inferiorly the contour will be discontinued on the CT slice where no portion of small bowel or colon is visible. The contours will include the volume surrounding loops of bowel out to the edge of the peritoneum as bowel may occupy this space at any time during the course of treatment. Bowel space will include the small bowel and large bowel in one bowel bag contour. Attempts should be made to keep Bowel space V_{40Gy} <50%, but V_{40Gy} of 50 – 70% would be variation acceptable.

Rectum: The rectum contour will include the rectum and anal canal and will be contoured on every slice from the rectosigmoid junction superiorly to the level of the ischial tuberosities inferiorly. Attempts should be made to keep Rectum V_{45Gy} <80%, but V_{45Gy} of 80 – 90% would be variation acceptable.

5.5.6 Dose Prescription

Normalization of Dose: The initial plan is normalized such that 97% of the PTV_5040 volume receives the prescription dose of 50.4 Gy. The bladder tumor boost plan is normalized such that 97% of the PTVp_6480 volume receives the prescription dose of 64.8 Gy. If involved nodal boost is delivered beyond 50.4 Gy then that plan is normalized such that 97% of the PTVn volume receives the chosen prescription dose.

5.5.7 Daily Treatment Localization/Image Guided Radiation Therapy (IGRT)

The patient should void to empty the bladder immediately prior to treatment. Daily IGRT images should be obtained to ensure proper alignment of the isocenter of the simulated fields. These IGRT images may include 1) conebeam CT (CBCT) with MV or kV x-ray; or 2) paired kV 2D images.

5.6 Pre-medication and Hydration

Premedication and hydration prior to durvalumab will be provided according to institutional standards, per treating physician discretion. It is not essential to give any anti-nausea or anti-allergic drug prior to durvalumab, but premedication such as ondansetron, diphenhydramine, etc. are allowed if clinically indicated. Steroids should not be given as a premedication.

5.7 Preparation of durvalumab doses for administration with an IV bag

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. The dose of durvalumab will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (e.g., 30.0 mL for 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients weighing ≤30 kg total body weight, the baseline weight or the weight on day of dosing can be used to calculate each dose, as per institutional standard. However, if there is a ≥10% change in weight from baseline, the day of dosing weight should be used. See dose calculation example in the Documents/ Info tab of the EDC.

5.8 Durvalumab Administration

Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm or 0.22-µm in-line filter. The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

5.8.1 Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2

infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be permanently discontinued and the subject will be followed up per protocol. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature. See also Section 10.4.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.9 Concomitant Medications

5.9.1 Allowed Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 5.8.2. Premedication is not required prior to durvalumab but can be given per physician discretion

For local recurrence T1 or CIS lesions in bladder detected by cystoscopy during adjuvant monotherapy with durvalumab, intravesical mitomycin C will be permitted if clinically necessary.

5.9.2 Prohibited Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies. For local recurrence T1 or CIS lesions in bladder during adjuvant monotherapy with durvalumab, intravesical BCG is prohibited. However intravesical BCG is permitted post completion of adjuvant durvalumab.
2. Any concurrent chemotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable by local surgery.
3. **Patient should not get any palliative RT during the study. If the treating physician deems palliative RT as clinical necessity then patient needs to come off the study.**
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for select indications, at the discretion of the sponsor-investigator (e.g., asthma, chronic obstructive pulmonary disease, radiation, nausea, etc. a temporary

course of steroid upto a maximum of 1mg/d for 7 days will be allowed). Topical steroids are not contraindicated.

5. Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Table. Rescue Medications	
Rescue/supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support (except during durvaRT), correction of metabolic disorders, optimal symptom control, and pain management [including palliative surgery, etc])	Should be used when necessary for all patients

5.3.3 Restrictions during the study

Contraception

Females of childbearing potential who are sexually active with a non-sterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for at least 90 days following the last infusion of durvalumab; cessation of birth control after this point should be discussed with the treating physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use 2 acceptable methods of effective contraception as described below.
- Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see table below) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Effective methods of contraception (two methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill Minipill Patch

[a] This is also considered a hormonal method.

Blood donation
Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

During durvaRT:
Treatment may be delayed ≤ 3 weeks from the expected date of the next treatment for any reason during durvaRT. If treatment is delayed ≤ 3 weeks, subjects will proceed with the next cycle of treatment according to the tables below. If the treatment delay is due to toxicity from durvalumab alone, RT will continue as planned. However, grade 3 or 4 adverse events due to durvalumab that persist for more than 7 days should result in discontinuation from study treatment.

If the dose of durvalumab is held without a delay in RT, then those doses will not be given at a later date. But if durvalumab and RT are both held for any reason, then the durvalumab can resume upon re-start of RT.

During adjuvant durvalumab:
Treatment delay of no more than 12 weeks is permitted during adjuvant durvalumab. This is to allow recovery from any adverse events or unexpected events such as need for repeat TURBT and intravesical mitomycin, etc. See also Appendix 5 for guidelines during COVID-19.

Held or missed doses will be made up during adjuvant durvalumab.
A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC ≥ 1,000× 10^9/L
- Hb ≥8.0 g/dL (transfusion is allowed to reach Hb 8.0)
- Platelets ≥ 75× 10^9/L
- Non-hematologic treatment related toxicities have improved to ≤ Grade 2 or to the subject's baseline values (except alopecia).

If blood counts are below this threshold, blood work is to be repeated weekly until counts are at an acceptable level. If treatment is unable to restart within 3 weeks during durvaRT or within 12 weeks during adjuvant durvalumab of the planned treatment date, the subject will be

Joshi M, *et al. J Immunother Cancer* 2023; 11:e006551. doi: 10.1136/jitc-2022-006551

permanently discontinued from study therapy.

Please note that radiation-induced local side effects will be documented and treated by radiation oncology and medical oncology team according to local practice. Adjustments or discontinuation of radiation therapy will be made by radiation oncology. This is to avoid any unnecessary delay during RT for local side effects such as radiation proctitis or radiation dyspareunia etc. as these would be expected and, as a standard of care, RT is not usually delayed in these circumstances. The radiation related local toxicities will be managed per standard of care. **However, radiation oncology should promptly notify medical oncology and discuss any unexpected adverse events or potential inflammatory or immune-mediated adverse events.** The final radiation treatment records will be sent to medical oncology for review of clinical and safety-related data.

6.2 Durvalumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab, the following guidance will be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, continue durvalumab along with appropriate continuing supportive care according to Appendices 1-4.
- All dose delays should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab will be managed based on toxicities observed (see Appendices 1-4). Dose delays during phase 1 should follow rules listed in DLT section, 5.3.2 and 5.3.3.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune mediated Adverse Events (imAEs) during the conduct of this study. Potential imAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendices 1-4.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 5. All toxicities will be graded according to NCI CTCAE v4. Please refer to dose modification guidelines listed in appendices 1-4 for durvalumab-related toxicities.

Hematological Toxicity and Recommendation for Treatment Delay during durvaRT:

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Description	Treatment Delay
Any other grade 3 non-hematologic toxicity	Up to 3 week delay
Any other grade 4 non-hematologic toxicity	Discontinue treatment
Neutrophils 990-500 cells/mm^3	Up to 3 week delay
Neutrophils <500 cells/mm^3	Up to 3 week delay
Febrile Neutropenia (Fever+ANC <500cells/mm^3)	Discontinue treatment
Platelets 50,000 /mm^3 to 75,000/mm^3	Up to 3 week delay
Platelets >25,000 but <50,000/mm^3	Up to 3 week delay
Platelets <25,000/mm^3	Discontinue treatment
Any other grade 4 hematologic toxicity	Discontinue treatment

Recommendation for Treatment Delay during Adjuvant Durvalumab as monotherapy: Please follow toxicity guidelines, as durvalumab has no direct bone marrow toxicity.

If treatment delay necessities >3 weeks during concurrent durvaRT, treatment is stopped and the subject is discontinued from the study.

If treatment delay necessitates a period longer than 12 weeks during adjuvant durvalumab, treatment is stopped and the subject is discontinued from the study. See also Appendix 5 for guidelines during COVID-19.

6.3 Radiation Treatment Interruption

If a grade 3 hematologic toxicity (ANC, platelets) develops during immunoradiotherapy, all treatment should be discontinued for a minimum of one week. Treatment may be resumed when the hematologic toxicity resolves to < grade 2. If these laboratory values have not been reached after a one-week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis. Please refer to table in section 6.4 for recommendations for hematological toxicities during concurrent durvaRT

For a grade 3 acute colitis, or any immune related toxicity during any week, treatment should be delayed until the toxicity subsides to the < grade 2 level. Use of anti-diarrheal agents, such as loperamide or diphenoxylate/atropine, is strongly encouraged at an early point in treatment to avoid worsening of treatment-related diarrhea.

Radiation-induced toxicities such as radiation cystitis, radiation- proctitis, radiation dyspareunia or any other grade 3 infield (radiation-related) will be documented and treated by radiation oncology according to local practice. Treatment interruption or discontinuation will be decided by the treating radiation oncologist. Radiation to the bladder is associated with significant local toxicity but current standard of care is to continue RT while conservatively managing local toxicities. Similar toxicity is expected during durvaRT, hence treatment should be continued per standard of care. **However, radiation oncology should promptly notify medical oncology and discuss any unexpected adverse events or potential**

inflammatory or immune-mediated adverse events. The final radiation treatment records will be sent to medical oncology for review of clinical and safety-related data.

Potential toxicities associated with radiation therapy to the pelvis include loss of pubic hair, cutaneous erythema in the treated area, increased urinary frequency (which could be permanent), fatigue, nausea, vomiting, rectal irritation, dyspareunia, ovarian failure in women, and sterility. Less likely but potential serious toxicities include weight loss, rectal ulcers, hematochezia, bowel obstruction, bowel perforation, ureteral obstruction, and fistula formation. Bleeding from the mucosal surface is potentially both an acute and chronic complication.

6.4 Toxicity management guidelines for combination treatment regimen

In addition to the individual toxicity management guidelines for durvalumab and RT described above, Table 1 outlines what actions are recommended for the management of any potential overlapping toxicities that may occur following treatment with this combination (e.g., which agent should be modified first, etc).

Table 1: Toxicity management for durvalumab and radiation therapy during concurrent durvaRT phase

Toxicity	Action for durvalumab	Action for Radiation Therapy
Any grade 1 toxicity	Continue treatment	Continue treatment
Grade 2, hematological toxicity (ANC, platelet)	Continue treatment	Continue treatment
Grade 3 hematological toxicity (ANC or platelets)	Hold till AE ≤grade 2 If these laboratory values have not been reached after a one-week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis.	Hold till AE ≤grade 2 If these laboratory values have not been reached after a one-week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis.
Grade 2,3 acute colitis, or immune related side-effect from durvalumab	Treatment should be delayed until the toxicity subsides to grade 1. Refer to **appendices 1-4.** Assess weekly and if after 3 weeks, the toxicities have not recovered to grade 1 or less, all protocol treatment needs to be discontinued	Treatment should be continued if the side-effect is thought to be not related to RT. Please note colitis can be seen with RT too, hence if this occurs treatment should be delayed until it is grade 1. Assess weekly and if after 3 weeks it does not recover to grade 2, discontinue treatment on study.
Any other grade 1-3 infield (radiation-related) toxicity during any week such as but not limited to-skin toxicity, radiation proctitis, radiation cystitis, radiation dyspareunia.	Treatment should be continued if the side-effect is not related to durvalumab	Treatment should be delayed as medically necessary per treating radiation oncologist. Radiation to the bladder is associated with significant local toxicity but current standard of care is to continue RT while conservatively managing local toxicities. Similar toxicity is expected during durvaRT, hence treatment should be continued per standard of care.

6.5 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression per protocol.
- The treating physician thinks a change of therapy would be in the best interest of the subject
- Grade 3 or 4 adverse events that persist for more than 7 days
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for >3 weeks during concurrent durvaRT or >12 weeks during adjuvant durvalumab as monotherapy. See also Appendix 5 for guidelines during COVID-19.

Permanent discontinuation of durvalumab

A subject will not receive any further durvalumab if any of the following occur:

- Withdrawal of consent or lost to follow-up.
- Adverse event that, in the opinion of the treating physician, contraindicates further dosing.
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Pregnancy or intent to become pregnant.
- Dose-limiting toxicity as above.
- Grade ≥ 3 infusion reaction.
- Subject noncompliance that, in the opinion of the treating physician or sponsor-investigator, warrants withdrawal; eg, refusal to adhere to scheduled visits.
- Initiation of alternative anticancer therapy including another investigational agent.
- Criteria met for discontinuation of treatment as described in the protocol.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety according to the study calendar, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up. All subjects will be followed for survival.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

7. TREATMENT CALENDAR & EVALUATIONS

	Screen	**DurvaRT**[1] (±3)				**Post durvaRT**	**Adjuvant Durvalumab**[2]	
	-28 d	W1	W3	W5	W7	W10-11 (±7)	Q4W (±5)	Q12W (±7)
REQUIRED ASSESSMENTS								
Informed Consent; Medical History[5]	X							
Diagnosis and Staging[6]	X							
Physical Exam[7] and ECOG PS[8]	X	X	PhI	X	X		X	
Vital signs[9]	X	5x		3x	X		3x	
Weight, height (screen only)	X	X		X			X	
ECG[10]	X	X (x2)					C1D1 only	
AEs and AESIs[7]	X	X	PhI	X	X		X	
Concomitant Medications[11]	X	X	PhI	X	X		X	
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)[12]	X	Weekly[12,13]					X	
Comprehensive Metabolic Profile (CMP)[14]	X	X[13]		X	X		X	
GGT (baseline), Mg, Phos, Uric Acid, LDH	X	X[13]		X	X		X	
Phase Ib only: liver enzymes[15]		PhI only: Weekly						
TSH (free T3, free T4 if TSH abnormal)[16]	X	X[13]			X		X	
Pregnancy test (serum or urine) WOCBP[17]	-3 d							
Urinalysis[18]	X	X		X	X		X	
Hepatitis serologies; HIV testing[19]	X							
Coagulation panel[20]	X							
DISEASE ASSESSMENT								
Cystoscopy (TURBT, if applicable)[21]	-8 wks					X		X
CT of chest, abdomen and pelvis[22]	X					X		X
TREATMENT EXPOSURE								
Radiation Therapy (36 fractions)		daily Mon-Fri[1]						
Durvalumab		X		X			X	
CORRELATIVE STUDIES (SPECIMEN COLLECTION)								
Archival tumor tissue for PD-L1, if available[23]		X						
Fresh tumor biopsy[24]	X					X		
Urine sample for cell free DNA[23]		X						
Blood PBMCs and inflammatory cytokines [25]		X					C1D1 only	
Blood for somatic baseline[26]		X						
Prior NGS results, if performed[27]		X						
BANKING SAMPLES (SPECIMEN COLLECTION)								
Serum and Plasma[29]		X						
Unstained Slides[28] (if available)		X						

FOLLOW UP CALENDAR & EVALUATIONS

	Safety follow up[3] (±7)	**Long-term follow up**[4] for a total of 3 years from the start of adjuvant treatment (±14)						
	30 days post	3-month	6-month	9-month	12-month	18-month	24-month	36-month
REQUIRED ASSESSMENTS								
Physical Exam[7] and ECOG PS[8]	X	X*	X*	X*	X*	X*	X*	X*
Vital signs[9]	X	X*	X*					
ECG[10]	X							
AEs and AESIs[7]	X	X*	X*					
Concomitant Medications[11]	X	X*	X*					
LABORATORY ASSESSMENTS								
Complete Blood Count with diff (CBC)[12]	X	X						
Comprehensive Metabolic Profile (CMP)[14]	X	X						
GGT (baseline), Mg, Phos, Uric Acid, LDH	X	X						
TSH (free T3, free T4 if TSH abnormal)[16]	X							
DISEASE ASSESSMENT								
Cystoscopy (TURBT, if applicable)[21]								
CT of chest, abdomen and pelvis[22]	X	X[4]*	X[4]*	X[4]*	X[4]*	X[4]*	X[4]*	X[4]*
CORRELATIVE STUDIES (SPECIMEN COLLECTION)								
NGS results, if performed[27]	@ PD							
Blood for PBMCs and inflammatory cytokines [25]	X							
BANKING SAMPLES (SPECIMEN COLLECTION)								
Serum and Plasma[29]	X							
FOLLOW-UP								
Survival status, subsequent therapy		X	X	X	X	X	X	X

* Assessments for subjects who have discontinued durvalumab *without* disease progression.

Calendar Footnotes: (See also Appendix 5 for guidelines during COVID-19.)

1. **DurvaRT**: durvalumab will be started on Day 1 of Week 1; RT will be started on Day 1 or 2 of Week 1. RT will be 64.8 Gy combined with Q4 week durvalumab on weeks 1 and 5. RT may be performed at the research institution or local institution for patient convenience.
2. **Adjuvant Durvalumab**: Single agent durvalumab will be given every 4 weeks for up to 12 months (13 doses) during adjuvant durvalumab. Adjuvant durvalumab will be started 3-4 weeks post completion of durvaRT.
3. **Safety follow up visit**: The safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.
4. **Long-term follow up**: Long-term follow up will occur in all subjects for a total of 3 years from the start of adjuvant treatment. If a subject did not begin adjuvant treatment, long-term follow up will start 4 weeks after the last dose of radiation or from the time of first imaging for evaluation of response whichever is earliest. Subjects who discontinue treatment for any reason without documented disease progression, prior to completion of 12 month period of adjuvant therapy, will be followed every 12 weeks (±4 wks) for year 1, every 6 months (±4 weeks) for year 2, and annually for year 3 (or per local guidelines) or until confirmed PD for a total of 3 years from the start of adjuvant treatment. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 3 years for a total of 3 years from the start of adjuvant treatment. For subjects who achieve disease control after 12 months of adjuvant treatment or discontinue due to toxicity or symptomatic deterioration, tumor assessments should be performed every 3 months post completion of adjuvant therapy for 12 months, and thereafter every 6-months for the remainder of the following year or according to local practice. E.g., post completion of 12 months of adjuvant therapy- follow up for imaging Q3 months x 1 year then Q6 months for the following year.
5. **Medical History**: to include demographics, tobacco and alcohol use, trial awareness question, prior treatments, and surgical history.
6. **Diagnosis and staging**: to include pathology report and Tumor Node Metastasis (TNM) staging
7. **Physical exam and AE assessment**: <u>During durvaRT</u>: with radiation oncology as per local practice; W1, W3, W5 and W7 by medical oncology during DLT assessment in **phase Ib only**; W1, W5 and W7 by medical oncology in phase II. <u>During adjuvant durvalumab monotherapy</u>: every 4 weeks with med onc; with rad onc as per local practice.
8. **ECOG PS**: screen, Day 1, and at each visit by medical oncology.
9. **Vital signs**: Non-durvalumab visits: to include temperature, blood pressure, pulse rate, respiratory rate. Durvalumab visits: Blood pressure and pulse will be measured before, during, and after the infusion at the following times (based on a 60-minute infusion): At the beginning of the infusion (within 1 hr prior to start); at 30 minutes during the infusion (±5 minutes); at the end of the infusion (at 60 minutes ±5 minutes); During the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) for the first infusion only and then for subsequent infusions as clinically indicated. If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.
10. **ECG**: An ECG is required during screening, pre and post study treatment on Week 1 Day 1 of concurrent durvaRT, at the start of adjuvant durvalumab, at the safety follow up visit, as well as at any other time point when clinically indicated. All ECGs will be single tracings. Week 1 Day 1 ECGs will be performed within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.
11. **Concomitant medications:** assessed at each med onc physical exam visit.
12. **CBC**: to be drawn weekly during durvaRT and q4 weeks during adjuvant durvalumab.
13. If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.

14. **CMP**: to include albumin, alk phos, ALT, AST, amylase, bicarbonate, calcium, chloride, creatinine, Gamma glutamyltransferase (GGT; baseline and if clinically indicated); glucose, lactate dehydrogenase (LDH), lipase, magnesium, potassium, sodium, total bili, total protein, urea/BUN, uric acid. CMP to be drawn prior to each durvalumab infusion (Weeks 1, 5, 7 during durvaRT; Q4 weeks during adjuvant durvalumab).
15. **Liver enzyme panel, Phase Ib only:** To include AST, ALT, alk phos, bilirubin. To be drawn weekly during phase 1 part of durvaRT only (if not already included in the CMP).
16. **Thyroid stimulating hormone**: Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
17. **Pregnancy testing**: Urine hCG or serum βhCG in women of childbearing potential (WOCBP). Perform within 3 days of registration and repeat during Treatment Period as clinically indicated.
18. **Urinalysis**: performed at Screening, pre-dose W1 and W5 of durvaRT, W7, and q4 weeks during adjuvant durvalumab.
19. **Hepatitis serologies and HIV**: if applicable, per physician discretion. Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.
20. **Coagulation panel**: to include prothrombin time (PT), aPTT and INR. To be performed at screening and as clinically indicated.
21. **Cystoscopy** (maximum TURBT if applicable): Baseline: Maximum TURBT within 8 weeks prior to starting durvaRT. Another cystoscopy will be done between Weeks 9-10 (around 2-3 weeks post completion of durvaRT). During adjuvant durvalumab: Every 12 weeks. TURBT if indicated.
22. **Disease imaging**: Baseline CT scans (IV contrast preferred) of chest and abdomen and pelvis are required within 28 days of study registration. Obtain urogram at baseline if possible. CT scans to be performed at screening and 2-3 weeks post completion of all durvaRT. Timing of adjuvant durvalumab CT scans is every 12 weeks (± 7 days); timing of follow up CT scans is every 12 weeks (± 14 days). At screening, CT scans are preferred but MRI of abdomen and pelvis are acceptable. Follow up imaging of chest: CT chest preferred but CXR is allowed. The study requires scans to confirm progression for patients who are deemed clinically stable by the treating Investigator. The confirmatory scan is acquired preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of PD. CR, PR, SD need to be confirmed with another scan on next clinic visit and no sooner than 4 weeks.

Correlative Studies: See CLM for collection, processing, labelling and shipping instructions.

23. Please note that any tissue specimen remaining after PD-L1 testing at baseline and post durvaRT will be used to determine mutational sequencing of tumor. Between 15 FFPE slides or tissue block (preferred) are requested (minimum of 10 slides x 10 micron (μm) thick and 5 slides x 4 μm thick). If 15 slides are not available, the investigator must discuss this with the sponsor-investigator on a case by case basis. Similarly, for urine sample at baseline, we will use leftover sample to perform mutational sequencing.
24. Obtain **fresh tumor biopsy** for PD-L1 assay with cystoscopy, if applicable (pts undergoing TURBT).
25. Flow cytometry collection of whole blood for PBMCs to determine PD-1 on T cells. Plasma will be collected. Inflammatory cytokines such as IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular IFN-γ release by T cells will be assessed by flow cytometry.
26. Submission of whole blood for somatic baseline is to be collected at Pre-Treatment Cycle 1 Day 1.
27. **Prior NGS results**: enter into EDC if performed as per standard of care prior to study and/or at progression.
28. **Banking Studies:** See CLM for collection, processing, labeling and shipping instructions. Submission of unstained slides for banking from an archived FFPE tumor block (if available).
29. Submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the Safety Follow up visit.

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

Screening procedures will be performed up to 28 days before registration, unless otherwise specified. All subjects must sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history to include demographics, tobacco and alcohol use, prior treatments, and surgical history
- Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging
- Complete physical exam. Patient must be seen by medical oncology prior to starting Day 1 of treatment with durvaRT. Radiation therapy planning will be performed according to institutional standards.
- ECOG Performance Status
- Vitals signs to include temperature, blood pressure, pulse rate, respiratory rate
- Weight and height
- 12-lead ECG. A 12-lead ECG should be obtained after the subject has been resting in a supine position for at least 5 minutes.
- Baseline signs and symptoms
- Concomitant medications
- Complete blood count with differential (CBC): to include basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, total white cell count.
- Comprehensive metabolic panel (CMP): to include albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen (depending on local practice), uric acid. If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin. GGT at baseline and as clinically indicated.
- Thyroid stimulating hormone. Free T3 and free T4 will only be measured if TSH is abnormal.
- [Within 3 days of registration] Urine hCG or serum βhCG pregnancy test for women of childbearing potential (WOCP)
- Urinalysis: to include bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

- Hepatitis serologies and HIV: if applicable, per physician discretion. Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.
- Coagulation panel: to include prothrombin time (PT), aPTT and INR.
- Cystoscopy with maximal TURBT within 8 weeks of study registration.
- CT chest, abdomen and pelvis with contrast (contrast is preferred but patients with contraindication for contrast may have non-contrast imaging); urogram at baseline if possible; MRI abdomen and pelvis are acceptable but CT is preferred.

Correlative studies:

- Tumor biopsy specimen from recent TURBT (preferred) or LN core biopsy within 8 weeks prior to enrollment. Tissue block is preferred, if available. An alternative is to submit at least 15 FFPE slides with tumor specimen (a minimum of 10 slides x 10 µm thick and 5 slides x 4 µm thick). If 15 slides are not available, the investigator must discuss this with the sponsor-investigator on a case by case basis.
- Prior NGS results: enter into EDC if performed as per standard of care prior to study

7.2 On Treatment Evaluations

Each cycle of durvalumab during concurrent durvaRT= 28 days or 4 weeks; Delay of 3 weeks is permitted during the concurrent durvaRT phase for any unexpected/adverse events/need for a repeat TURBT. Please see details in dose delay section.

Each cycle of durvalumab as monotherapy=28 days or 4 weeks. A maximum 12-week delay is permitted between cycles due to a treatment related adverse event or need to repeat cystoscopy and TURBT.

7.2.1 Concurrent durvaRT

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Week 1 Day 1 of concurrent durvaRT- both phase Ib and II

- Physical exam and ECOG PS
- Vital signs: blood pressure and pulse rate will be measured before, during and after the infusion at the following times (based on a 60-minute infusion):
  1. At the beginning of the infusion (within 1 hour prior to start)
  2. at 30 minutes after the start of infusion (± 5 minutes),
  3. at the end of infusion (at 60 minutes ± 5 minutes)
  4. at 30 minutes post-infusion (90 minutes from the start of the infusion ± 5 minutes)
  5. at 60 minutes post-infusion (120 minutes from the start of the infusion ± 5 minutes)
     - The 1-hour post-infusion observation period will apply to the first infusion only and then for subsequent infusions as clinically indicated.
     - If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should follow the principles described here (e.g. every 30 minutes), or more frequently if clinically indicated.
- Weight

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- Single tracing 12-lead ECGs within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion. ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes.
- Adverse events; concomitant medications
- CBC with differential: Weekly x 7 weeks during durvaRT. If performed locally, results must be forwarded to medical oncology.
- CMP including magnesium, phosphorus, uric acid and LDH
- Thyroid stimulating hormone. Free T3 and free T4 will only be measured if TSH is abnormal.
- Urinalysis
- Durvalumab infusion: prior to RT is preferred but not mandatory.
- Radiation therapy: start on a Monday, Tuesday, or Wednesday; after durvalumab is preferred. RT may begin on Day 1 or Day 2.
- Correlative and Banking samples. See Correlative Laboratory Manual for specific instructions.

Phase Ib subjects only: Weekly x 7 weeks (± 3 days):

- Liver enzymes –ALT, AST, alkaline phosphatase, bilirubin

Phase Ib subjects only: Week 3 (± 3 days) during durvaRT:

- Vital signs: to include temperature, blood pressure, pulse rate, respiratory rate
- Physical exam and ECOG PS
- Assess adverse events (AE) and adverse events of special interest (AESI) by medical oncology
- Concominant medications

Week 5 (prior to the infusion, ± 3 days)- both phase Ib and II:

- Physical exam; ECOG PS
- Vital signs: blood pressure and pulse rate will be measured before, during and after the infusion. 1-hour post-infusion vitals only if clinically indicated. See Week 1 Day 1 schedule for time points.
- Weight
- Assess adverse events (AE) and adverse events of special interest (AESI) by medical oncology
- Concomitant medications
- CBC with differential: Weekly x 7 weeks during durvaRT. If performed locally, results must be forwarded to medical oncology.
- CMP including magnesium, phosphorus, uric acid and LDH
- Urinalysis
- Durvalumab infusion
- Radiation therapy (daily M-F)

Week 7 (± 3 days)- both phase Ib and II:

- Physical exam and ECOG PS
- Vital signs: to include temperature, blood pressure, pulse rate, respiratory rate
- Assess adverse events (AE) and adverse events of special interest (AESI) by medical oncology
- Concominant medications
- CBC with differential
- CMP including magnesium, phosphorus, uric acid and LDH
- Urinalysis

Please note that more frequent follow-ups can be done as clinically indicated by the treating physicians.

Weeks 10-11: 2-3 weeks post completion of durvaRT (±7 days)- both phase Ib and II:

- Cystoscopy evaluation
  - If sufficient tissue is available, obtain fresh tumor biopsy for PD-L1 assay with cystoscopy (pts undergoing TURBT). See Correlative Laboratory Manual for specific instructions.
- Follow up disease imaging

7.2.2 Adjuvant durvalumab as monotherapy

See also Appendix 5 for guidelines during COVID-19.

C1D1 of adjuvant monotherapy with durvalumab (within 4 weeks post durvaRT [±5 days])

- Physical exam, ECOG PS
- Vital signs blood pressure and pulse rate will be measured before, during and after the infusion. 1-hour post-infusion vitals only if clinically indicated. See Week 1 Day 1 schedule for time points.
- Weight
- ECG-12 lead
- Assess AEs and AESIs by medical oncology
- Concomitant medications
- CBC with differential
- CMP including magnesium, phosphorus, uric acid and LDH
- Thyroid stimulating hormone. Free T3 and free T4 will only be measured if TSH is abnormal.
- Urinalysis
- Durvalumab infusion
- Correlative samples. See Correlative Laboratory Manual for specific instructions.

The following will be performed on day 1 of subsequent cycles of adjuvant monotherapy with durvalumab (Q4 weeks [± 5 days]):

- Physical exam, weight
- Vital signs
- ECOG PS

- CBC with differential
- CMP including magnesium, phosphorus, uric acid and LDH
- Assess AEs and AESIs by medical oncology
- Concomitant medications
- Durvalumab

Every 12 weeks while on treatment with adjuvant durvalumab [± 7 days]:

- Imaging for evaluation of response ***
- Follow up by radiation oncology according to local standard of care
- Cystoscopy

***Please note: CT scans, preferably with IV contrast, to be performed during screening (for baseline) and 2-3 weeks post completion of entire durvaRT (Week 10-11). Timing of on-treatment (follow-up during adjuvant durvalumab) CT scans is every 12 weeks (± 1 week) until PD or off-study. The study requires a confirmation of progression scan for patients who are deemed clinically stable by the Investigator, then the confirmatory scan is acquired preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of PD. MRI of abdomen and pelvis are acceptable instead of CT but CT scans are preferred. Follow up imaging of chest- CT chest preferred but CXR is allowed if CT chest not possible.

Please follow study calendar for schedules of cystoscopy and imaging, clinic visits etc.

7.3 Safety Follow-up Evaluations at End of Treatment

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of study drug.

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

The following will be performed 30 days (± 7) after the last dose of study drug:

- Physical exam, weight
- Vital signs
- ECOG PS
- ECG-12 lead
- CBC with differential
- CMP including magnesium, phosphorus, uric acid and LDH
- Assess AEs and AESIs by medical oncology
- Concomitant medications
- Correlative and Banking samples. See Correlative Laboratory Manual for specific instructions.
    - Prior NGS results: enter into EDC if performed as per standard of care at progression.

7.4 Long Term Follow-up Evaluations (±14 days)

All subjects will be followed for a total of 3 years from the start of adjuvant treatment. If a subject did not begin adjuvant treatment, long-term follow up will start 4 weeks after the last dose of radiation or from the time of first imaging for evaluation of response whichever is earliest. Subjects who discontinue treatment for any reason without documented disease progression prior to completion of 12 month period of adjuvant therapy, will be followed every 12 weeks (±4 wks) for 1 year, every 6 months (±4 wks) for year 2, and annually for year 3 (or per local guidelines) or until confirmed PD for a total of 3 years from the start of adjuvant treatment (see Follow Up Study Calendar).

Once disease progression is documented, subjects will enter a survival follow up period and will be followed every 3 months for a total of 3 years from the start of adjuvant treatment. Follow up may be accomplished via clinic visit, or phone call. See Follow Up Study Calendar.

7.5 Description of study procedures

7.5.1 Urologic Evaluation:

- The treating urologist in all patients will perform an initial maximal TURBT no more than 8 weeks prior to initiation of therapy. The goal of the initial resection will be maximal reduction of tumor volume and confirmation of unresectable status where applicable. Photographic imaging will be performed to provide a record of baseline local disease.

  Follow up cystoscopies: When appropriate, bladder biopsy will be performed to document the presence or absence of CIS. Photographic imaging will be performed to document progression or lack thereof. Any suspected tumor progression will trigger a brief cessation of therapy to allow for TURBT with repeat maximal resection and pathologic confirmation of viable tumor. Confirmed disease progression, defined as an increase in volume of a three-dimensional, viable, histologically confirmed cancer will be recorded as PD.

- The post-durvaRT cystoscopic assessment will be performed approximately 2-3 weeks (±7 days) following the completion of 36 fractions of radiotherapy. Flexible cystoscopy is optional. At this time, if a CR is suspected, confirmatory directed and random biopsies will be performed to rule out residual CIS. In the event that CIS is the only finding, the patient will be deemed a CR but patient may be offered appropriate resection and intravesical mitomycin C therapy for CIS. Intravesical BCG is not allowed for this study. Patient will need to come off the study should patient decide to use BCG therapy per discussion by urologist. However, intravesical BCG is permitted after completion of adjuvant durvalumab.

It should be noted that the use of cytology and FISH to determine presence of disease within the bladder is discouraged due to the potential confounding effects of the therapy on cytologic findings.

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8. BIOSPECIMEN STUDIES AND PROCEDURES

8.1 Source and Timing of Biospecimen Collections

Our correlative tests will include research testing on peripheral blood sample and on available tissue from TURBTs or biopsy of lymph node. TURBT specimens are preferred. We will also be collecting urine for further testing. The timings of collection of biospecimens are detailed in the study calendar.

8.2 PD-L1 Testing in tissue

PD-L1 testing will be performed utilizing the Ventana SP263 assay. Testing will be restricted to the Ventana SP263 assay and will be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

For this study, PD-L1 biomarker will be used for exploring its predictive and prognostic implications. It will not be used for clinical decision-making. Please see the study calendar for details of time period for collection of tissue for PD-L1 testing. In addition, we will also be testing for PD-1 and FOXP3.

Immunohistochemistry (IHC) will be performed as previously reported [41], and all IHC will be assessed by clinical pathologists through the use of the Allred system, which consists of the summation of IHC intensity and distribution of immunoreactivity. Correlations amongst IHC scores for PD1, PDL1 and FOXP3, and between the extent of positive staining and tumor stage will be assessed using Spearman rank coefficients. The extended Mantel-Haenszel test will be used to assess correlations between IHC scores after adjusting for tumor stage. The association between IHC score and response to durvalumab (DCR, PFS, OS) will be tested via the application of Mann-Whitney U test following dichotomization at the mean. For progression-free survival (recurrence) analysis, univariate analyses will be performed using log rank tests and visualized using Kaplan-Meier survival curves. Variables associated with adverse prognosis based on previous studies and variables with a $P < 0.10$ on univariate analysis will also be included in a multivariate analysis using a Cox proportional hazards model if needed.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.
- In our study, baseline archival sample of tissue by TURBT or LN within 8 weeks of treatment is acceptable for PD-L1 testing.
- Samples should have been collected via a core needle of 18 gauges or larger or be collected per institutional guidelines. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized. Preferred archival sample is a specimen collected within 8 weeks from the start of treatment. When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.

- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.
- If sufficient tissue is available at the post durvaRT cystoscopy, obtain fresh tumor biopsy for PD-L1 assay (pts undergoing TURBT). Sample collection will follow the guidelines described above and below.

Sample data collection for PD-L1 testing
The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following data fields should be assessed at the PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly?
- Is the H&E material acceptable?
- Is morphology acceptable?
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

<u>Preparing Stored samples for testing</u>

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.
- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. TURBT specimens are preferred. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.
- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
  - Adequate fixation
  - Good preservation of morphology
  - Presence of tumor tissue
  - Histopathology consistent with indication
  - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block for sectioning to occur at the laboratory. Blocks should be shipped containing enough material to to allow a minimum of 5, and preferably 10, sections to be cut (each 4 micron thick) for PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:
  - A minimum of 10 slides x 10 micron (μm) thick and 5 slides x 4 μm thick, unstained sections should be provided for PD-L1 testing
  - A new disposable microtome blade must be used for each block to prevent contamination between patient samples
  - Slides are stable under these conditions for 6 months.
  - Apply one section per slide to positively-charged Superfrost glass slides
  - The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

8.3 PD-1 expression on T cells from peripheral blood and IFN-γ in plasma

Peripheral blood will be collected prior to starting durvaRT, 3-4 weeks post durvaRT and at the safety follow up visit-post completion of adjuvant durvalumab. Expression of PD-1 on CD4+ and CD8+ T cells will be assessed by flow cytometry. Correlation between the level of PD-1 expression and clinical outcomes (DCR, PFS, OS) will be analyzed.

Volume of blood: 3 green tops, each with 8cc of blood for each time point per patient- Time periods include- baseline, 3-4 weeks post completion of durvaRT and at the safety follow up visit post completion of adjuvant durvalumab.

The blood samples need to be shipped on ice (4° C) to Dr. Zheng's lab within 24 hours for processing before saving in liquid nitrogen.

Study Description

Peripheral blood will be collected at above time periods. Samples will be diluted 1:1 with PBS before separation of peripheral blood mononuclear cells (PBMCs) by density gradient centrifugation. Cells will be frozen and stored in liquid nitrogen. When assays are performed, frozen cells will be thawed and washed in staining buffer. Cells will be then incubated with directly conjugated monoclonal antibodies CD3-APC, CD8-APCcy7, CD4-FITC and PD-1-PE for 30 minutes at 4°C. Flow cytometry will be performed on a BD Fortessa with subsequent analysis using FlowJo Version 8.8.7 software. Analysis will be performed after gating on live singlet cells. Percentage of PD-1 positive cells among CD3+CD4+ and CD3+CD8+ T cells respectively will be evaluated. Correlation between PD-1 expression clinical outcomes (DCR, PFS, OS) will be analyzed.

Plasma cytokines such as IFN-γ: Plasma obtained from peripheral blood collected above for PD-1 expression will also be used to analyze inflammatory cytokines including but not limited to IFN-γ. IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular IFN-γ release by T cells will be assessed by flow cytometry.

8.4 Urine cell free DNA (ucfDNA):

Urine volume of about 30cc will be collected at baseline and stored for further testing- ucfDNA at baseline will be used for further testing.
We will store the urine at baseline for performing NGS (somatic mutation) on ucfDNA if possible. Please note that this correlative testing will be done only if additional funding is available.

8.5 Next generation sequencing:

NGS of tumors pretreatment and post durvaRT and their correlation with response rate for durvaRT +adjuvant durvalumab. In addition, we will do next generation sequencing of urine at pretreatment and will correlate with tumor sequencing at pretreatment stage. If subjects have genetic sequencing analyses performed as per standard of care prior to study and/or at progression, those results should be entered into the study database. In that case, NGS testing may not be repeated by the study.

We will explore the correlation between somatic mutational statuses- upregulation of specific mutation/pathway, mutational burden with clinical outcome. We will also do NGS at baseline on ucfDNA and compare it to the tumor NGS for specificity and sensitivity. This will help us determine the role of circulating DNA in urine as a non-invasive surrogate marker for tumor biopsies.

The samples of available tissue at baseline and post durvaRT will be stored to do NGS for future. These will include DNA and RNA sequencing and we will also explore subtyping based on RNA expression. NGS will be done upon receipt of funding. The samples will be collected as stated above for PD-L1 testing (either a tissue block OR 15 FFPE slides [minimum of 10 slides x 10 micron (μm) thick and 5 slides x 4 μm thick] plus any leftover surplus tissue after standard of care procedure). We will use the leftover specimen after PD-L1 test on tissue for performing NGS. Similarly, we will use the available ucfDNA for performing NGS. Please note that this correlative testing will be done if additional funding is available.

Pre-treatment whole blood will be collected for germline comparison. This is also known as a somatic baseline sample.

8.6 Storage of Biospecimens

The tissue and urine samples will be shipped from all sites to be stored in the Institute of Personalized Medicine's lab of Penn State Hershey Medical center. Tissues will be collected when biopsies are done as part of standard of care so no extra risk is associated with it. Tissue and urine will be shipped per standard of care as listed in the lab manual.

The peripheral blood will be shipped to Dr. Hong Zheng's lab at Penn State Hershey Medical Center within **24hours of lab draw. The PBMCs should be shipped on ice (4° C).** To avoid delays, lab needs to be drawn between Mon-Thursday. Labs should not be drawn on holidays, weekends or Fridays.

Some experiments would be performed in Dr. Todd Schell's lab at Penn State Hershey Medical Center. These would include immune biomarkers- Intracellular cytokine release by CD4 and

CD8 T cells, and their phenotypic subsets, will be assessed by flow cytometry. Correlation between cytokine production and clinical outcomes (RR, PFS, OS) will be analyzed.

8.7 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.8 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at Safety Follow Up.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at Safety Follow Up.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

8.9 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be coded and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following [42] [43]:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

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 wishes to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence

of clinically significant deterioration. Treatment with durvalumab will continue between the initial assessment of progression and confirmation for progression.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. The efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on modified RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

Please note that local PD after concurrent durvaRT can be evaluated by flexible cystoscopy. Local PD must be biopsy proven as mentioned in section 7.5.1.

9.1 Safety and Efficacy variables

- **Safety Assessment during phase Ib as primary end point:**
  - **Safety will be assessed using common terminology criteria for adverse event (CTCAE), version 4 at each clinical visit during the course of treatment.**

Dose limiting toxicity (DLT) details have been provided in section 5.3.2 and 5.3.3.

DLTs will be counted based on the number of subjects with DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event.

- **Efficacy:**

Efficacy will be determined by modified RECIST v1.1. Local response in bladder will also be determined by serial cystoscopy. Progression will be determined by modified RECIST v1.1 with help of imaging and cystoscopy. Patients will be allowed to continue on the study after 1st progression until the PD is confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration.

Efficacy by cystoscopy:
At each cystoscopy, tumor staging of disease in the bladder will be decided based upon the intra-operative findings by urologist, radiology and the pathology report if applicable (flexible cystoscopy exam is acceptable if deemed necessary by treating urologist; pathology confirmation is needed for confirmation of recurrence in bladder).

Suspected progression by cystoscopy will be defined as any new growth of a three-dimensional tumor within the bladder. The appearance of possible carcinoma in situ, defined as flat velvety erythematous mucosal patches, will not be deemed disease progression at interval cystoscopy. Any suspected tumor progression will trigger a brief cessation of therapy to allow for TURBT with repeat maximal resection and pathologic confirmation of viable tumor. Confirmed disease

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progression, defined as an increase in volume of a three-dimensional, viable, histologically confirmed cancer will be recorded as PD. Progressive disease per cystoscopy must be confirmed by pathological diagnosis. **CIS, T1 will not be defined as disease progression. Photographic imaging will be performed to provide a record of baseline local disease and at any other time cystoscopy is performed if possible. Recording of photographic imaging is strongly encouraged by urologist.**

If a CR is suspected, confirmatory directed and random biopsies will be performed to rule out residual CIS. In the event that CIS is the only finding, the patient will be deemed a CR and may be offered appropriate intravesical mitomycin therapy for CIS. Intravesical BCG is not allowed for this study. Patient will need to come off the study should patient decide to use BCG therapy per discussion by urologist. BCG intravesically is permitted after completion of adjuvant durvalumab. If T1 recurrence is proven, interruption for TURBT is allowed on the study. Intravesical mitomycin is allowed but intravesical BCG is not permitted during the course of durvalumab, but can be given after completion of adjuvant durvalumab.

Any cystoscopical findings that suggests persistence of one or more lesion(s) will be classified as non-CR/non-PD

The following will be used to define the tumor staging based on NCCN guidelines.
Tx: Primary tumor cannot be assessed
Ta: Noninvasive papillary carcinoma Tis: Carcinoma in situ
T1: Tumor invades lamina propria
T2: Tumor invades muscularis propria
- T2a: Invades superficial muscularis propria (inner half)
- T2b: Invades deep muscularis propria (outer half)

T3: Tumor invades perivesical tissue/fat
- T3a: Invades perivesical tissue/fat microscopically
- T3b: Invades perivesical tissue fat macroscopically (extravesical mass)

T4: Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
- T4a: Invades adjacent organs (uterus, ovaries, prostate stoma)
- T4b: Invades pelvic wall and/or abdominal wall

Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 include the following.

9.2 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. 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. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.2.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.3 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.4 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 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.

9.5 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.6 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment 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

9.7 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 site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor-investigator with another evaluation by imaging at next clinic visit, no sooner than 4 weeks.

9.8 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. But confirmaory scans need to be done no sooner than 4 weeks to confirm PD for this study prior to discontinuing treatment. **Cystoscopy evaluation will be counted as non-target lesion.			

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.

9.9 Definitions for Response Evaluation – RECIST 1.1

9.9.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

9.9.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed at next clinic visit no less than four weeks after the criteria for response are first met. Stable disease response is defined as disease response that meets the criteria for SD for at least duration of 8 weeks. Confirmatory scans for stable disease must be performed at next clinic visit, no less than 4 weeks after the criteria for response are first met.

9.9.3 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.9.4 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.9.5 Complete Response Rate
The objective response rate is the proportion of all subjects with confirmed CR according to modified RECIST 1.1 and cystoscopy, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.9.6 Disease Control Rate:
The disease control rate is the proportion of all subjects with stable disease (SD) or 8 weeks, or partial response (PR), or complete response (CR) according to modified RECIST 1.1 and cystoscopy, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.9.7 Progression Free Survival Rate at 1year:
Progression free survival rate at one year is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 and cystoscopy at 1 year from the start of durvalumab treatment, D1 of durvaRT.

9.9.8 Progression Free Survival
A measurement from the date of initiation of durvalumab until the criteria for disease progression is met as defined by modified RECIST 1.1 and cystoscopy or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

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9.9.9 Overall Survival

Overall survival is defined by the date of initiation of durvalumab to date of death from any cause.

10. DRUG INFORMATION

10.1 Durvalumab (MEDI4736)

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD] 274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

The results from phase I study have led FDA to grant breakthrough therapy designation to durvalumab in Feb 2016, for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen.

Encouraging results from this study has led to the design of a phase III study in bladder cancer. DANUBE is a phase III study that is evaluating the efficacy of durvalumab alone vs. durvalumab plus anti-CTLA4 Mab, tremelimumab vs. standard of care in 1st line setting for metatstatic chemo naïve cisplatin eligible and cisplatin ineligible patients. The results are expected by 2018. Please refer to section 1.2 for more details.

10.2 Supplier/How Supplied

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the site investigator as a 500-mg vial solution for infusion after dilution.

AstraZeneca/MedImmune will supply durvalumab at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.3 Preparation

See also Section 5.7. See Documents/ Info tab of the EDC for dose calculations on subjects less than or equal to 30 kg.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.
An additional volume of 0.9% (w/v) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.

The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

10.4 Storage and Stability

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Unopened vials of liquid durvalumab must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Store in original carton to protect from light. Durvalumab must be used within the individually assigned expiry date on the label.

In-use storage and stability

Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. The table below summarizes time allowances and temperatures.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	4 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein.

The dose of durvalumab for administration must be prepared by the site's designated Investigational Pharmacy using aseptic technique. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm or 0.22-µm in-line filter.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

10.6 Precautions

Owing to the drug's mechanism of action and nonclinical findings, subjects should be monitored for the development of immune-mediated adverse events such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, neuropathy, serious infection, infusion-related reactions, anaphylaxis or serious allergic reaction, and immune complex disease.

10.7 Dispensing

Durvalumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Durvalumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.8 Adverse Events

Adverse events for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These adverse events are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

The identified risks with durvalumab monotherapy include the following: cough/productive cough, pneumonitis, ILD, dysphonia, ALT/AST increased, hepatitis, diarrhea, abdominal pain, colitis, hypothyroidism, hyperthyroidism, blood TSH increased, blood TSH decreased, adrenal insufficiency, type 1 diabetes mellitus, hypophysitis/hypopituitarism, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis, myocarditis, pyrexia, peripheral edema, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, myositis, polymyositis and infusion related reaction.

The following events have been seen with other checkpoint inhibitors (Naidoo et al 2015, Champiat et al 2016) and/or may possibly occur due to the mechanism of action of the PD-1/PD-L1 class or mAb therapeutics in general.

- Potential imAEs including:

  - Pancreatitis
  - Other rare or less frequent events with a potential immune-mediated aetiology, eg, pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg, keratitis and optic neuritis), skin (eg, scleroderma and vitiligo), and haematological (eg, haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis), neuropathy/neuromuscular toxicities (eg, myasthenia gravis, Guillain Barre syndrome), vasculitis, non-infectious meningitis and non-infectious encephalitis.
- Hypersensitivity reactions including:
  - Anaphylaxis and allergic reaction
  - Cytokine release syndrome
  - Immune complex disease
- Other infections

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical

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event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. **NOTE**: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Definition of Immune-Mediated Adverse Events (imAEs)

Immune-mediated AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential imAEs, AstraZeneca/Medimmune has defined a list of specific adverse event terms (see AESIs below) that are selected adverse events that **must be reported to Big Ten Cancer Research Consortium Administrative Headquarters (BTCRC AHQ) within 24 hours** from the time the site investigator is aware of such an occurrence, regardless of whether or not the site investigator considers the event to be related to study drug(s). The AESI must be reported via entry into OnCore.

11.1.4 Definition of Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the local investigator to sponsor-investigator via the BTCRC project manager. An AESI may be serious or non-serious.

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If the Investigator has any questions in regards to an adverse event (AE) being an imAE, the Investigator should promptly contact the sponsor-investigator via the BTCRC project manager.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

11.1.4.1 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated adverse events including pneumonitis are outlined in Appendix 2.

11.1.4.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Appendix 3.

11.1.4.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea, and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix 2

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, these cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

11.1.4.4 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Appendix 2.

11.1.4.5 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 2.

11.1.4.6 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix 2.

11.1.4.7 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 2.

11.1.4.8 Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc).

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 2.

<u>Criteria for Hy's Law (FDA Guidance 2009)</u>

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

11.1.5 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.6 Relatedness

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)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent, throughout the treatment period, and until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- Adverse events will be assessed by the site investigator for severity, relationship to the investigational product, and possible etiologies.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to BTCRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent, throughout the treatment period, and until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported via entry into the OnCore SAE tab **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- SAEs will be assessed by the site investigator for severity, relationship to the investigational product, and possible etiologies.
- All SAEs, regardless of relation to study drug, will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

During the course of the study all SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events. Once the SAE has resolved, sites must submit a follow up via OnCore within a reasonable timeframe.

11.2.2.2 Other events requiring immediate reporting

Requirements for Reporting Overdose
An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported to BTCRC AHQ via entry into OnCore within **within 1 business day** of knowledge of the event. BTCRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

Requirements for Reporting Hepatic function abnormality
Hepatic function abnormality (as defined in Section 11.1.4.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to BTCRC AHQ via entry into OnCore, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. BTCRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the site investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the site investigator and evaluated by the sponsor-investigator and AstraZeneca/MedImmune.

Requirements for Reporting Pregnancy
If a subject becomes pregnant during the course of the study, durvalumab and RT should be discontinued immediately. Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may

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have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of any conception occurring from the date of the first dose until 90 days after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study drug.

Pregnancy in a female subject who has received investigational product is required to be reported ***within 1 business day of knowledge of the event*** to BTCRC AHQ at safety@hoosiercancer.org on the Pregnancy Report form (See Documents/Info tab of the EDC). BTCRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 1 business day using the designated Safety e-mailbox.

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to BTCRC AHQ after outcome is known.

BTCRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox. The designated AstraZeneca representative will work with BTCRC AHQ and the Sponsor Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Any pregnancy in the partner of a male study subject from the date of the first dose until 90 days after the last dose should be reported ***within 1 business day of knowledge of the event*** to BTCRC AHQ at safety@hoosiercancer.org on the Pregnancy Report form (See Documents/Info tab of the EDC). The site investigator will endeavor to collect follow-up information on such pregnancies, provided the partner of the study subject provides consent.

11.2.2.3 BTCRC AHQ Requirements for Reporting Events to AstraZeneca

BTCRC AHQ will report all SAEs, AESIs, and other reportable events to AstraZeneca within **1 business day** of knowledge of the event. Follow-up information will be provided to AstraZeneca as reasonably requested.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca, preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

11.2.2.4 BTCRC AHQ Responsibilities for Reporting SAEs to FDA

BTCRC AHQ has been designated to manage the Investigational New Drug Application associated with this protocol on behalf of the sponsor-investigator. BTCRC AHQ will cross-reference this submission to AstraZeneca's parent IND at the time of submission.

BTCRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, BTCRC AHQ will submit a copy of these reports to AstraZeneca at the time of submission to FDA.

BTCRC AHQ will inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. BTCRC AHQ will work with the site and sponsor-investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines. These reports will also be submitted to AstraZeneca at the same time.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

11.2.3 Sponsor-Investigator Responsibilities

BTCRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE data from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.4 IND Safety Reports Unrelated to this Trial

AstraZeneca will provide BTCRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. BTCRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. BTCRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via OnCore.

Upon receipt from BTCRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a single arm, open-label study phase Ib/II study of durvaRT followed by adjuvant durvalumab. Phase Ib will be conducted to determine the safety of durvalumab in combination with RT. Phase II will estimate the 1-year PFS and DCR (post completion of durvaRT followed by adjuvant durvalumab).

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

Phase Ib :
To assess the safety of combining durvalumab with RT in that the DLT rate is smaller than 33%. Documenting DLTs during the combined durvaRT period. Subjects will be monitored for DLTs for 7-weeks.

Phase II:
1. *Estimate the progression free survival (PFS) rate at 1 year.* Progression free survival rate at one year is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 and cystoscopy at 1 year from the start of durvalumab treatment, D1 of durvaRT.

2. *To estimate the DCR to concurrent durvaRT followed by durvalumab. DCR will be defined for this study as rates of patients achieving CR, PR or SD, post completion of concurrent durvaRT and adjuvant durvalumab*. Response will be determined by modified RECIST 1.1

12.2.2 Definition of Secondary Endpoints

Phase Ib:
1. Estimate the DCR post completion of concurrent durvaRT.
2. To correlate the expression of PD-L1 on immunohistochemistry at pre-treatment (TURBT specimen if possible) and post- durvaRT treatment (cystoscopy-biopsy 2-3 weeks post durvaRT) with DCR.

Phase II:
1. Estimate the median progression free survival (PFS) time. Median PFS for this cohort will be calculated.
2. Estimate the rate of complete remission (CR) post durvaRT by modified RECIST 1.1
3. Estimate the overall survival (OS), defined as time from start of treatment, D1, to the date of death due to any cause.

12.3 Sample Size and Accrual
Statistical Power and Sample Size Considerations: The Phase Ib component consists of one dose level only so it requires a maximum of 6 patients. **Given the safety is not dose dependent; no dose de-escalation will be allowed.** For the Phase II component, we hope our therapy will increase the rate of PFS at 12 months from 50% to 75%. There is paucity of literature to support the exact PFS rate for this subgroup of patients. As this study is expected to enroll higher stage patients with T4 or node positive disease, it is assumed that the historic PFS rate is around 50%

at 1-year (PFS rate for stage IV patients who achieve CR is around 80% but those who do not achieve CR it falls between 0-40%). To reach a statistical power of at least 80% at one-sided alpha level of 5% and to allow for 10% drop out rate, a total of 26 patients are needed for this part which allows for 10% dropout. The second primary objective of Phase II is to estimate the disease control rate (DCR), which we assume to be about 75%. With 26 combined patients in Phase Ib and Phase 2, we can, with 90% confidence, estimate DCR within 14% error.

6 patients from the in Phase Ib will be included in the analysis with patients from the Phase II portion for a total number of patients of 26.

12.4 Analysis Datasets

Patients to be included for analyses in phase Ib:

1. All patients who complete the entire course of durvaRT.
2. All patients who get at least one dose of durvalumab who experience DLTs. However if a patient permanently discontinued the trial due to non-toxicity reasons related to RT or durvalumab, then that patient will not be included in the phase 1 analyses.

Patients to be included in the phase II analyses:

PFS analyses: We will follow the intent-to-treat principle and therefore will include all patients who are enrolled and completed at least one dose of the treatment. We will also include roll over patients from phase Ib. For PFS, the survival analysis can handle censoring data for those who drop out early for reasons unrelated to disease or toxicity. For those who may drop out for reasons pertaining to disease or toxicity, they will be followed up for an accurate time of disease progression/survival unless patient withdraws consent.

DCR analyses: For DCR, the co-primary end point for phase II part, we will include all patients who complete the entire course of durvaRT followed by adjuvant durvalumab (regardless of duration of adjuvant period of treatment) and whose disease response could be determined. Patients who discontinue the trial due to non-disease related or non-toxicity reasons whose disease response cannot be determined during the course of therapy will be excluded from the DCR analyses. We will also include roll over patients from the phase Ib part provided they complete the entire course of treatment per protocol.

12.5 Assessment of Safety

Any subject who receives at least one dose of treatment on this protocol should be evaluable for toxicity. We will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4, to record toxicity. Please refer back to the Study Calendar for the schedule of toxicity assessment.

12.6 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of progression free survival and objective response. Please refer to section 9.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

Descriptive statistics will be used in the study to analyze patient's characteristics and demographics. In particular, patient age, race, weight, ECOG performance status will be described. For phase Ib, the incidence and type of DLTs will be tabulated and reported at the dose level. Other toxicity information will be summarized via frequency tables by type and grade of toxicity. DLTs will be recorded during the entire course of durvaRT. The combined treatment will be considered safe to continue to phase II part of the study if 0 or 1 patient (out of 6) experiences DLT.

For phase II, the primary endpoints are the progression free survival (PFS) status at 1 year, and the disease control status (CR+PR+SD) post completion of concurrent durvaRT followed by adjuvant durvalumab. The PFS will be analyzed using the Kaplan–Meier estimator with particular emphasis for one-year survival rate. The disease control status will be summarized using point estimate values of the relative frequency and their 95% confidence intervals. Appropriate statistical tests will be used to compare the PFS rate and the disease control rate from the study sample to the existing values from historical cohorts.

12.7.2 Analysis Plans for Secondary Objectives

The secondary endpoints include the progression-free survival (PFS) time, overall survival (OS) time, and the rate of complete remission (CR) post durvaRT by RECIST/cystoscopy. The survival (PFS and OS) time will be graphical displayed by the Kaplan-Meier survival curve. The median survival time and its 95% CI will be reported. The statistical methods use for analyzing the CR rate and relapse rate will be similar to that for the disease control rate. The bi-variate relationship between the outcome variables and some key some key clinical and demographic variables, such as tumor stage, ECOG status, smoking status, and gender, etc. will be examined by Fisher's exact test or Kaplan-Meier test when appropriate. For the factors that show marginally significant relationship (for example, $p<0.1$), their relationship with the outcome variable will be reexamined by using some multiple regression methods, such as multiple logistic regression or multiple Cox proportional hazard regression. All analyses will be performed using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA). The statistical significance level to be used is 0.05.

12.7.3 Analysis Plans for Exploratory Objectives

For the exploratory objectives, the relationship between PD-L1 expression on tumor and tumor infiltrating cells when compared to clinical outcome (DCR, PFS, OS): IHC will be performed as previously reported [41], and all IHC will be assessed by clinical pathologists through the use of the Allred system, which consists of the summation of IHC intensity and distribution of immunoreactivity. Correlations amongst IHC scores for PD1, PDL1 and FOXP3, and between the extent of positive staining and tumor stage will be assessed using Spearman rank coefficients. The extended Mantel-Haenszel test will be used to assess correlations between IHC scores after adjusting for tumor stage. The association between IHC score and response to durvalumab (DCR, PFS, OS) will be tested via the application of Mann-Whitney U test following dichotomization at the mean. For progression-free survival (recurrence) analysis, univariate analyses will be performed using log rank tests and visualized using Kaplan-Meier survival

curves. Variables associated with adverse prognosis based on previous studies and variables with a P <0.10 on univariate analysis will also be included in a multivariate analysis using a Cox proportional hazards model if needed.

For other exploratory objectives in phase II study: PD-1 expression on T-cells in PBMC will be correlated with clinical outcome using two-sample T-test or nonparametric Wilcoxon Rank-Sum test. The correlation of selected genes obtained by next generation sequencing (NGS) will be correlated to clinical outcomes using similar statistical methods. The overall false discovery rate (FDR) will be controlled at 0.05 level.

12.7.4 Subgroup Analyses

Planned subgroup analysis will be done to compare differences in clinical outcome (DCR and PFS rate, mPFS, OS) with tumor stage (T2, T3, T4), lymph node positivity, ECOG PS (0/1 vs. 2), histology (pure urothelial vs. mixed with predominant urotheial component), chemotherapy exposure prior to starting durvaRT (chemonaïve subjects vs. post chemotherapy patients), maximal TURBT (yes vs. no).

12.7.5 Other Planned Analyses

Descriptive statistics will be used in the study to analyze patient's characteristics and demographics. In particular, patient age, race, weight, ECOG performance status will be described.

12.8 Interim Analysis/Criteria for Stopping Study

Interim analysis will be performed at the discretion of the Data Safety Monitoring Committee to monitor study progress. Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

a) Patient accrual rate with a projected accrual completion date,
b) Pretreatment characteristics of accrued patients, and
c) Frequency and severity of toxicities.

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (1-year progression-free survival rate, disease control rate, etc.). The Data and Safety Monitoring Committee will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Penn State Cancer Institute's DSMP.

BTCRC AHQ oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting

- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Board for review as per their DSMP

13.2 Penn State Cancer Institute Data Safety Monitoring Board

The study will undergo review by the Penn State Cancer Institute Data Safety Monitoring Board.

BTCRC AHQ will provide the Penn State Cancer Institute DSMB with the following:

- Adverse event summary report
- Audit results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Penn State Cancer Institute DSMB will review study data semi-annually. Documentation of DSMC reviews will be provided to sponsor-investigator and BTCRC AHQ. Issues of immediate concern by the DSMB will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with BTCRC AHQ to address the DSMB's concerns.

13.3 Data Quality Oversight Activities

Remote validation of Oncore data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites will be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by BTCRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by AstraZeneca/ MedImmune or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-investigator has delegated responsibility to BTCRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a

central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

BTCRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through the web-based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. BTCRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in OnCore and correlative results will be captured in OnCore or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until BTCRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, BTCRC AHQ, AstraZeneca/ MedImmune, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Joshi M, *et al. J Immunother Cancer* 2023; 11:e006551. doi: 10.1136/jitc-2022-006551

If the results of the study are published, the subjects's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to BTCRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

APPENDIX 1

Appendix 2. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications		Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4 (unless indicated otherwise). In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.		It is recommended that management of immune-mediated adverse events (imAEs) follow the guidelines presented in this table: −It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines −Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event −In the absence of a clear alternative etiology, all events should be managed as if they were immune related. General recommendations follow. −Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events −For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone PO 1-2mg/kg/day or IV equivalent −Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialistsubspecialty consultation. −If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid
Grade 1	No dose modification	
Grade 2	Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed once event stabilizes to grade ≤1 after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per site Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below.	
Grade 4	Permanently discontinue study drug/study regimen	
Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently		

Appendix 2. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)	
discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper **Note**: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper) − More potent immunosuppressives such as TNF inhibitors (e.g. infliximab; also refer to the individual sections of the immune mediated adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. − With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. − Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient.

APPENDIX 3

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)

	Grade of Event (NCI CTCAE v 4)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	Any Grade	General Guidance	**For Any Grade:** − Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. − Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	**For Grade 1 (Radiographic Changes Only)** − Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated. − Consider pulmonary and infectious disease consult.
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (Mild to Moderate New Symptoms)** − Monitor symptoms daily and consider hospitalization − Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent). − Reimaging as clinically indicated. − If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. − If still no improvement within 3-5 days despite IV methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once improving, gradually taper steroids over ≥28

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)

	Grade of Event (NCI CTCAE v 4)	Dose Modifications	Toxicity Management
			days and consider prophylactic antibiotics, antifungal or anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections) – Consider pulmonary and infectious disease consult – Consider, as necessary, discussing with study sponsor-investigator.
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult; consider, as necessary, discussing with sponsor investigator. – Hospitalize the patient – Supportive Care (eg, oxygen) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. **Caution**: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and, in particular, anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
Diarrhea/ Colitis Large intestine perforation/ Intestine perforation	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus).

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			− When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event, including perforation. − Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarreha: stool frequency of <4 per day over baseline) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modification	**For Grade 1:** − Close monitoring for worsening symptoms − Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4-6 per day over baseline) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤Grade 1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** − Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy, to confirm colitis and rule out

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	indicated*) * "medical intervention" is not invasive		perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5mg/kg once every 2 weeks. **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with sponsor-investigator if no resolution to ≤ Grade 1 in 3-4 days. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 per day over baseline; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/ study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective		current NCCN guidelines for treatment of cancer-related infections).
Hepatitis (Elevated LFTs) Infliximab should not be used for management of Immune Related Hepatitis	**Any Elevations in AST, ALT or Total Bili (TB) as Described Below**	**General Guidance**	**For Any Elevations Described:** − Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin − Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and	No dose modification • If it worsens, treat as described for elevations in the row below	− Continue LFT monitoring per protocol

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Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients	**≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal**		
	AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5- 3.0×baseline if baseline abnormal	Hold Study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens then treat as Grade 3 or Grade 4. • If improves to ≤ Grade 1 or baseline, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with with sponsor-investigator. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil)[a]. Discuss with sponsor-investigator if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)[a].
	AST or ALT >5.0×ULN if baseline normal,	For elevations in transaminases ≤ 8 × ULN, and/or in TB ≤5×ULN if baseline normal, or for elevations	– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3-5 days despite 1 to 4

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	>5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days. For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study	mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with sponsor-investigator if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)[a].

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
		drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT and /or AST > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alk phos) and in the absence of any alternative cause.[b]	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
bilirubin or signs of DILI/liver decompensation			
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. • If toxicity improves to to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	− Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. − Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. − Consider, as necessary, discussing with study physician. − If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**For Grade 4:** Same as above (except would recommend obtaining liver biopsy early)
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise. For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline) - For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen			
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	**Any Grade**	General Guidance	**For Any Grade**: − Consult with nephrologist − Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 [Serum Creatinine > 1-1.5 × baseline; > ULN to 1.5 × ULN]	No dose modification	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3 or 4. − Consider symptomatic treatment including hydration,

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			electrolyte replacement, and diuretics.
	Grade 2 [Serum Creatinine>1.5-3.0 × baseline; >1.5-3.0 × ULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** − Consider symptomatic treatment including hydration, electrolyte replacement, and diuretics. − Carefully monitor serum creatinine every 2-3 days and as clinically warranted. − Consult nephrologist and consider renal biopsy if clinically indicated. − If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. − Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).[a] − When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 × baseline; >3.0-6.0 × ULN Grade 4: Serum Creatinine > 6.0 × ULN)	Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** − Carefully monitor serum creatinine on daily basis − Consult nephrologist and consider renal biopsy if clinically indicated. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE v. 4 for definition of severity/ grade depending on type of skin rash)	General Guidance	**For Any Grade**: – Monitor for signs and symptoms of dermatitis (rash and pruritus) – IF THERE IS ANY BULLOUS FORMATION, THE SPONSOR-INVESTIGATOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modification	**For Grade 1**: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3. • If toxicity improves ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper.	**For Grade 2**: – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid. Consider, as necessary, discussing with sponsor-investigator and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if persistent for >1-2 weeks or recurs

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4**: Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** − Consult dermatology − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Consider hospitalization. − Monitor extent of rash [Rule of Nines]. − Consider skin biopsy (preferably more than 1) as clinically feasible. − Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)[a] − Consider, as necessary, discussing with sponsor-investigator.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/ lipase increased also included in this section)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4 for defining the CTC grade /severity)	General Guidance	**For Any Grade:** − Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with sponsor-investigator. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polypipsia, polyuria, hypotension and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis,

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modification	**For Grade 1: (including those with asymptomatic TSH elevation)** − Monitor patient with appropriate endocrine function tests − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinologist consult.
	Grade 2	For Grade 2 endocrinopathy other than amylase/lipase elevation, hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until subject is clinically stable. • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or	**For Grade 2: (including those with symptomatic endocrinopathy)** − Consult endocrinologist to guide evaluation of endocrine function, and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine work up, except those with amylase/lipase elevation, isolated hypothyroidism or Type 1 DM, and as guided by endocrinologist, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones).

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
		continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are ≤ 10mg/day or equivalent.	− Patients with asymptomatic amylase/lipase elevation may continue study drug/ regimen without interruption. For patients with symptomatic amylase/lipase elevation hold study drug/ regimen until subject is clinically stable, asymptomatic, and amylase/lipase is ≤ grade 2. Consider steroids and further tests at physician discretion per standard of care to rule out any alternative etiology (e.g., pancreatitis). − Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)[a]. − For patients with normal endocrine work up (lab assessment or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4	• For Grade 3 or 4 endocrinopathy other than amylase/lipase elevation, hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. • Study drug/study regimen can	**For Grade 3 or 4**: − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. − For all patients with abnormal endocrine work up, except those with amylase/lipase elevation, isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
		be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1) The event stabilizes and is controlled. 2) The patient is clinically stable as per investigator or treating physician's clinical judgement. 3) Doses of prednisone are ≤10 mg/day or equivalent.	methylprednisolone 1 to 2 mg/kg/day or equivalent as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). − For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. − Patients with asymptomatic amylase/lipase elevation: hold study drug/ regimen until subject is clinically stable and amylase/lipase is ≤ grade 2. For patients with symptomatic amylase/lipase elevation hold study drug/ regimen until subject is clinically stable, asymptomatic, and amylase/lipase is ≤ grade 2. Consider steroids and further tests at physician discretion per standard of care to rule out any alternative etiology (e.g., pancreatitis) − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not limited to limbic encephalitis, autonomic	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4 for defining the	General Guidance	**For Any Grade:** − Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). − Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness).

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	CTC grade/ severity)		− Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations). − Symptomatic treatment with neurological consult as appropriate.
	Grade 1	Permanently discontinue study drug/study regimen	**For Grade 1:** See "Any Grade" recommendations above.
	Grade 2	Permanently discontinue study drug/study regimen	**For Grade 2:** − Consider, as necessary, discussing with the sponsor-investigator − Obtain neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent . − If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IV IG).
	Grade 3	Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** − Consider, as necessary, discussing with sponsor-investigator. − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IV IG). − Once stable, gradually taper steroids over ≥28 days.
	Grade 4	Permanently discontinue study drug/study regimen	
Peripheral neuromotor	Any Grade	General Guidance	**For Any Grade:** − The prompt diagnosis of immune-mediated

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
syndromes (such as Guillain-Barre and Myasthenia Gravis)			peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modification	**For Grade 1:** – Consider, as necessary, discussing with the sponsor-investigator

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1. Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the sponsor-investigator – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat myasthenia gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids

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	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3**: Hold study drug/study regimen dose until resolution to ≤ Grade 1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or life threatening events): − Consider, as necessary, discussing with sponsor-investigator − Recommend hospitalization − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4	• If Grade 2 -- Hold study drug/study regimen dose until	**For Grade 2-4:** – Monitor symptoms daily, hospitalize.

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
	Grade 2: Symptoms with mild to moderate activity or exertion Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. • If Grade 3-4, permanently discontinue study drug/study regimen.	– Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/ Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	– No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.

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Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)			
	Grade of Event (NCI CTCAE v 4)	**Dose Modifications**	**Toxicity Management**
			– Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (pain associated with severe	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization.

Appendix 4. Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)

	Grade of Event (NCI CTCAE v 4)	Dose Modifications	Toxicity Management
	weakness; limiting self-care ADLs)	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

a: ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
b: FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation
Abbreviations: AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

APPENDIX 5

Appendix 6. Dosing Modification and Toxicity Management Guidelines for Infusion Related Reactions for Durvalumab Monotherapy (17 October 2019 Version)		
Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade	**General Guidance**	**For Any Grade:** − Manage per institutional standard at the discretion of investigator − Monitor for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia)
Grade 1 or Grade 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or Grade 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or Grade 4	For Grade 3 or 4: Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

APPENDIX 7

Appendix 8. Dosing Modification and Toxicity Management Guidelines for Non Immune-mediated Reactions for Durvalumab Monotherapy (17 October 2019 Version)		
Non-immune Mediated Reactions		
CTC Grade/ Severity	**Dose Modification**	**Toxicity Management**
Any Grade	**Note**: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose modifications	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note: for Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and in consultation with the sponsor-investigator via the BTCRC project manager)	Treat accordingly as per institutional standard

APPENDIX 5

Guidelines During COVID-19 Pandemic or Other National Crisis

The following changes may be implemented and/or adapted without causing a deviation during COVID-19 or other national crisis. HOWEVER, the usual protocol parameters must be reinstated when the emergency is over or whenever local authorities and policies permit.

Subjects on active treatment:

1. Treatment infusions and clinic visits may be delayed by maximum of 4 weeks from the date of expected visit if the safety of the subject is of concern. Any further delay should be entered as deviation and marked as due to COVID-19.
2. Any subject on treatment who develops COVID-19 infection or complications due to COVID-19, should be captured as SAE/AE not related to treatment. Treatment should be temporarily held for those subjects due to lack of safety data in this situation. However, if a subject recovers and can restart study drug within the 12 week period per protocol, the sponsor investigator must be consulted prior to restarting. All subjects should be followed up per protocol (subjects who discontinue without progression).
3. If subjects are unable to get labs and imaging done at the enrolling Institution, these may be performed locally but must be reviewed by the treating physician. The enrolling Institution should make all effort to obtain the local imaging and it be re-read by a radiologist at enrolling Institution.
4. Telephone or telemedicine visits may be counted as a clinic visit. Physical exam, including vitals (for clinic note), may be marked as missed provided that the treating physician has done a thorough interim history and determines there probably would not be any significant change in exam. These will NOT be counted as deviations but MUST be captured as limited PE due to COVID-19.
5. Imaging and cystoscopy:
    a. Disease imaging: may be delayed by 4 -6 weeks based on subject safety and will NOT be captured as a deviation. If the imaging needs to be further delayed, please consult the sponsor investigator; these delays should be entered as deviations due to COVID-19.
    b. Cystoscopy: may be delayed by 4-6 weeks based on subject safety and will NOT be captured as a deviation. If the cystoscopy needs to be further delayed, please consult the sponsor investigator; these delays should be entered as deviations due to COVID-19.

Subjects on Follow up:

1. Subjects who have not had disease progression: Follow up visits including imaging and cystoscopy may be delayed by 1-2 months, depending upon the need to maintain safety. Any further delay should be captured as a deviation related to COVID-19. Telemedicine or telephone visits will be allowed without physical exam and vitals. See #5 above.
2. Subjects who are being followed for survival: Survival follow up may be done via telephone or may be obtained from clinic/telemedicine note, etc. when possible.
3. Any subject who develops COVID-19 infection should be captured as SAE/AE not related to treatment.

COVID-19 Guidelines from AstraZeneca (23 April 2020)

In relation to the current outbreak of COVID-19 disease, AstraZeneca is providing guidance to investigators and treating physicians on the management of patients taking durvalumab and/or tremelimumab as part of a clinical trial based on our current understanding of the scientific data and the known safety profile of durvalumab/tremelimumab. We are closely monitoring the emerging literature and adverse event reports to continually assess this position in the light of new information and will provide updated information if this position changes.

Risk of pneumonitis associated with the use of durvalumab and/or tremelimumab vs COVID-19

Symptoms of durvalumab/tremelimumab-induced pneumonitis include fever, cough, shortness of breath, difficulty breathing and an abnormal chest scan. Please note that these symptoms are similar to symptoms of coronavirus pneumonia. Physicians should consider coronavirus infection and other infectious and non-infectious etiologist versus symptoms suggestive of pneumonitis. A thorough evaluation should be performed to accurately identify the underlying pathology.

Since current knowledge about COVID-19 infection is limited, please review available literature that could be a useful aid when considering diagnosis and treatment options. A case-by-case assessment of the benefit/risk balance for an individual patient should be done for decisions on discontinuing or pausing treatment.

To help ensure patient safety, please confirm that all site personnel involved in one or more studies involving durvalumab and/or tremelimumab familiarize themselves with the pneumonitis monitoring and management guidelines in the protocol.

Patients should be reminded that, if a potential exposure to COVID-19 is suspected, they should notify health authorities and medical personnel of their participation in a study on a drug with known risk of pneumonitis. If a patient exhibits symptoms consistent with those of either drug-induced pneumonitis or COVID-19, it is recommended that she/he should be advised to contact both the recommended COVID-19 point of contact (as per local guidance), as well as her/his investigator/oncologist by phone.

Risk of COVID-19 severity associated with the use of durvalumab and/or tremelimumab

To date, it is unknown whether durvalumab and/or tremelimumab can increase the risk of severity of COVID-19. We are in the process of gathering the data to better understand the risk or severity in the context of COVID-19. In addition, we are in the process of gathering the data on the effect of durvalumab/tremelimumab on the immune response to viruses like COVID-19.

Suspected/Confirmed COVID-19

- New Patients: For potential participants who are exhibiting symptoms consistent with COVID-19 or have tested positive, these patients are recommended, following your medical assessment, to not be enrolled in the study until their symptoms have resolved.
- Ongoing Patients: For patients who are exhibiting symptoms consistent with COVID-19, study medication can be continued if feasible and if considered medically appropriate by your criteria.

16. REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.
2. Stein, J.P., et al., *Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients.* J Clin Oncol, 2001. **19**(3): p. 666-75.
3. Stein, J.P. and D.G. Skinner, *The role of lymphadenectomy in high-grade invasive bladder cancer.* Urol Clin North Am, 2005. **32**(2): p. 187-97.
4. Sternberg, C.N. and A.B. Apolo, *Everything old is new again! Neoadjuvant chemotherapy in the treatment of muscle-invasive bladder cancer.* J Clin Oncol, 2014. **32**(18): p. 1868-70.
5. Grossman, H.B., et al., *Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer.* N Engl J Med, 2003. **349**(9): p. 859-66.
6. Advanced Bladder Cancer Meta-analysis, C., *Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration.* Eur Urol, 2005. **48**(2): p. 202-5; discussion 205-6.
7. Choueiri, T.K., et al., *Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates.* J Clin Oncol, 2014. **32**(18): p. 1889-94.
8. Plimack, E.R., et al., *Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity.* J Clin Oncol, 2014. **32**(18): p. 1895-901.
9. Shipley, W.U., et al., *Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer.* Urology, 2002. **60**(1): p. 62-7; discussion 67-8.
10. Rodel, C., et al., *Organ preservation in patients with invasive bladder cancer: initial results of an intensified protocol of transurethral surgery and radiation therapy plus concurrent cisplatin and 5-fluorouracil.* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1303-9.
11. Efstathiou, J.A., et al., *Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience.* Eur Urol, 2012. **61**(4): p. 705-11.
12. Mak, R.H., et al., *Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233.* J Clin Oncol, 2014. **32**(34): p. 3801-9.
13. James, N.D., et al., *Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer.* N Engl J Med, 2012. **366**(16): p. 1477-88.
14. Muller, A.C., et al., *Organ-sparing treatment of advanced bladder cancer: paclitaxel as a radiosensitizer.* Strahlenther Onkol, 2007. **183**(4): p. 177-83.
15. M. Dror Michaelson, et al., *The initial report of RTOG 0524: Phase I/II trial of a combination of paclitaxel and trastuzumab with daily irradiation or paclitaxel alone with daily irradiation following transurethral surgery for noncystectomy candidates with muscle-invasive bladder cancer. J Clin Oncol 32, 2014 (suppl 4; abstr LBA287).*

16. Mu, C.Y., et al., *High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation.* Med Oncol, 2011. **28**(3): p. 682-8.
17. Thompson, R.H., et al., *Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma.* Cancer, 2005. **104**(10): p. 2084-91.
18. Thompson, R.H., et al., *Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up.* Cancer Res, 2006. **66**(7): p. 3381-5.
19. Krambeck, A.E., et al., *Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma.* Clin Cancer Res, 2007. **13**(6): p. 1749-56.
20. Nomi, T., et al., *Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.* Clin Cancer Res, 2007. **13**(7): p. 2151-7.
21. Loos, M., et al., *Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer.* Cancer Lett, 2008. **268**(1): p. 98-109.
22. Wang, L., et al., *Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma.* World J Surg, 2010. **34**(5): p. 1059-65.
23. Andorsky, D.J., et al., *Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells.* Clin Cancer Res, 2011. **17**(13): p. 4232-44.
24. Keir, M.E., et al., *PD-1 and its ligands in tolerance and immunity.* Annu Rev Immunol, 2008. **26**: p. 677-704.
25. Park, J.J., et al., *B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance.* Blood, 2010. **116**(8): p. 1291-8.
26. Zou, W. and L. Chen, *Inhibitory B7-family molecules in the tumour microenvironment.* Nat Rev Immunol, 2008. **8**(6): p. 467-77.
27. Brahmer, J., et al., *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(2): p. 123-35.
28. Dang, T.O., et al., *Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer.* Expert Rev Anticancer Ther, 2015: p. 1-8.
29. Larkin, J., et al., *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.
30. Powles, T., et al., *MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer.* Nature, 2014. **515**(7528): p. 558-62.
31. Peter H. O'Donnell, et al., *Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study. J Clin Oncol 33, 2015 (suppl 7; abstr 296).*
32. Jean H. Hoffman-Censits, et al., *IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). J Clin Oncol 34, 2016 (suppl 2S; abstr 355).*
33. Park, B., C. Yee, and K.M. Lee, *The effect of radiation on the immune response to cancers.* Int J Mol Sci, 2014. **15**(1): p. 927-43.
34. Dewan, M.Z., et al., *Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody.* Clin Cancer Res, 2009. **15**(17): p. 5379-88.
35. Verbrugge, I., et al., *Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies.* Cancer Res, 2012. **72**(13): p. 3163-74.

Joshi M, *et al. J Immunother Cancer* 2023; 11:e006551. doi: 10.1136/jitc-2022-006551

36. Formenti, S.C. and S. Demaria, *Combining radiotherapy and cancer immunotherapy: a paradigm shift.* J Natl Cancer Inst, 2013. **105**(4): p. 256-65.
37. Obeid, M., et al., *Calreticulin exposure is required for the immunogenicity of gamma-irradiation and UVC light-induced apoptosis.* Cell Death Differ, 2007. **14**(10): p. 1848-50.
38. Obeid, M., et al., *Calreticulin exposure dictates the immunogenicity of cancer cell death.* Nat Med, 2007. **13**(1): p. 54-61.
39. Sternberg, C.N., et al., *Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse.* Cancer, 1989. **64**(12): p. 2448-58.
40. Brisuda, A., et al., *Urinary Cell-Free DNA Quantification as Non-Invasive Biomarker in Patients with Bladder Cancer.* Urol Int, 2016. **96**(1): p. 25-31.
41. Joshua I. Warrick, M.D., et al., *Enhancer of Zeste Homolog 2 (EZH2) Expression in Invasive and Non-invasive Bladder Cancer.Urologic Oncology Seminars and Original Investigations.*
42. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.
43. Nishino, M., et al., *Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements.* Clin Cancer Res, 2013. **19**(14): p. 3936-43.
44. Wu, C.E., et al., *Prognostic value of complete response in patients with muscle-invasive bladder cancer undergoing concurrent chemoradiotherapy.* Anticancer Res, 2013. **33**(6): p. 2605-10.