ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA8185

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

EA8185 represents a joint scientific collaboration between ECOG-ACRIN and NRG Oncology Research Groups, with ECOG-ACRIN as the lead group for trial conduct

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ACTIVATION DATE

August 25, 2020
Addendum #1
Addendum #2
Addendum #3
Addendum #4
Addendum #5
Addendum #6
Addendum #7

Agents	IND#	NSC#	Supply
Durvalumab	[redacted]	778709	NCI
Cisplatin		119875	Commercial
5-Fluorouracil		19893	
Mitomycin		26980	
Gemcitabine		613327	

IND Sponsor: DCTD, NCI

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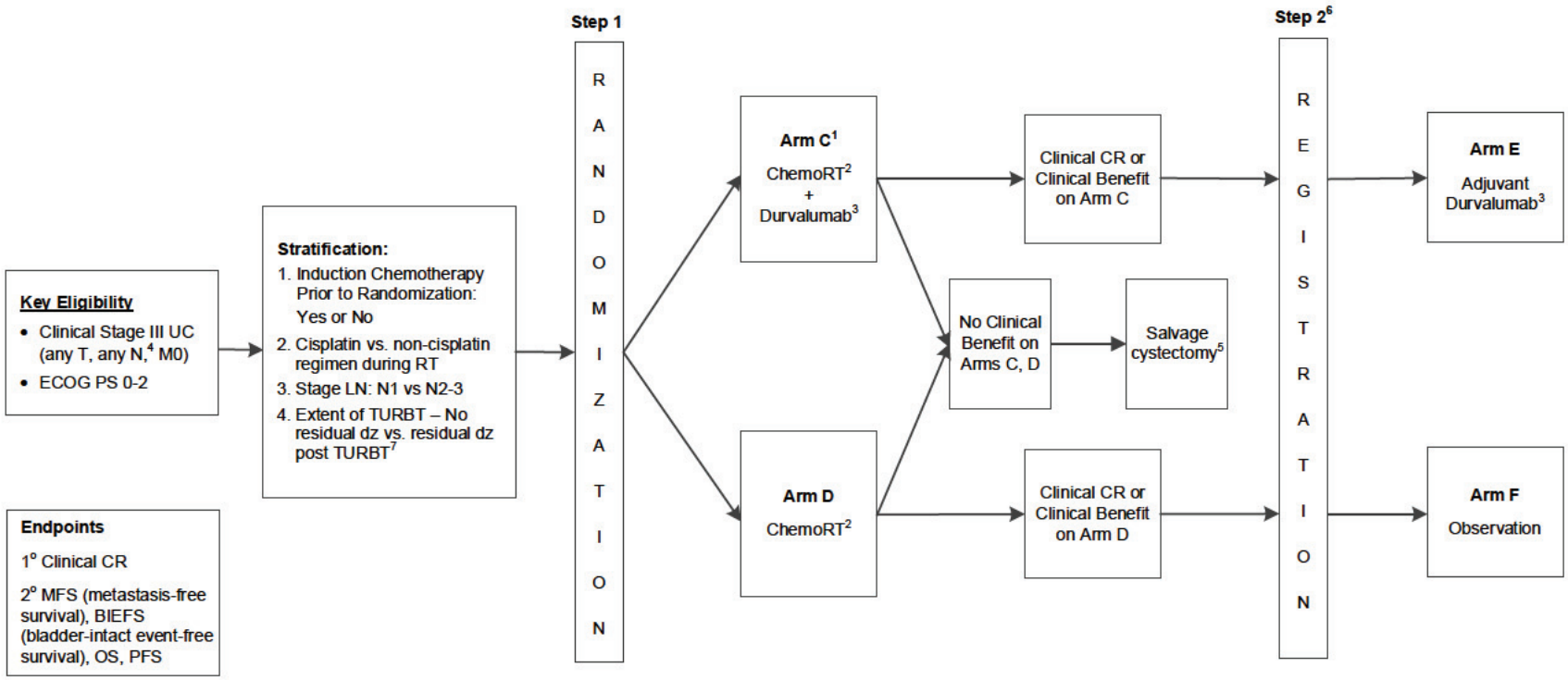
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For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com . Please refer to the patient enrollment section of the protocol for detailed instructions.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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Schema



N=95

1. 1st 6 patients randomized to Arm C (ChemoRT + Durvalumab) will be evaluated for safety run.
2. Chemosensitizing options: (weekly Cisplatin or 5-FU+MMC, or twice weekly Gemcitabine) +EBRT. See Section 5.1 for treatment options and descriptions.
3. Durvaluamb will be given Q3 weekly x 3 doses on Arm C and it will be given Q4 weekly x 6 doses on Arm E.
4. Node positivity must have been defined prior to using any systemic chemotherapy or induction chemotherapy.
5. Salvage cystectomy when possible.
6. Restaging 8 weeks (+/-2 weeks) with imaging and cystoscopy and biopsy.
7. TURBT: trans-urethral resection of bladder tumor.

NOTE: Arms A and B removed in Addendum 4.

1. Introduction

1.1 Background

Bladder cancer remains the fourth most common cancer in men and it accounts for about 80,470 new cases (about 61,700 in men and 18,770 in women) and around 17,670 deaths from bladder cancer (about 12,870 in men and 4,800 in women) in the United States of America.[1]

Recently, bladder cancer staging was modified to clearly separate node positive disease from distant metastatic disease. The AJCC 8th Edition Staging System for bladder cancer has re-classified node positive disease [N+ (N1-N3)] as stage III disease (previously being included with stage IV disease). Node positive bladder cancer patients tend to behave differently than those with metastatic [M1] disease. A prospective observational study for patients treated with definitive surgery (radical cystectomy and lymph node dissection [RC]) showed 5-year cancer specific survival (CSS) to be 81% for node negative vs. 40% for node positive bladder cancer patients.[2] The 5 year CSS has been reported as 20% for M1 disease which appears to be lower than node positive bladder cancer.[3] Based on our recent survey of ECOG-ACRIN/NRG physician specialists for bladder cancer (medical oncologist, urologist, radiation oncologist), most bladder cancer experts treat node positive patients with neoadjuvant chemotherapy (NAC) followed by definitive therapy such as chemoRT or RC. However, there is a paucity of data on the best treatment approach for this group of patients. The use of neoadjuvant and adjuvant therapy post-surgery is variable,[4] most clinical studies for metastatic disease have few node positive, non-metastatic patients and previous bladder preservation clinical studies have excluded node positive patients. Given the lack of clinical studies, it is hard to tease out the benefit of systemic therapy or a bladder preservation approach in this subset of patients. Thus, there is need to develop new therapeutic approach in node positive bladder cancer patients who have no evidence of distant metastases. Thus, there is an opportunity to determine and optimize the outcomes of this group of patients with local therapy.

1.2 Role of Immunotherapy in Bladder Cancer

The advent of immunotherapy has revolutionized the care of bladder cancer patients. Programmed cell death ligand 1 (PD-L1) is part of a complex immune system of receptors and ligands that play an essential role 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.[5,6] 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.[7]

PD-1/PD-L1 immune Checkpoint Inhibitors (CPI) have shown efficacy in chemotherapy naive[8] and in cisplatin refractory patients with advanced disease.[9,10] In the past few years, the FDA has approved 5 drugs that target the

PD-1 axis for use in bladder cancer (Atezolizumab, Pembrolizumab, Durvalumab, Avelumab and Nivolumab). Out of these 5 drugs, Pembrolizumab has received full approval for use in refractory urothelial cancer to Cisplatin, and Atezolizumab and Pembrolizumab are also approved for chemotherapy naïve patients who are either not fit for platinum chemotherapies or have high PD-L1 expression on their tumor. CPI are also being studied in earlier stages of bladder cancer with promising efficacy. The PURE-01 study in 50 patients with muscle-invasive bladder cancer (MIBC) demonstrated a 42% rate of pathological complete response when treated with 3 cycles of Pembrolizumab q3 weekly as NAC.[11] There are several studies that are currently evaluating the efficacy of CPI in MIBC as shown in Table 1.1. However none of these active studies is exclusively enrolling node positive M0 patients with bladder cancer.

Table 1.1: Active Trials Studying Immune Checkpoint Inhibitor Therapy in Muscle Invasive Bladder Cancer

Drug	Clinical Trials.gov ID	Regimens	N	Patient population	Primary End Point
Pembrolizumab					
	NCT03319745	Pembro as NAC	20	T1-4 N0 M0	Toxicity
	NCT02736266	Pembro as NAC	90	T2-T4a N0 M0	pCR
	NCT02365766	Pembro + Gem ± Cis as NAC	81	T2-4aN0M0	pCR
	NCT02690558	Pembro +Gem +Cis as NAC	39	T2-T4a N0/X M0	<pT2
	NCT02560636	Pembro+ hypofractionated RT	34	T2-4, N0-3, M0-1	Toxicity
	NCT02662062	Pembro+Cis + EBRT	30	T2-T4a, Nx or N0	Toxicity
	NCT02621151	Pembro+Gem+EBRT	54	T2-T4a, N0, M0	2yr BIDFS
	NCT03244384	Pembro vs. obs as adjuvant in upper tract +MIBC	739	>=pT2 pN+ M0	OS, DFS
Durvalumab					
	NCT02891161	Durva+EBRT	42	T2-4N0-2 M0	DCR, PFS
	NCT02812420	Durva+Treme as NAC	35	cT2-3aN0M0	Toxicity
	NCT03773666	Durva+/- Oleclumab as NAC	24	T2-T4a N0 M0	Toxicity
	NCT03234153	Durva+Treme as NAC	68	T2-T4 and/or N+	ORR
	NCT03732677	Durva+ Gem+ Cis as NAC followed by Durva Vs. Gem+ Cis as NAC	1050	T2-4N0M0	pCR, EFS
	NCT03702179	Durva+Treme +EBRT	32	Not available	pCR

Drug	Clinical Trials.gov ID	Regimens	N	Patient population	Primary End Point
	NCT03549715	ddMVAC+ Durva +/- Treme as NAC	120	T2−T4a and ≤N1	pCR
Atezolizumab					
	NCT02451423	Atezo as NAC	42	NMIBC + T2-4N0M0	Change in CD3+T cell, pCR
	NCT02662309	Atezo as NAC	96	T2-T4a N0M0	pCR
	NCT02450331	Atezo vs. obs as adjuvant in MIBC and Upper tract	809	pT2-4a or pN+	DFS
	NCT03775265 (SWOG/NRG 1806)	ChemoRT+/- Atezolizumab	475	T2-T4a N0M0	BIEFS
Nivolumab					
	NCT03294304	Nivo+ gem + Cis as NAC	41	T2-T4a and N<1	≤pT1pN0
	NCT02845323	Nivo+/- Urelumab as NAC	44	MIBC	CD8+ T cell
	NCT03171025	Nivo as adjuvant post chemoRT	28	T2-4a, N0 or N+, M0	2yr FFS
	NCT02632409	Nivo vs. obs as adjuvant	640	pT2-4 pN+	DFS
	NCT03532451	Nivo +/- Lirilumab as NAC	43	T2-T4a, N0-N1, M0	Toxicity
Avelumab					
	NCT03674424	Avelumab +/- Gem+Cis/ddMVAC/PG	196	T2-T4a N0-2 M0	pCR
	NCT03747419	Avelumab +EBRT	24	≥T2 N0	Clinical CR
	NCT03617913	Avelumab+ 5-FU+Mito OR Cis + EBRT	27	T2-T4a N0M0	CR

Pembro=Pembrolizumab; pCR=Pathological complete remission; N=total number of patients; NAC=neoadjuvant chemotherapy; Gem=gemcitabine; Cis=cisplatin; RT=radiation; EBRT= External beam RT; DCR=disease control rate; BIDFS= Bladder Intact Disease Free Survival; MEDI4736 Durva=Durvalumab; Treme=Tremelimumab; ddMVAC=dose dense Methotrexate, Vinblastin, Doxorubicin, Cisplatin; Atezo=Aezolizumab; NMIBC= non muscle invasive bladder cancer; DFS= disease free survival; FFS= failure free survival; 5-FU+Mito= 5-fluorouracil + mitomycin

1.3 Chemoradiotherapy in Bladder Cancer

Radiation therapy is a critical component of bladder-preserving trimodality therapy and definitive therapy for MIBC patients. In the setting of operable muscle invasive urinary bladder cancer, selective bladder preserving trimodality

therapy utilizes maximum TURBT, chemotherapy, and radiation therapy, resulting in 5-year disease-specific survival rates of 60 – 70%.[12,13,14,15] 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 (DFS) of 67% versus 54% and 5-year overall survival (OS) of 48% versus 35%.[16] Thus, concurrent chemotherapy is an important part of this paradigm. There has been a long history of Radiation Therapy Oncology Group (RTOG) trials and studies conducted by other groups that have aimed at optimizing the care of bladder cancer (Table 1.2)[44]. In general, a Complete Response (CR) is seen in about 70% of patients undergoing chemoradiotherapy. However, the modern prospective trials delivering chemoradiotherapy have included primarily node-negative patients with MIBC, and there are limited data describing the outcomes of patients undergoing chemoradiotherapy who have node-positive disease. Two retrospective studies have described clinical outcomes of node-positive patients, but both studies consisted of ≤ 5 node positive patients[40, 41]. A national cancer database study suggested that chemoradiotherapy was associated with improved overall survival compared to chemotherapy alone in this patient population, with a median survival of 19 months in the chemoradiotherapy group[42]. However, more granular data on clinical outcomes such as clinical response and subsequent progression were not available from the dataset.

Table 1.2: Modern Studies Describing Outcomes of Patients Undergoing Chemoradiotherapy for Bladder Cancer

Study	Study Design	N	% Node+	Concurrent Chemotherapy Regimen	RT Regimen	CR Rate	Disease Control
BC2001	Ph III	360	None	5-Fluorouracil/ Mitomycin C	64 Gy / 32 fractions or 55 Gy / 22 fractions	NR	5-year DFS: ~50%
RTOG pooled analysis	Ph II, III	468	None	Various	Various	69%	5-year BI-DFS: 56%
BCON	Ph III	333	None	Carbogen and nicotinamide	64 Gy / 32 fractions or 55 Gy / 22 fractions	81%*	5-year RFS: 41%
RTOG 0712	Ph II	70	None	5-FU and Cisplatin (FC) or Gemcitabine (G)	64.3 Gy / 42 fractions or 64 Gy / 32 fractions	88% (FC) and 78% (G)	3-year BI-MDFS: 67% (FC) and 72% (G)
MGH	Retrospective	475	None	Various	Various	75%	5-year BIDSS: 52%
Princess Margaret	Retrospective	56	18%	Cisplatin	66 Gy / 33 fractions	NR	Recurrence rate: 41%
University Hospital	Retrospective	5	All	5-Fluorouracil/ Mitomycin C (4 patients)	64 Gy / 32 fractions	60%	3 patients free of disease
UChicago	Retrospective	11	3	Capecitabine	55 Gy / 25 fractions	82%	2-year PFS: 41%

RT: Radiotherapy
CR: Complete response
DFS: Disease-free survival
&: RTOG 8802, 8903, 9506, 9706, 9906, 0233
BI-DFS: Bladder-intact disease-free survival
*: Free of muscle-invasive disease
RFS: relapse-free survival
BI-MDFS: Bladder-intact metastatic-disease-free survival
BIDSS: Bladder-intact disease-specific survival
PFS: progression-free survival

1.4 Durvalumab

1.4.1 Overall Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism, and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

1.4.1.1 Durvalumab

Risks with durvalumab (MEDI4736) include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

For further information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab Investigator's Brochure (IB).

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 7% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case

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of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated (Section 5.6.2).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.4.1.2 Rationale for Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I 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 the 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 (5th, median and 95th 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-patient variability with fixed dosing regimen.

Similar findings have been reported by others Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters.

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.

Several ongoing studies have been using 15mg/kg Q3 weekly; thus we will be also using 1125mg based on median 75 kg weight during the chemoRT+ durvalumab part of the study. Thus, patients on the experimental arm will get 1125mg IV q3 weekly to match their 3 weekly chemotherapy schedules and will get a total of 3 doses of durvalumab. For patients who will be receiving single agent durvalumab post chemoRT+ durvalumab phase will be getting Q4weekly regimen of IV durvalumab. The Q4 weekly regimen has been used in many clinical studies with durvalumab and was also used for our phase I/II DUART study. No major safety issues were observed with

this dosing in our previous study. Thus patients who qualify to get adjuvant durvalumab post chemoRT+ durvalumab treatment will be getting 1500mg IV Q4weekly dosing for total of 6 doses.

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1.5 Rationale for combining Chemoradiotherapy with Durvalumab in Node-positive Bladder Cancer Patients

There are preclinical and clinical data to support that both radiotherapy and chemotherapy can augment the immune response. Radiotherapy has been shown to stimulate the immune system by causing immunogenic cell death that leads to production of neo-antigens, which eventually causes activation of effector T cells, recruitment of T cells to the irradiated tumor and overall increased vulnerability towards T cell mediated cell killing.[17] Hence, the assumption is that combining RT with CPI would be synergistic for response in cancer patients. Synergy between RT and CPI was demonstrated in lung cancer in the PACIFIC study.[18] This was a phase III study, where durvalumab (PD-L1 targeting antibody) prolonged the progression free survival (PFS) by 11.2 months over placebo as consolidation therapy in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.[18] Recently the updated results of the PACIFIC study demonstrated a significant OS benefit with adjuvant durvalumab. A recent study has also shown safety of combining RT with durvalumab concurrently in locally advanced bladder cancer patients.[19] The investigators reported no significant grade 3 or more treatment-related adverse events (TRAEs) in the phase Ib cohort of 6 patients;[19] Table 1.3. In addition, post durvalumab +RT, 5 out of 6 patients had overall clinical response; 1 patient had progression (discussion with PI). Of note, 4 out of the 5 responders post durvalumab +RT were node positive. This provides us with preliminary evidence for safety and efficacy for combining RT+ durvalumab in locally advanced bladder cancer.

Table 1.3: Most Common TRAEs any Grade During the DurvaRT

TRAE	**# of Patients (%)**
Fatigue	3 (50%)
Dermatitis due to radiation	1 (17%)
Lymphopenia	(17%)
Thrombocytopenia	(17%)
Urinary tract related TRAE	(17%)

The phase II part of this study is ongoing. The study has completed accrual with 24 patients, who are now on follow-up (personal communication with PI, Dr. M. Joshi) and the most common AEs were, anorexia, diarrhea, fatigue, UTI. Grade 2 asymptomatic electrolyte imbalances such as hypocalcemia were also observed. Two patients had immune related nephritis. Grade 2 radiation burn was reported in 1 patient. Asymptomatic increase in lipase grade 3 was observed in 1 patient. One patient died due to a lung infection (determined by the treating physician to be related to his underlying lung disease and not related to treatment). Despite ongoing studies such as this, there are currently no published data for combining CPI with definitive RT in localized node positive cancer patients.

It is thought that chemotherapy also primes the immune system and could be effective in enhancing the immune response when combined with CPI. Chemotherapeutic agents can cause increase in antigen presentation, a decrease in T cell-regulation, an increase in expression of co-stimulatory molecules such as B7-1, and can downregulate the expression of inhibitory molecules such as PD-L1 thus, promoting the immune-mediated killing effect on the cancer cells.[20] Anthracycline has shown to increase the production of interferon type I, which in turn could increase the release of chemokine ligand 10 (CXCL10) and this plays an important role in tumor death.[21] Overall, chemotherapy can increase antigenicity via immunogenic cell death of tumor cells. Thus, combining chemotherapy with CPI could prove synergistic and this approach has already demonstrated positive outcome in lung cancer patients.[22] The safety of combining CPI with chemotherapy has been demonstrated before in lung cancer[23] and is currently being studied in several clinical studies in metastatic bladder cancer.

Given that both chemotherapy and RT are synergistic, and both have immune harnessing capabilities, we plan to combine chemoRT with the PD-L1 inhibitor, durvalumab, to evaluate the safety and efficacy of this therapy in node positive non-metastatic bladder cancer patients.

SN1806, an intergroup (SWOG/NRG) bladder preservation study is due to open and will evaluate the role of chemoradiation +/- atezolizumab inT2-4 N0 M0 patients with bladder cancer patients. This study will be opened prior to our proposed study and will provide data for the safety of chemoRT+/- CPI in that population. Our study is not competing for the same population as we are targeting node positive patients and we believe that this study would complement SN1806. Thus, we would like to test the efficacy of combining chemotherapy with radiation +/- durvalumab in patients with node positive bladder cancer.

1.6 Importance of the study design

Node positive, non-metastatic bladder cancer has recently been recognized as a separate entity from metastatic disease, and is classified as clinical stage III per the current AJCC staging system. Retrospective studies suggested better outcomes in this patient population compared to those with M1 disease.[2,3] There is no clear-cut standard of care for node positive disease, as we discovered through a survey of bladder cancer experts we conducted through ECOG-ACRIN/NRG. Per our survey, a majority of treating physicians use locoregional therapy for this patient population, most frequently NAC followed by RC or NAC

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followed by chemoRT. However, there are some circumstances such as patient preference, other comorbidities where patients do not wish to get any systemic therapy before undergoing definitive therapy, hence we adapted the design to be able to enroll those patients as well. Patients will be stratified based on whether they received chemotherapy before enrollment to this study step. Node positive bladder cancer appears to be an area of unmet need warranting more research. Hence, we are designing a phase II study in node positive bladder cancer with multimodality treatment. Our study EA8185, *Randomized Phase II Study of Bladder-Preserving Chemoradiation with durvalumab in Clinical Stage III, Node positive Urothelial Carcinoma* aims to address the node positive patients with a bladder sparing approach. The clinical CR (cCR)- primary endpoint was chosen to get early signal of efficacy and safety in this unique subset of patients to help design a subsequent phase III definitive trial. Post-determination of the primary

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endpoint, patients on the chemoRT+ Durvalumab arm with clinical CR + clinical benefit would get adjuvant durvalumab q4 weekly for 6 doses, as described in treatment plan. Patients in the standard chemoRT group with a clinical CR or clinical benefit after chemoRT will undergo observation. We have several long-term outcomes as secondary end points that may prove to be more meaningful and help in further designing the phase III study. We hope that with a clinical CR endpoint, if we see a signal, the planning and design of a definitive registration trial can begin much sooner in parallel while the more durable study endpoints are maturing. This study could help planning for definitive phase III study that would be important to define standard of care for N+ patients.

Recent phase Ib study results in bladder suggested that the combination of RT with durvalumab was safe in locally advanced bladder cancer.[19] Post durva-RT, efficacy was seen in 22/24 patients .[46] The phase II component of this study is still ongoing. Our study plans to randomize patients with node positive bladder cancer to chemoRT +/- durvalumab. Currently, the majority of N+ M0 patients are treated with systemic chemo followed by either chemoRT or surgery. Our hope is to develop a bladder sparing approach for this subset of patients. Our experimental arm would be chemoRT + durvalumab. As discussed above, we believe that the addition of durvalumab to chemoRT would enhance the response rate. Our preliminary results from the phase Ib DUART clinical trial did demonstrate an upregulation of PD1+ CD8+ and CD4+ T cells in the peripheral blood after durvalumab + RT in bladder cancer patients (results not shown here). As mentioned above, patients who achieve clinical CR and clinical benefit on experimental arm would then get adjuvant durvalumab. The addition of adjuvant component has been designed to understand the role of additional durvalumab after achieving clinical response. At this point, there is no standard of care for adjuvant therapy in node positive patients post definitive therapy; thus, patients on chemoRT arm who achieve CR would undergo observation. In addition, we believe that those patients who have ≥T2 in bladder after chemoRT+/- durvalumab, and are resectable should get salvage cystectomy.

Dosing of durvalumab would be 1125mg >30 kg or 15 mg/kg if ≤ 30 kg Q3 weekly to match the chemotherapy schedule and to ensure 3 doses of CPI while getting chemoRT. AstraZeneca has established before the safety of this dose in combination with chemotherapy in early clinical study. Dosing of durvalumab as single agent during adjuvant part would be 1500 mg Q4 weekly if >30 kg or 20 mg/kg if ≤30 kg Q4 weekly. We plan to give only 6 doses of adjuvant therapy so that the overall treatment for patients with chemoRT + durvalumab followed by adjuvant durvalumab would be approximately 9 months.

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Lymph Node (LN) positivity status: This will be defined per RECIST 1.1 criteria based on non-target LN size. It has been described in the Section 6. We had discussions within ECOG-ACRIN and NRG as well as with Bladder Cancer Task Force and GU steering committee regarding definition of LN+ bladder cancer. Duska et. al., has shown safety of combining pelvic RT + chemotherapy with pembrolizumab in cervical cancer including large RT fields (including para-aortic LNs). Amongst 52 patients, there were no grade 4 or higher diarrhea observed. Six patients had grade 2 diarrhea and only 2 patients had grade 3 diarrhea. Thus we believe that the combination of chemoRT+ durvalumab should be tolerable in N1-3 bladder cancer patients.[45]

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Lymph node positivity will be defined by imaging (CT scan or MRI or PET/CT) read prior to starting any systemic or induction chemotherapy as LN measuring ≥

1.0 cm in short axis with or without biopsy (although patients with a negative biopsy of enlarged lymph nodes will be excluded. If a patient has LN<1.0cm that is biopsy-proven, those patients are eligible to be included in the study. The SN1806 study requires patients with ≥ 1 cm to have a negative biopsy of these nodes. Thus, we will not be competing with the same population of patients. We will be using RECIST 1.1 to evaluate for response in involved lymph nodes. CT scan showing LN size < 10mm in short axis will define as a cCR in the lymph nodes that are radiologically ≥1.0cm at initial diagnosis. CT scan showing LN size <1cm but biopsy proven at diagnosis would need to resolve completely for it to be called cCR. The study will also stratify patients based on LN, N1 vs. N2-3.

Rationale for relaxing the need for induction chemotherapy prior to randomization: Since the study is enrolling newly diagnosed high-risk patients for distant metastases, after discussion with Bladder Cancer Task force, we had initially mandated chemotherapy prior to randomization. Given that this subset of patients have high likelihood of developing distant metastases, systemic chemotherapy should help minimize this risk. In addition, per our initial survey it seems most physicians would consider these patients for chemotherapy prior to proceeding more definitive consolidative approach of either surgery or chemoRT. Thus, we assumed that systemic chemotherapy is probably considered standard of care prior to consolidation. Since the study has been open, we had multiple discussions with site PIs and with NRG, SWOG, Alliance and ECOG-ACRIN and we have realized that some patients and providers are disinclined for induction chemotherapy prior to chemoRT +/- durvalumab. This is a rare category for bladder cancer patients, and we need to capture all patients in order to meet our accrual. Hence, in Nov 2021, after discussions with various cooperative groups experts, we have relaxed the requirement for induction chemotherapy. Induction chemotherapy is encouraged but it is per physician discretion. We do believe that induction chemotherapy prior to chemoRT +/- durvalumab could influence our primary outcome, thus patients will be stratified based on whether systemic chemotherapy was received prior to enrollment. For the purposes of this study, systemic chemotherapy prior to randomization would be referred to as induction chemotherapy in the protocol.

Rationale for stratification: This is a small phase II study that is evaluating the role of chemoRT+/- PD-L1 directed immunotherapy in node positive patients. This is an area of unmet need as this will be the first study focusing on N1-3 patients alone. Most of the previous bladder preservation studies have not included node positive patients. Coen et al. had shown in their retrospective review that presence of incomplete TURBT, presence of hydronephrosis, higher T stage, are negative predictors for response to chemoradiation.43 We assume that node positive patient will do worse than node negative and would likely have higher T stage such as cT3a or cT4, presence of hydronephrosis and may have higher incidences of incomplete TURBT. We believe that there are many baseline characteristics in the patient population that could influence the overall outcome such as size of node at baseline, induction chemotherapy, response to induction chemotherapy, type of radiosensitizer- cisplatin vs. non-cisplatin, extent of TURBT, PD-L1+ at baseline, extent of TURBT, etc. We wish to include induction chemotherapy as a stratification factor since some patients may not want to get induction chemotherapy prior to enrollment. Thus, we will not be using hydronephrosis as a factor but would be looking at the subset of patients with hydronephrosis during interim analyses and will be adjusting the eligibility criteria to exclude these patients should we find them to have lower clinical CR.

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Details have been provided in the statistical analyses. We will also not include pathological vs. clinical node positivity as a stratification factor. Per literature 10% of radiological positive LN could be negative upon surgery, thus per our statistician, this should not be a major factor in influencing the clinical outcome. Since we are only focusing on node positive subset of patients in this phase II study, it is not feasible to include every factor that could influence the results of the study. However we felt that there is need to ensure some balance between both groups, thus we chose to follow the Simon-Pocock's minimization method that allows more number of stratification factors to be included in the design. The Simon-Pocock minimization method for randomization, a method of adaptive stratified sampling, will be employed to assign enrolled patients to one of the two treatment groups (treatment – chemoRT+ durvalumab vs. control - chemoRT). The purpose of using minimization is to ensure the treatment arms are balanced with respect to several pre-defined patients prognosis factors that could influence the primary clinical endpoint. In this trial we will take four prognosis factors into consideration for minimization: (1) radiosensitizing options (Cisplatin vs non-Cisplatin), (2) induction chemotherapy prior to enrollment (yes or no), (3) LN Stage N1 vs N2-3, and (4) Extent of TURBT- no residual disease vs. residual disease post TURBT. This purpose of minimization is to minimize the imbalance between the numbers of patients in each treatment group over the four prognosis factors listed above.

2. Objectives

2.1 Primary Objective

2.1.1 To compare the clinical complete response rate [cCR] after chemoRT with or without durvalumab in node-positive bladder cancer patients.

2.2 Secondary Objectives

2.2.1 To compare the toxicity profile in both arms using the CTCAE.

2.2.2 To estimate the progression-free survival [PFS] in both arms.

2.2.3 To estimate overall survival [OS] post randomization in both arms.

2.2.4 To estimate the bladder intact event free survival [BIEFS] in both arms.

2.2.5 To estimate the metastasis free survival [MFS] in both arms.

2.2.6 To estimate bladder cancer specific survival in both arms.

2.2.7 To estimate the complete clinical response duration in both arms.

2.2.8 To estimate salvage cystectomy rates in both arms.

2.3 Exploratory Objective

2.3.1 Planned subgroup analyses for clinical outcome (Clinical CR rate post chemoRT+/- durvalumab, MFS, OS, PFS) based on stratification factors.

2.4 Translational Objectives:

2.4.1 To collect and bank tumor tissue and blood specimens at pre- and post-treatment with chemoRT +/- durvalumab to determine predictive or prognostic markers.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

NOTE: In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Step 1 (Randomization) Eligibility Criteria:

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have an ECOG Performance Status of 0-2 at the time of Step 1 randomization.

_____ 3.1.3 Patient must have histologically proven pure or mixed urothelial cancer of the bladder.

NOTE: Small cell carcinoma is excluded, however other variant histologies are permitted provided a component of urothelial carcinoma is present.

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_____ 3.1.4 Patient must have documented node-positive and non-metastatic disease (any T, any N, M0). Node positivity must have been defined prior to receiving any systemic chemotherapy or induction chemotherapy.

Node positivity can fall into either of the following categories and will be defined by imaging and/or biopsy:

1. A lymph node ≥1.0 cm in short axis on imaging (i.e., CT or MRI or PET/CT).
2. A lymph node that is < 1 cm on imaging with either a biopsy confirming involvement with cancer or high suspicion of cancer.

_____ 3.1.5 Disease Assessment Requirements

3.1.5.1 For patients who have received induction chemotherapy (any type of systemic chemotherapy) for node positive bladder cancer prior to enrollment, there must be no signs of disease progression (CR/PR or SD) based on restaging imaging and cystoscopy, which consists of:

- CT Chest, Abdomen, and Pelvis obtained after completion of induction chemotherapy and within 8 weeks prior to Step 1 randomization.

  NOTE: MRI can be used instead of CT per treating physician discretion.

- Cystoscopic evaluation and attempt to perform maximal TURBT performed by the participating urologist after completion of induction chemotherapy and within 12 weeks prior to Step 1 randomization. If maximal TURBT is not possible for medical reasons, the enrollment must be discussed and approved with the study chair. Documentation of correspondences with the study chair must be kept on file.
- Patients who achieve CR upon cystoscopy per urologist with no visible tumor (i.e., no need for additional TURBT), are allowed to proceed in the study as adequate resection with no residual disease in bladder.

3.1.5.2 For patients who have did not receive induction chemotherapy (any type of systemic chemotherapy) for node positive bladder cancer prior to enrollment, the following must be obtained:

- CT Chest, Abdomen, and Pelvis completed within 8 weeks prior to Step 1 randomization.

  NOTE: MRI can be used instead of CT per treating physician discretion.

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- Cystoscopic evaluation and attempt to perform maximal TURBT performed by the participating urologist within 12 weeks prior to Step 1 randomization. If maximal TURBT is not possible for medical reasons, the enrollment must be discussed and approved with the study chair. Documentation of correspondences with the study chair must be kept on file.
- For patients who may need repeat TURBT if their old TURBT has fallen out of window: If urologist determine no visible tumor (i.e., no need for additional resection) upon cystoscopy, they are allowed to proceed in the study as complete resection.

_____ 3.1.6 Patient must not have received any previous radiation therapy to the pelvic area.

Rev. Add4 _____ 3.1.7 Patient must agree to undergo CT simulation and treatment planning (detailed in Section 5.3). If this is the first case registered at the site, then a Pre-Treatment RT review will be required and will take up to 3 business days. The patient cannot start radiation treatment prior to successful completion of this Pre-Treatment review. Therefore, careful planning is necessary to meet the deadline of starting radiation within 20 business days of Step 1 randomization.

_____ 3.1.8 Patient must not have presence of concomitant active upper tract tumors or urethra tumors. History of previously adequately treated non-muscle invasive bladder cancer [NMIBC] are eligible. Previously treated urothelial cancer or histological variant at any site outside of the urinary bladder are allowed, provided they have been Ta/T1/Carcinoma in situ (CIS) and post treatment follow up imaging and endoscopic evaluation shows no evidence of disease.

Rev. Add4 _____ 3.1.9 Patients with previous exposure to immune checkpoint inhibitor for non-muscle invasive disease are eligible. If given for NMIBC, the last dose must have been completed >12 months prior to Step 1 randomization.

_____ 3.1.10 Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All patients of childbearing potential must have a blood test or urine study within 14 days prior to Step 1 randomization to rule out pregnancy.

A patient of childbearing potential is defined as any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

Rev. Add3 _____ 3.1.11 Patients must not expect to conceive or father children by using accepted and effected method(s) of contraception or by abstaining from sexual intercourse from the time of Step 1 randomization for the duration of their participation in the study and continue for at least 3 months after the last dose of protocol treatment. See Section 8.1.11 for acceptable methods of contraception.

_____ 3.1.12 Patient must have adequate organ and marrow function (labs must be obtained < 14 days prior to Step 1 randomization) as defined below:

_____ Leukocytes ≥ 3,000/mcL

Leukocytes: _____ Date of Test: _____

_____ Absolute neutrophil count (ANC) ≥ 1,500/mcL

ANC: _____ Date of Test: _____

_____ Hemoglobin ≥ 9g/dL

Hemoglobin: _____ Date of Test: _____

_____ Platelets ≥ 100,000/mcL

Platelets: _____ Date of Test: _____

_____ Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

Total bilirubin: _____ Institutional ULN: _____

Date of Test: _____

_____ AST (SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN

AST: _____ Institutional ULN: _____

Date of Test: _____

ALT: _____ Institutional ULN: _____

Date of Test: _____

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_____ Adequate renal function as evidenced by calculated (Cockcroft's formula) creatinine clearance or 24 hours actual creatinine clearance ≥ 30mL/min. The creatinine used to calculate the clearance result must have been obtained within 14 days prior to Step 1 randomization. Actual body weight, not ideal body weight, must be used in the calculation.

Estimated creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

Creatinine: _____ Date of Test: _____

Creatinine clearance: _____ Date of Test: _____

_____ 3.1.13 Patients with human immunodeficiency virus (HIV) on effective anti-retroviral therapy with undetectable viral load within 6 months of Step 1 randomization are eligible for this trial.

_____ 3.1.14 For patients with autoimmune conditions, patient must not have history of prior documented autoimmune disease within 2 years prior to Step 1 randomization.

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NOTE: Patient with vitiligo, Grave's disease, eczema or psoriasis (not requiring systemic treatment within 2 years prior to Step 1 randomization) are not excluded. Patients with history of completely resolved childhood asthma or atopy are not excluded. Patients with asthma not requiring more than 10mg/d or equivalent of prednisone are not excluded. Patients with well-controlled hypothyroidism on thyroxine replacement will be eligible as well. Patients with known history of hypoadrenalism on maintenance steroids will be eligible. Patients with type I Diabetes Mellitus will be

eligible, provided their disease is well controlled. History of autoimmune related alopecia is also not an exclusion criteria.

Patient with active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) are not eligible.

Patient with a history of and/or confirmed pneumonitis are not eligible.

Patient with a history of primary immunodeficiency are not eligible.

Patient with history of allogeneic organ transplant are not eligible.

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_____ 3.1.15 Patient must not have an active infection, including:

- **Tuberculosis** (based on clinical evaluation that includes clinical history, physical examination, and radiographic findings, and tuberculosis testing in line with local practice)
- **Hepatitis B** (known positive HBV surface antigen [HBsAg] result). Past or resolved HBV infection (defined as the presence of hepatitis b core antibody [anti-HBc] and absence of HBsAg) are eligible.
- **Hepatitis C**. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction test is negative for HCV RNA.

_____ 3.1.16 Patient must not have clinically significant liver disease that precludes patient from treatment regimens prescribed on the study (including, but not limited to, active viral, alcoholic or other autoimmune hepatitis, cirrhosis or inherited liver disease).

_____ 3.1.17 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. Site is encouraged to discuss with the study chair if needed prior to enrollment.

_____ 3.1.18 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class IIB or better.

_____ 3.1.19 Patient must not have received live attenuated vaccine within 30 days prior to the first dose of durvalumab.

NOTE: Patient, if enrolled, must not receive live vaccine whilst receiving durvalumab and up to 30 days after the last dose of durvalumab.

NOTE: Patient is permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza

vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily in order to minimize an overlap of adverse events).

_____ 3.1.20 Patient must not have current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. See Section 5.1 for an expanded list of prohibited concomitant medications. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

Rev. Add4 _____ 3.1.21 Patient must not have any unresolved toxicity (NCI CTCAE Grade ≥2) from previous anti-cancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in Section 3.1.12.

NOTE: Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the study chair.

NOTE: Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the study chair. Documentation of correspondences with the study chair must be kept on file.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add4 3.2 Step 2 (Registration: Adjuvant Durvalumab vs. Observation) Eligibility Criteria

_____ 3.2.1 Patient must have evaluation to determine clinical outcome post Step 1 treatment (chemoRT+/- durvalumab) with imaging (CT chest, abdomen, and pelvis (preferably contrast with urogram, if not contraindicated) and cystoscopy with biopsy confirmation to ensure no progression and absence of ≥ T2 disease in the bladder. Patient should be registered to Step 2 within 28 days from the determination of primary response to Step 1 treatment . However, for patients previously on Arm C, an additional 4 week delay to Step 2 registration is allowed (see Section 3.2.2 below).

_____ 3.2.2 Patient on the chemoRT+ durvalumab (Arm C) must meet the following:

- Patient must have achieved either complete clinical response OR have demonstrated clinical benefit prior to continuing onto adjuvant durvalumab.

- Patients who are to go on the adjuvant durvalumab (Arm E) must have recovered to at least grade 2 or less immune related AE prior to starting treatment except for immune related alopecia, clinically asymptomatic endocrinopathies. **For patients who may have gotten immune related AEs during chemoRT+ durvalumab (Arm C), Step 2 registration could be delayed up to additional 4 weeks to ensure recovery to at least grade 2 or lower prior to starting adjuvant therapy. However patients with durvalumab related AEs that require permanent discontinuation of durvalumab per Section 5.6 will not continue on the adjuvant treatment regardless of the response.**
- Patient must not have experienced immune related neurological disorder described as Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, or meningoencephalitis during chemoRT+ durvalumab treatment.
- Patient must not have experienced immune related myocarditis or immune related pericarditis during chemoRT+ durvalumab treatment.
- Patient must have adequate recovery of ANC, hemoglobin, and platelets (labs must be obtained < 28 days prior to Step 2 registration), as defined below.

NOTE: If recovery is not achieved, blood counts could be repeated weekly and Step 2 registration could be delayed up to additional 4 weeks.

_____ ANC ≥ 1,000 mcL

ANC: _____ Date of Test: _____

_____ Hemoglobin ≥ 8g/dL

Hemoglobin: _____ Date of Test: _____

_____ Platelets ≥ 70,000 mcL

Platelets: _____ Date of Test: _____

_____ 3.2.3 Patient on the chemoRT arm (Arm D) must have achieved either complete clinical response OR have demonstrated clinical benefit prior to be placed on the observation alone arm (Arm F).

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave) acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL)

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a

participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. **Error! Hyperlink reference not valid.**For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.govmailto:>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its

supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select ECOG-ACRIN, and protocol number EA8185;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Requirements For EA8185 Site Registration:

- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Credentialing Status Inquiry Form	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	**X**	An IMRT Head & Neck phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).

Credentialing Notification Issued to:		
Institution		Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and that all desired credentialing requirements have been met.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

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To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of individuals is assigned to the task and have met the training requirements.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on Regulatory at the top of the screen;
- Click on Site Registration; and
- Enter the sites 5-character CTEP Institution Code and click on Go.
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to Step 1 randomization.

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For Step 1 patients, treatment should start within 20 days after randomization. Step 2 registration should occur within 28 days from the determination of response to Step 1 treatment (chemoRT+/- durvalumab). For patients who may have gotten immune related AEs during Step 1, registration could be delayed up to additional 28 days to ensure recovery to at least grade 2 or lower prior to starting adjuvant therapy.

For Step 2 Arm E patients, treatment should start within 15 days after registration.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- The registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in the Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot- reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Step 1: Randomization

4.1.1 Protocol Number

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4.1.2 Investigator Identification

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- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.4 Additional Requirements

4.1.4.1 Specimens are to be submitted for future undefined research studies per patient consent as outlined in Section 10.

4.1.5 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.6 Stratification Factors

- Induction chemotherapy prior to randomization: Yes or No
- Cisplatin vs. non-cisplatin regimen during RT
- Stage of LN: N1 vs N2-3
- Extent of trans-urethral resection of bladder tumor (TURBT) – No residual disease vs. residual disease post TURBT

4.2 Step 2: Registration

4.2.1 Protocol Number

EA8185

4.2.2 Investigator Identification

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- Institution CTEP ID

- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

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4.3 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and

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- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must

log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Digital RT Data Submission Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.

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- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

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4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA8185 Forms Completion Guidelines.

5. Treatment Plan

NOTE: As a result of addendum #4 which removed the requirement for induction chemotherapy prior to randomization to ChemoRT +/- durvalumab, treatment descriptions for Arm A (patients registered post completion of > 3 cycles of induction chemotherapy) and Arm B (patients registered prior to induction chemotherapy who will undergo induction chemotherapy on study) have been removed throughout the protocol.

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5.1 Step 1 – Randomization (Concurrent ChemoRT +/- durvalumab):

Patients will be randomized 1:1 to Arm C (chemoRT + durvalumab) vs. Arm D (chemoRT). The first 6 patients randomized to Arm A will be monitored for dose-limiting toxicities (DLTs) as described in Section 5.6.1.

The duration of concurrent chemoRT+ durvalumab or chemoRT should be 6.5-8 weeks.

If this is the first case registered at the site, a Pre-Treatment RT review will be required and will take up to 3 business days. The patient cannot start radiation treatment prior to successful completion of this Pre-Treatment review. Therefore, careful planning is necessary to meet the deadline of starting radiation within 20 business days of Step 1 randomization.

Arm C: ChemoRT+ durvalumab: Patients starting on Arm C will get Durvalumab once every 21 days for a total of 3 doses along with physician's choice for concurrent chemotherapy as described below, starting 4 days (before or after) the start of radiation therapy. Durvalumab must also be started within 4 days (before or after) the start of radiation therapy.

Arm C	Chemotherapy IV*	Durvalumab IV	RT
	Physician's choice: Cisplatin** OR 5-FU/Mitomycin OR Gemcitabine	Once every 21 days x 3 doses; 1125mg if >30kg OR 15mg/kg if ≤ 30kg	Total of 64-64.8 Gy. Refer to Section 5.3

Arm D ChemoRT: Similarly, patients on the chemoRT arm will receive physician's choice of concurrent chemotherapy as described below. Chemotherapy will start 4 days (before or after) the start of radiation therapy.

Arm D	Chemotherapy IV*	RT
	Physician's choice: Cisplatin** OR 5-FU/Mitomycin OR Gemcitabine	Total of 64-64.8 Gy. Refer to Section 5.3

*The detailed description of the three choices of chemotherapy available to the physician are described in detail below.

**This protocol recommends avoiding cisplatin-based chemotherapy in patients with calculated GFR less than 50ml/min.

Concurrent Chemotherapy – Arms C and D

Premedication for chemotherapy infusion will be based on institutional practices. Please follow institution's routine antiemetic regimen for nausea control. This protocol recommends avoiding dexamethasone higher than 4 mg IV weekly as an antiemetic and strongly recommends using long acting 5HT-3 inhibitors like palonosetrone and Nk1 inhibitor like fosprepitant to avoid delayed nausea especially if using cisplatin as the chemotherapy regimen. The treating physician using institutional policies should address the management of acute allergic reactions, toxicities and dose adjustments.

Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen), may be administered for subsequent infusions if an infusion reaction is observed with durvalumab at the discretion of the treating physician. See section below for the management of Infusion-Related Reactions.

Concurrent chemotherapy during RT will be based on physician choice from the following options listed in table below. The treating physician MUST state the choice of chemotherapy prior to randomization. Dosage for each regimen has been described below. If the radiation is held due to toxicity then chemotherapy should be held during this time as well. We recommend avoiding Cisplatin as an option for patients with creatinine clearance less than 50ml/min. Chemotherapy can be stopped if deemed to be the primary reason for toxicity while continuing on RT. Chemotherapy must be started within 4 days (before or after) the start of radiation therapy.

Patients are not permitted to switch chemotherapy regimens while on study for any reason.

Chemotherapy choices (choose ONE prior to Step 1 randomization):

a. Gemcitabine: 27 mg/m^2 IV twice weekly for 6 weeks, concurrently with RT regimen.

AGENT	DOSE	ROUTE	SCHEDULE
Gemcitabine	27 mg/m^2	IV	Twice weekly for 6 weeks

b. Cisplatin: 35 mg/ m^2 IV weekly for 6 weeks, concurrently with RT regimen.

AGENT	DOSE	ROUTE	SCHEDULE
Cisplatin	35 mg/m^2	IV	Weekly for 6 weeks

c. 5-Fluorouracil (5-FU) and Mitomycin: Mitomycin 12 mg/ m^2 IV on Day 1 of radiation; 5-FU 500 mg/ m^2/day from days 1-5 and days 16-20 of radiation. Both Mitomycin and 5-FU will start on the same day of day 1 of RT (+/- 4 days) per institutional standards.

AGENT	DOSE	ROUTE	SCHEDULE
5-FU	500 mg/m^2	IV	5-FU given on same days as doses 1-5 and 16-20 of RT
Mitomycin-C	12 mg/m^2	IV	Mitomycin-C given on day 1 of 5-FU RT

NOTE:

- If chemotherapy is held for more than 21 days then chemotherapy will be permanently discontinued. Radiation can continue based on physician discretion.
- Suggested Infusion times (OR per institutional guidelines) for the above chemotherapeutic agents are below:

Option	Agent	Infusion time
1	Gemcitabine	Over 30-60 minutes
2	Cisplatin	Over 30-60 minutes
3	5-FU	Continuous infusion over 5 days
4	Mitomycin	30 minutes

While the doses of each drug are standardized, the duration of infusion can vary between institutions and standard institutional protocols may be followed.

- Refer to package insert of specific chemotherapy for any contraindication for use of concomitant medications during the concurrent chemotherapy.

Concurrent Durvalumab – Arm C: Patients will receive intravenous durvalumab (1125mg if > 30 kg OR 15 mg/kg if ≤ 30kg) once every 21 days for a total of 3 doses during the concurrent ChemoRT+ durvalumab therapy.

Durvalumab treatment may be administered up to four days before or after the start of RT. Durvalumab treatment will be administered on an outpatient basis.

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Infuse durvalumab over approximately 60 minutes using an infusion set containing a 0.22 or 0.2 µm in-line filter. Please refer to Section 8.1 for compatible infusion set materials including in-line filter. Flush the IV line with a volume of IV bag diluent equal to the priming volume of the infusion set used at the completion of infusion. Please also note above is suggested infusion guidelines but infusion details could be adapted to institutional policy.

Administration of durvalumab will be performed in an infusion room per institutional policies, with availability of emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. No premedication is indicated for administration of Cycle 1 of durvalumab. Patients who experience an infusion-related reaction with durvalumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.

Patients will be monitored before, during and after the infusion with assessment per institutional policy. Documentation of vital signs including infusion start and completion times should be performed per institutional policy. If the infusion is interrupted or delayed, the reason for doing that must be documented.

Prohibited concomitant medications while on durvalumab:

- Any investigational anticancer therapy other than those under investigation in this study
- Monoclonal antibodies (mAbs) against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study
- Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study
- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers
- EGFR TKIs
- Live attenuated vaccines

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NOTE: Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily in order to minimize an overlap of adverse events)

- Herbal and natural remedies which may have immune-modulating effects

The management of **Infusion-Related Reactions (IRRs)** will be according to severity as follows:

- 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 patients 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 treating physician.
- If the infusion-related reaction is Grade 3 or higher in severity, durvalumab will be permanently discontinued and the patient 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.

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 patient to an intensive care unit if necessary.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during durvalumab infusion, the following procedures should be performed:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

- Continue to observe the patient and document observation.

Adverse events monitoring and dose interruptions should be performed per protocol.

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5.2 Step 2: Registration (Adjuvant Durvalumab vs Observation)

Patients will be evaluated for clinical response 8 weeks (+/-2 weeks) post completion of concurrent chemoRT+/- durvalumab as described in Section 6.1.1.

Patients will undergo CT chest abdomen and pelvis (preferably contrast with urogram, if not contraindicated) to document response per RECIST 1.1 criteria in lymph nodes (LN). Response in bladder will be documented by cystoscopy and biopsy of the previous tumor affected sites +/- random biopsies as documented in Section 6.1.1.1.

Patients will be classified based on clinical outcome as described below.

Definition of clinical outcome post chemoRT +/- durvalumab has been described in detail in Section 6.1.1.

a) Clinical CR
b) Clinical benefit
c) No clinical benefit
d) Progressive Disease [PD]

Patients on Arm C (ChemoRT + Durvalumab) with Clinical CR or Clinical benefit will continue on adjuvant durvalumab therapy as described below and will be registered to Arm E. Patients on Arm D who achieve clinical CR or clinical benefit will be observed and will be registered to Arm F.

All other patients (with no clinical benefit or progressive disease) will be followed for secondary endpoints per protocol for 3 years.

Arm E: Adjuvant durvalumab

Patients previously on Arm C (ChemoRT + durvalumab) who achieve clinical CR or clinical benefit, as defined above, will be registered to Arm E (Adjuvant durvalumab).

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Durvalumab dose: (1500mg if > 30 kg OR 20mg/kg if ≤ 30kg) once every 28 days x 6 doses. Each dose would be counted as a cycle; 1 cycle in adjuvant phase = 4 weeks.

Durvalumab will be administered as described in Section 5.1. Treatment delay and modifications have been described in Section 5.6. If treatment delay necessitates a period longer than 12 weeks during adjuvant durvalumab, treatment will be stopped and the patient will discontinue protocol treatment. All patients will be followed for secondary endpoints per protocol.

Arm F: Observation

Patients previously on Arm D (chemoRT) who achieve clinical CR or clinical benefit, as defined above, will be registered to Arm F (Observation) and followed for secondary endpoints per protocol.

NOTE: For patients registered to Arm F who did NOT receive any induction chemotherapy prior to Step 1 randomization, if the treating physician feels it is warranted adjuvant chemotherapy is allowed, but the patient will still need to be followed for response and survival per protocol. The treatment information must be captured in Medidata Rave (i.e.: dates and type of adjuvant therapy, number of cycles).

NOTE: Patient cannot receive any checkpoint inhibitors while on Arm F. Since the study's main end point is cCR post chemoRT, this would not affect our primary end point.

No Clinical Benefit:

Patients previously on Arm C or D who do NOT achieve clinical CR or clinical benefit, as defined above, will be considered for salvage cystectomy if possible. The treating surgeon will determine the safety and feasibility of salvage cystectomy. They will be followed for survival data per protocol and treated per standard of care. If patients in this group cannot undergo salvage cystectomy, then they will be treated per physician discretion and followed for survival.

For patients with progressive disease, they will come off study treatment and will be treated per physician discretion. Patient will be followed for overall survival per protocol.

5.3 Radiation Therapy

General

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- Radiation therapy should start within 20 business days after Step 1 randomization. CT simulation should occur with adequate time to meet the deadline of starting radiotherapy within the allotted time from randomization, particularly for patients who require pre-treatment review (below).
- Radiotherapy should be delivered over approximately 6.5-8 weeks.
- **Pre-Treatment review and approval from the Imaging and Radiation Oncology Core IROC Philadelphia of the first case registered by each institution is required PRIOR TO INITIATING DELIVERY of radiation treatment.**
- The Pre-Treatment Review process requires 3 business days from the receipt of complete data to TRIAD.

NOTE: If the Pre-Treatment Review is unacceptable, the process and clock starts over with the receipt of a complete resubmission of data. If an unacceptable deviation occurs the next case may require a Pre-treatment review.

5.3.1 Detailed Specifications

Radiation Therapy Schema:

All patients will have a pelvic nodal field which includes the bladder tumor and clinically involved nodes, as well as sequential boosts to the involved nodes and bladder tumor.

The pelvic nodal field will include the regional pelvic nodes as well as the clinically involved nodes, whole bladder, bladder tumor, and prostate (in men). This will receive 45 to 50.4 Gy in 1.8 or 2 Gy per fraction for a total of 23-28 fractions.

The first boost will be to the grossly involved nodes and the bladder tumor. The whole bladder may also be included in this boost per physician discretion. This will be treated to 54-64.8 Gy in 1.8 or 2 Gy per fraction. The dose for this target will be based on clinician selection and the requirement to meet normal tissue constraints as per dose the constraints (i.e., small bowel) section below.

The second boost will be used in patients who do not receive the full dose to the bladder tumor in the first boost, and will be directed to the bladder tumor. The whole bladder can be included as well per physician discretion if the

bladder tumor cannot be reliably defined based on available data. This will be sequential and to a total dose of 64.8 Gy or 64 Gy in 1.8 Gy or 2 Gy per fraction, respectively. Dose reduction may be required to meet normal tissue (i.e., small bowel) constraints as per dose constraints section below.

Priority will be given to small bowel dose constraints over target coverage.

In situations where treatment of the larger field precedes the smaller boost fields, (e.g., pelvis followed by cone downs to whole bladder and involved nodes, then bladder tumor), the various phases would be preferably treated sequentially. Depending on physician judgement and institution standard, the cone down/boost treatments may precede the whole bladder or pelvic field treatments.

All individual PTVs must be created upfront and it must be ascertained that the smaller PTVs are encompassed within the larger PTV.

Concurrent Chemotherapy (and immunotherapy on the investigation arm) should start within 4 days of the start of RT. Chemo can be infused either prior or after RT treatments.

Radiation treatment times must be recorded on the daily treatment record.

Radiation therapy will be delivered once daily (Monday - Friday) continuously without a planned break for tumor assessment during treatment.

Hypo-fractionation is not allowed.

5.3.2 Treatment Technology

This protocol only allows for photon treatment. Only IMRT techniques, including helical IMRT, VMAT, and Rapid Arc are allowed. Some form of image guidance is required (kV/MV imaging, CBCT, CT on Rails, etc.). CBCT is the preferred form of daily IGRT.

No specific field arrangement is required for IMRT, although typically non-opposed 5-9 fields are used for fixed gantry treatment. However, different field arrangements or number of fields can be used as required for optimal CTV and PTV coverage.

The radiation treatment should be with a high energy linear accelerator with photon energies ≥6 MV. Intensity Modulated Radiation Therapy (IMRT) with 6MV-18MV photons can be used.

5.3.3 Immobilization and Simulation

CT simulation required. A planning CT must be obtained with the patient in the treatment position. The patient should be simulated in the supine position. Each patient will be positioned in an immobilization device in the treatment position on a flat table. The choice of immobilization depends on institutional preference. The GTV, CTV, and PTV and normal/critical organs at risk will be outlined (as described below) on contiguous CT slices taken at a minimum of 2-5 mm intervals and obtained starting from the below the bottom of the ischial tuberosities to the L2/L3 junction, 3 cm above the dome of the bladder, or 3 cm above the most superior nodal contour of the radiation nodal field (whichever is higher). Co-registration of other imaging such as MRI and/or PET may be used for refining target delineation. With MRI, 3D T2 sequence

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with 2-5mm spacing is recommended. The treatment plan has to be computed on a CT dataset.

CT simulation, planning and treatment on an empty bladder is highly encouraged. Use of bladder or rectal contrast is not recommended as the insertion of contrast tends to distort the bladder and rectal volume and shape. Use of a urinary catheter at the time of simulation is not recommended. However, cystoscopic placement of bladder fiducials (such as gold or lipoidal) prior to simulation is optional. Use of an Ultrasound-based bladder scanner to monitor the bladder volume prior to the simulation and each treatment is optional. The rectum should be as empty of flatus and feces as possible for simulation; an enema may be given to accomplish this. Intravenous and oral bowel contrast may be used.

5.3.4 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

MRI and/or FDG-PET/CT may be used as part of staging and to assist in volume delineation in all eligible patients. Ideally, the planning CT and the MRI or PET are obtained with an empty bladder. The MRI or PET registration to the planning CT shall be bladder-to-bladder registration when delineating the bladder tumor, and lymph node to lymph node (i.e., soft tissue) when delineating the involved lymph nodes. Bone-to-bone registration of the pelvis only is not recommended unless the pertinent soft tissue anatomy registers appropriately. Appropriate image fusion techniques should be used for the image fusion. In the absence of fiducial markers, manual or automated registration must be performed. In the presence of fiducial markers, a manual point based registration is recommended. The quality of registration must be evaluated prior to treatment planning. Internal peer review of registration quality is strongly recommended. Errors in registration translate to systematic errors through a course of treatment, and must be minimized.

5.3.5 Definition of Target Volumes and Margins

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NOTE: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable as defined in Table 5.3.5.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 5.3.5: Definition of Structures for Planning

Standard Name	Description	Validation Profile Required/Required when applicable
Targets:		
GTVbt	Gross tumor volume (bladder tumor)	Required
GTVn	Gross tumor volume (clinically involved nodes)	Required
CTVwb	Clinical target volume whole bladder (entire bladder including the outer wall + GTVbt)	Required

Standard Name	Description	Validation Profile Required/Required when applicable
CTVpros	Clinical target volume prostate and prostatic urethra (in men)	Required in men
CTVn	Clinical target volume (regional pelvic lymph nodes). All clinically involved nodes must be included. See description in body of the protocol.	Required
CTV_Pelvis_xxxx (xxxx=4500-5040)	Clinical target volume including the regional pelvic lymph nodes (CTVn), prostate in men (CTVpros), whole bladder (CTVwb, and clinically involved lymph nodes (GTVn)	Required
CTV_Boost1_xxxx (xxxx=5400-6480)	First boost/cone down to the clinically involved nodes (GTVn) and bladder tumor (GTVbt). The whole bladder (CTVwb) can be included at clinician discretion.	Required
CTV_Boost2_xxxx (xxxx=5400-6480)	Second boost to the bladder tumor (GTVbt) in patients who do not receive the final dose to the bladder tumor during the first boost. Optional to include CTVwb at clinician discretion.	Required when the first boost/cone down does not complete treatment to the bladder tumor
PTVwb	CTVwb + 0.5-1 cm 3D expansion. Must also include PTV_Boost2_xxxx	Required
PTV_Pelvis_ xxxx (xxxx=4500-5040)	CTV_Pelvis_xxxx + 0.5-1 cm 3D expansion. Must also include PTVwb, PTV_Boost1_xxxx and PTV_Boost2_xxxx	Required
PTV_Boost1_xxxx (xxxx=5400-6480)	CTV_Boost1_xxxx + 0.5-1 cm 3D expansion. Must also include PTV_Boost2_xxxx. Optional to include PTVwb. Non-uniform expansions are acceptable for the GTVn and GTVbt (i.e., 0.5 cm 3D expansion around GTVn and 1 cm 3D expansion around GTVbt)	Required
PTV_Boost2_xxxx (xxxx=5400-6480)	CTV_Boost2_xxxx + 0.5-1 cm 3D expansion. Optional to include PTVwb.	Required when the first boost/cone down does not complete treatment to the bladder tumor

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5.3.6 Detailed Specifications

The definition of volumes will be in accordance with the ICRU Report #62: Prescribing, Recording, and Reporting Photon Beam Therapy

- GTV Bladder tumor (**GTVbt**)

  This structure will be the bladder gross tumor volume (GTVbt), which includes any original bladder tumor defined by TURBT, CT or other imaging modality (e.g., MRI, PET), bimanual examination, intraoperative reports and cystoscopy (surgical bladder map) constitutes this GTV.

Cystoscopically placed fiducial markers or lipiodol may be employed. The treating radiation oncologist should consult the urologist who performed the TURBT and the resulting cystoscopy report to determine the area and size of the original tumor as seen during exam under anesthesia and TURBT. If neoadjuvant chemotherapy was used, the TURBT prior to neoadjuvant chemotherapy and after neoadjuvant chemotherapy should be used in defining GTVbt.

- GTV clinically involved nodes (**GTVn**):

  This structure will include the clinically involved nodes based on all radiographic and pathologic data available, including CT, other imaging modalities (MRI or PET), and any biopsy pathological data. If neoadjuvant chemotherapy was used, the radiographic and pathologic data prior to neoadjuvant chemotherapy and after neoadjuvant chemotherapy should be used in defining GTVn.

- CTV whole bladder (**CTVwb**):

  The entire bladder (including the outer wall) plus GTVbt constitute this CTV.

- CTV prostate (**CTVpros**):

  The prostate and prostatic urethra (in men) constitute this CTV.

- CTV regional involved and uninvolved pelvic nodes (**CTVn**):

- Rev. Add3 The CTVn will include the GTVn (clinically involved nodes) and the regional pelvic lymph nodes. For N1 and N2 patients, CTVn includes the pre-sacral nodes, distal common iliac, external iliac, internal iliac, and obturator nodes. These can be created from the union of four sub-structures: GTVn, pre-sacral nodes, iliac nodes, and obturator nodes. The pre-sacral nodes will extend from the top of S1 to the top of S3 and will include 1.0 cm of tissue anterior to the sacrum and between the vessel contours. The iliac nodes will be derived by contouring the common iliac, external and internal iliac vessels starting superiorly at the top of S1. The external iliac vessels will be contoured inferiorly to the top of the femoral heads and the internal iliac vessels will be contoured inferiorly until they are no longer visible on the CT scan or exit through the true pelvis via the greater sciatic notch. The iliac nodes will be created by expanding the iliac vessels by 7 mm in the anterior, posterior and lateral dimensions, but not the superior and inferior dimensions. The obturator nodes will encompass 1.0 cm width of tissue medial to the obturator internus muscles extending from the anterior border of the ilium to the posterior border of the ilium. The obturator nodes will be contoured starting superiorly where the internal and external iliac vessel contours stop and extend inferiorly to the top of the symphysis pubis. This CTV should be trimmed to not extend outside the true pelvis, into the pelvic musculature or into adjacent identifiable organs, such as the bladder, rectum or other bowel or bone. If neoadjuvant chemotherapy was used, all of the clinically involved lymph nodes prior to neoadjuvant chemotherapy should be encompassed by this CTV.

Rev. Add3 For N3 patients, the above process should be followed but the common iliac nodes should be included up to the aortic bifurcation. The space in between the left and right common iliac vessels should be included with a thickness of 1 cm.

- CTV pelvic nodes and bladder (**CTV_Pelvis_xxxx**)

  The CTV_Pelvis_xxxx will include the CTVn, CTVwb, and the CTVpros (in men).
- CTV for first boost to involved nodes and bladder tumor (**CTV_Boost1_xxxx**)

  This CTV will include the grossly involved nodes (GTVn) and the bladder tumor (GTVbt). If the bladder tumor cannot be defined well, the whole bladder (CTVwb) can be included per clinician discretion.
- CTV for second boost to bladder tumor (**CTV_Boost2_xxxx**)

  This CTV will include the bladder tumor (GTVbt). If the bladder tumor cannot be defined well, the whole bladder (CTVwb) can be included per clinician discretion.
- PTV Whole Bladder (**PTVwb**):

  The PTV will provide a margin around the CTVwb to compensate for the variability of treatment set up and internal organ motion. This PTV will be a direct 3-D expansion of 0.5 cm - 1 cm beyond the CTVwb. Individual selection of a PTV margin should be based on the institutions' level of confidence in patient set-up and availability of image guidance.
- PTV pelvic nodes and bladder (**PTV_Pelvis_xxxx**)

  The PTV_Pelvis_xxxx will be a combination of a direct expansion of 0.5 - 1 cm beyond the CTVn and include the PTVwb. Individual selection of a PTV margin should be based on the institutions' level of confidence in patient set-up and availability of image guidance.
- PTV for the first boost to involved nodes and bladder tumor (**PTV_Boost1_xxxx**)

  This PTV will provide a margin around the CTV_Boost1_xxxx to compensate for the variability of treatment set up and internal organ motion. This PTV will be 0.5-1 cm 3D expansion beyond the CTV_Boost1_xxxx. Must also include PTV_Boost2_xxxx if applicable. Optional to include PTVwb per clinician discretion. Non-uniform expansions are acceptable for the GTVn and GTVbt (i.e., 0.5 cm 3D expansion around GTVn and 1 cm 3D expansion around GTVbt). Individual selection of a PTV margin should be based on the institutions' level of confidence in patient set-up and availability of image guidance.
- PTV for the second boost to the bladder tumor (**PTV_Boost2_xxxx**)

  This PTV will provide a margin around the CTV_Boost2_xxxx to compensate for the variability of treatment set up and internal organ motion. This PTV will be 0.5 cm - 1 cm 3D expansion beyond the CTV_Boost2_xxxx. Optional to include PTVwb per clinician discretion. Individual selection of a PTV margin should be based on the institutions' level of confidence in patient set-up and availability of image guidance.
- PTV margins can be reduced from those mentioned above where the PTV abuts small bowel in order to achieve small bowel constraints.

5.3.7 The ICRU Reference Points

The ICRU reference points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically, these points should be located on the beam axes or at the intersection of the beam axes.

5.3.8 Definition of Critical Structures and Margins

NOTE: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 5.3.8: Normal tissue organs at risk

Standard Name	Description	Validation Profile Required/Required when applicable/Optional
Organs at risk:		
Femur_Head_L	See text	Required
Femur_Head_R	See text	Required
Rectum	See text	Required
Bowel_Small	See description in OAR	Required
External	External patient contour	Required

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Detailed Specifications

1. Rectum (**Rectum**):

   The rectum is defined on CT as the entire rectal volume from its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior. The inferior extent would be to the inferior-most extent of the ischial tuberosities. The recto-sigmoid junction/flexure can be identified on the CT scan at the level the bowel turns anteriorly, close to the inferior level of the sacroiliac joints.

2. Bowel loops (**Bowel_Small**):

   The contouring of small bowel loops/segments is mandated. All bowel loops/segments proximal to the recto-sigmoid junction and within 2 cm of the PTV must be delineated. The recto-sigmoid junction can be identified on the CT scan at the level the bowel turns anteriorly, close to the inferior level of the sacroiliac joints. Small Bowel loops will include the entire small bowel, and does not include cecum, ascending colon, descending colon, transverse colon and sigmoid colon.

3. Femur heads (**Femur_Head_L or Femur_Head_R**):

   Each femoral head should be outlined down to the interface between the greater and lesser trochanter. Each femoral head should be considered separately.

5.3.9 Dose Prescription

Table 5.3.9: Dose prescriptions for each phase of treatment

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of fractions	Frequency	Total Cumulative Dose (Gy)	Dose specification technique
PTV_Pelvis_xxxx	45.0 - 50.4	1.8	25 - 28	Daily	45.0 - 50.4	Covering ≥95% of PTV
	46.0 - 50.0	2.0	23 - 25	Daily	46.0 - 50.0	Covering ≥95% of PTV
PTV_Boost1_xxxx	3.6 -19.8*	1.8	2 - 11	Daily	54.0 - 64.8	Covering ≥95% of PTV
	4.0 - 18.0	2.0	2 - 9	Daily	54.0 - 64.0	Covering ≥95% of PTV
PTV_Boost2_xxxx (if applicable)	0 - 10.8*	1.8	0 - 6	Daily	64.8	Covering ≥95% of PTV
	0 - 10.0	2.0	0 - 5	Daily	64.0	Covering ≥95% of PTV

*Dose reduction may be required to meet normal tissue (i.e., small bowel) constraints. A minimum of 61.2 Gy (1.8 Gy/fx) and 60.0 Gy (2.0 Gy/fx) is required to the bladder tumor.

5.3.10 Compliance Criteria

Table 5.3.10a: Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_Boost2_xxxx (if applicable)	V100% [%]	>=95	>=90*
	D0.03cc [%]	<=110	<=115
PTV_Boost1_xxxx	V100% [%]	>=95	>=90*
	D0.03cc [%]	<=110	<=115
PTV_Pelvis_xxxx	V100% [%]	>=95	>=90*
	D0.03cc [%]	<=110	<=115

Per Protocol range is excluded from Variation Acceptable range.

*PTV margins can be reduced from those mentioned above where the PTV abuts small bowel in order to achieve adequate PTV coverage and meet small bowel constraints.

Bowel, femoral and rectal structure doses must be assessed from dose-volume histograms (DVHs) calculated for composite (summed) treatment plans (Pelvis + all boost field plans). The following DVH criteria should be achieved.

Table 5.3.10b: Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
Rectum	V30Gy [%]	<=50	<=55
	V55Gy [%]	<=10	<=15
Femur_Head_L Femur_Head_R	D0.03cc [Gy]	<=50	<=55
	V45Gy [%]	<=50	<=55
Bowel_Small	V50Gy [cc]	<=15	<=20
	V55Gy [cc]	<=1	<=2
	V60Gy [cc]	<=0.1	<=0.5

Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

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Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Step 1 Randomization to first day of RT	≤ 20 business days	n/a
Interruptions	≤ 3 business days	> 3 and <= 7 days

5.3.11 Treatment Planning Priorities and Instructions:

In treatment planning, compromises are often made between getting full coverage to the PTV targets and sparing the normal structures. The following list of priorities can be used to guide how the compromises are made. The priorities are given in the order of decreasing importance.

1. Bowel_Small
2. GTVbt
3. GTVn
4. CTV_Boost2_xxxx (if applicable)
5. CTV_Boost1_xxxx
6. CTV_Pelvis_xxxx
7. All PTVs
8. Rectum
9. Femur Heads

Options in the scenario where dose to the target structures needs to be decreased are as follow (in order of preferred intervention):

1. Modify PTVs in areas where dose is making meeting dose constraints difficult
2. Prioritize coverage of the GTVs first, then the CTVs, then the PTVs
3. Target the bladder tumor only instead of the whole bladder for the final boost
4. Decrease the dose to the clinically involved nodes
5. Decrease the dose to the primary tumor

For further radiation target delineation and planning questions, please contact Dr. Abhishek Solanki at asolanki@luc.edu or Dr. Jason Efstathiou at jefstathiou@partners.org.

5.3.12 Required Algorithms

i. Heterogeneity corrections must be used.

Lists of Acceptable and Unacceptable dose calculation algorithms can be found at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by IROC Houston.

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported.

ii. Primary dataset for dose calculation

The primary data set for dose calculation must ideally be a CT. Respiration management such as 4DCT simulation or gating is optional and not recommended. Empty bladder is highly recommended in the planning CT. If bladder contrast (not recommended) is used in the simulation, the density of the contrast should be overridden to an appropriate background electron density (e.g., water).

iii. Dose matrix resolution

Dose calculation grid size should be ≤ 3 mm in all directions.

5.3.13 Patient specific QA

The delivered dose distributions of each plan must be independently verified and compared to the planned dose distribution. Detailed quality assurance measurements of dose distributions delivered by the planned treatment fields should be performed and verified by direct comparison with planned dose distributions. This must be done prior to treatment of the first fraction of any fresh IMRT course.

5.3.14 Treatment Localization/IGRT

Portal images are not required for IMRT but orthogonal verification images are required at the start of each IMRT plan.

Currently available and accepted daily on-line target localization/ or Image Guided Radiation therapy (IGRT) methods, either conebeam CT (CBCT) or kV/MV imaging are required to account for interfraction organ motion and setup variability. Daily CBCT is preferred when available. If not available, KV imaging is preferred.

When CT image guidance is used in daily treatment set-up, and where daily CT quality assurance includes imaging and treatment coordinate coincidence test(s), then weekly verification films or images are optional.

If the patient's bladder is found to be full on daily imaging but the treatment was planned on an empty bladder, then it is highly recommended that the patient be encouraged to void prior to treatment.

Prospective adaptive treatment is not planned on this protocol. In rare circumstances, re-planning may be needed for a clinical indication and this will be recorded. All as-treated plans will be archived for review. The use of image guidance or daily target localization including the specific type implemented must be documented by the treating physician. A computerized method for image registration (user-interactive or automated) is required for determination of the patient shift information.

For any x-ray imaging modalities used for verification, routine quality assurance should follow the guidelines found in Table VI of the report of Task Group 142 of the American Association of Physicists in Medicine (Klein et al, 2009).

5.3.15 RT Quality Assurance Reviews

The Radiation Oncology Study Chairs and their designees will perform RT Quality Assurance Reviews.

1. A pre-treatment review is required for the first case registered from each institution PRIOR TO DELIVERY of radiation treatment. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core IROC -Philadelphia. The Pre-Treatment Review process requires 3 business days from the receipt of complete data to TRIAD. If the Pre-Treatment Review is unacceptable, the process and clock starts over with the receipt of a complete resubmission of data.
2. After an institution has passed the required Pre-Treatment review of the first case all other case reviews will be ongoing and performed remotely. The Study Radiation Oncology Chairs, and their designees will perform the RT Quality Assurance Reviews after IROC Philadelphia has received complete data in TRIAD. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC Philadelphia has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is: Per Protocol, Variation Acceptable, and Unacceptable Deviation.

5.4 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.4.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.4.2 Routine reporting of Adverse Events (Medidata Rave):

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA8185 forms packet for instructions on where, when and what adverse events are to be reported routinely.

5.4.3 Expedited reporting of Adverse Events (CTEP-AERS):

In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provide information and instructions regarding expedited adverse event reporting.

5.4.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can 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.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

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ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.4.5 Expedited Adverse Event Reporting Procedure

This protocol is a Medidata Rave-CTEP-AERS Integration study.

The general procedures outlined below describe how to report an Adverse Event (AE) requiring expedited reporting on an Integration study.

CTEP's Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

AEs that occur after baseline are reported in Medidata Rave according to the instructions on the EA8185 Adverse Events Form/Late Adverse Events Form, including those that start during the report period, persist from the previous report period, or increase in grade since baseline. AEs that occur prior to the start of treatment are reported on the EA8185 Baseline Adverse Events Form which is not be included in the Medidata Rave-CTEP-AERS Integration.

Prior to sending AEs through the rules evaluation process to determine if expedited reporting is required, the site must verify the following on the EA8185 Adverse Events Form/Late Adverse Events Form in Medidata Rave:

- The reporting period (course/cycle) is correct and
- AEs are recorded and complete (no missing fields) and the form is query free

Upon completion of AE entry in Medidata Rave, the site must then submit the AE for rules evaluation by completing the Expedited Reporting Evaluation Form. Both NCI and EA8185 protocol-specific reporting rules evaluate the AEs

submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for all AEs that meet expedited reporting requirements. The site must then complete the expedited report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

NOTE: The site must report AEs in Rave at the time the investigator learns of the event.

NOTE: If an AE reported on the EA8185 Adverse Events Form is modified, it must be re-submitted for rules evaluation.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to:

- the AE Team at ECOG-ACRIN (857-504-2900) for patients on Arms C, D, E, and F
- the NCI (301-897-7497) for patients on Arm C and E
- the FDA (1-800-FDA-1088) for patients on Arms D and F

Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the Medidata Rave-CTEP-AERS Integration system is available on the CTSU website.

CTEP's guidelines for expedited AE reporting and CTEP-AERS can be found at http://ctep.cancer.gov.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 897-7404) for Arms C and E and FDA (800-332-0178) for Arms D and F in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

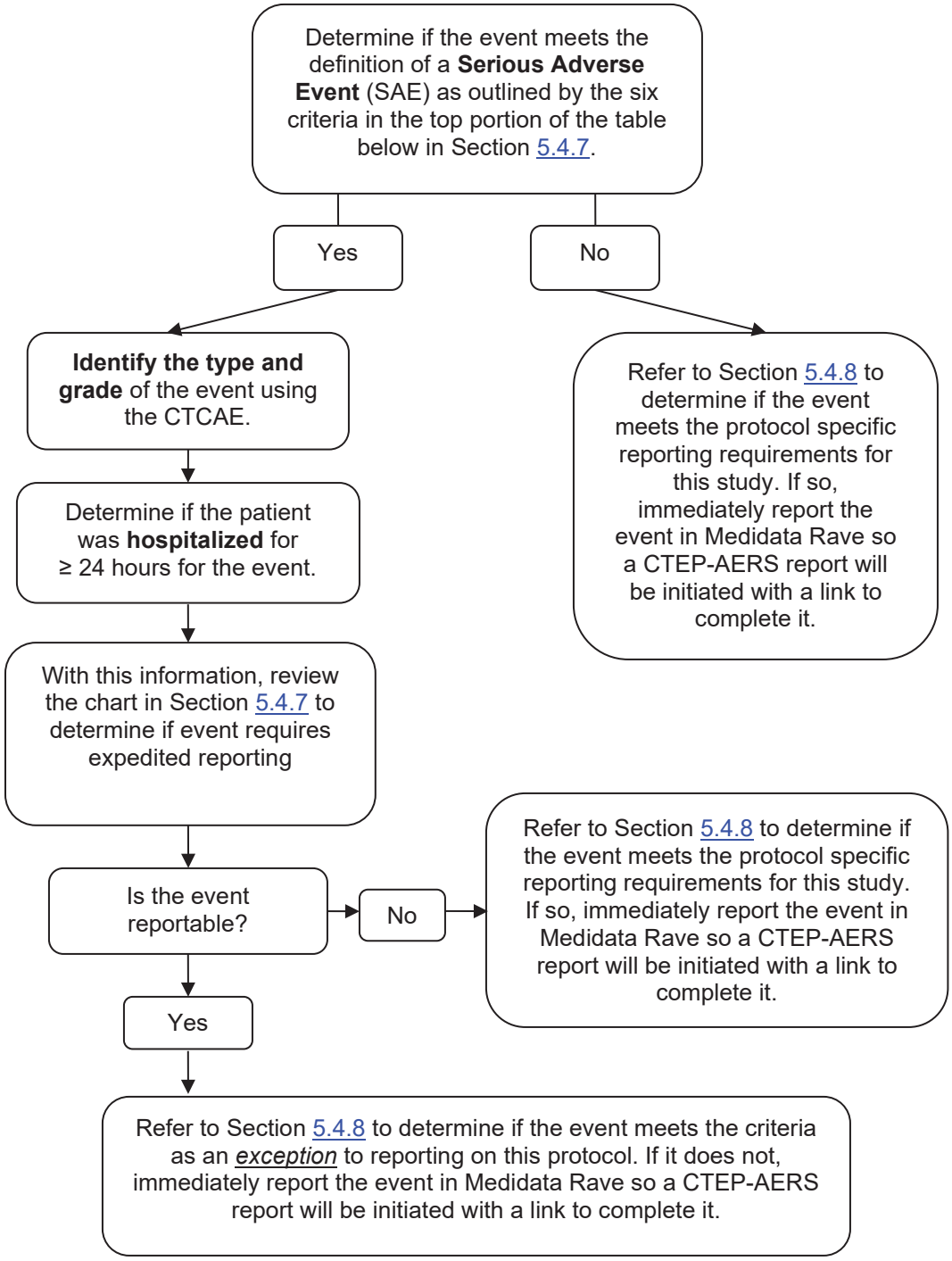
Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA8185 and outline the specific expedited adverse event reporting requirements for study EA8185.

5.4.6 Guidelines for to determining if an adverse event is to be reported in an expedited manner – Arms C and E

- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.4.7.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS report is completed, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

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5.4.6.1 Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.4.6.2 Guidelines for reporting adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

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If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.4.7, OR the protocol specific requirements in Section 5.4.8 AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported expeditiously in CTEP-AERS accessed via Medidata Rave even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.4.7 Expedited Reporting Requirements for Arms C and E on protocol EA8185

Investigational Agents: Durvalumab

Commercial Agents: Cisplatin, 5-FU, Mitomycin, and Gemcitabine

Other Treatment: Radiation

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents

Late Phase II and Phase III Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization
≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization
≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.4.8 Additional instructions, requirements and exceptions for protocol EA8185

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events in CTEP-AERS accessed via Medidata Rave, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Rev. Add3

- **Reporting a death on study:** A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

EA8185 specific expedited reporting requirements:

- **Adverse Events of Special Interest:** All of the following events, whether or not resulting in hospitalization, must be initially reported in Medidata Rave, triggering a CTEP-AERS report, within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
  - Any occurrence of myocarditis or pericarditis
  - Grade 3 or higher pneumonitis
  - Any occurrence of endocrinopathies or hypophysitis

Rev. Add4

- **Immune related adverse events (IRAE):** Any grade 3 or higher immune related adverse event (including hypophysitis, uveitis, pneumonitis, myocarditis, hepatitis, colitis) must be initially reported in Medidata Rave, triggering a CTEP-AERS report, within the timeframes outlined in the chart in Section 5.4.7, regardless of whether hospitalization is required. If available, please submit any supporting data as well (e.g.: autoimmune serology tests or biopsy reports). Any questions regarding if an event qualifies as an IRAE can be directed to the study chair.

  NOTE: In order for ECOG-ACRIN to appropriately report these events to regulatory agencies, please be sure

to state that the event being reported is an IRAE in the 'Description of Event' section of the CTEP-AERS report.

- **Dose-Limiting Toxicities (Arm C only):** We will be evaluating for dose-limiting toxicity (DLTs) on the first 6 patients randomized to the chemoRT+ durvalumab arm (Arm C) as described below. The following events require expedited reporting.

  NOTE: In order to avoid unnecessary queries, please be sure to include all relevant details in the 'Description of Event' and/or 'Abnormal or Relevant Normal Lab values' sections of the CTEP-AERS report so that the ECOG-ACRIN Operations Office can document that the adverse event meets the definitions of DLT below (i.e.: duration, grade, relevant lab values, etc.).

  i) Grade 3 or higher IRAE (immune related adverse event) including (hypophysitis, uveitis, pneumonitis, myocarditis, hepatitis, and colitis). This would exclude treatment-related hypothyroidism that is successfully treated with levothyroxine oral supplementation and does not cause a treatment delay in radiation by > 21 days (this is not considered a DLT event). When IRAEs are suspected, diagnostic confirmation (supporting labs, imaging, biopsies, etc.) should be provided in all reports.

  ii) Grade 3 or higher non-immune TRAE (treatment-related adverse event) which cause a delay in radiation therapy by > 21 days.

  DLTs will be counted based on the number of patients with a DLT, not the absolute number of DLTs. No single patient can trigger more than one DLT event.

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on durvalumab, or within 28 days of the female patient's last dose of durvalumab, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA8185 specific expedited reporting exceptions:

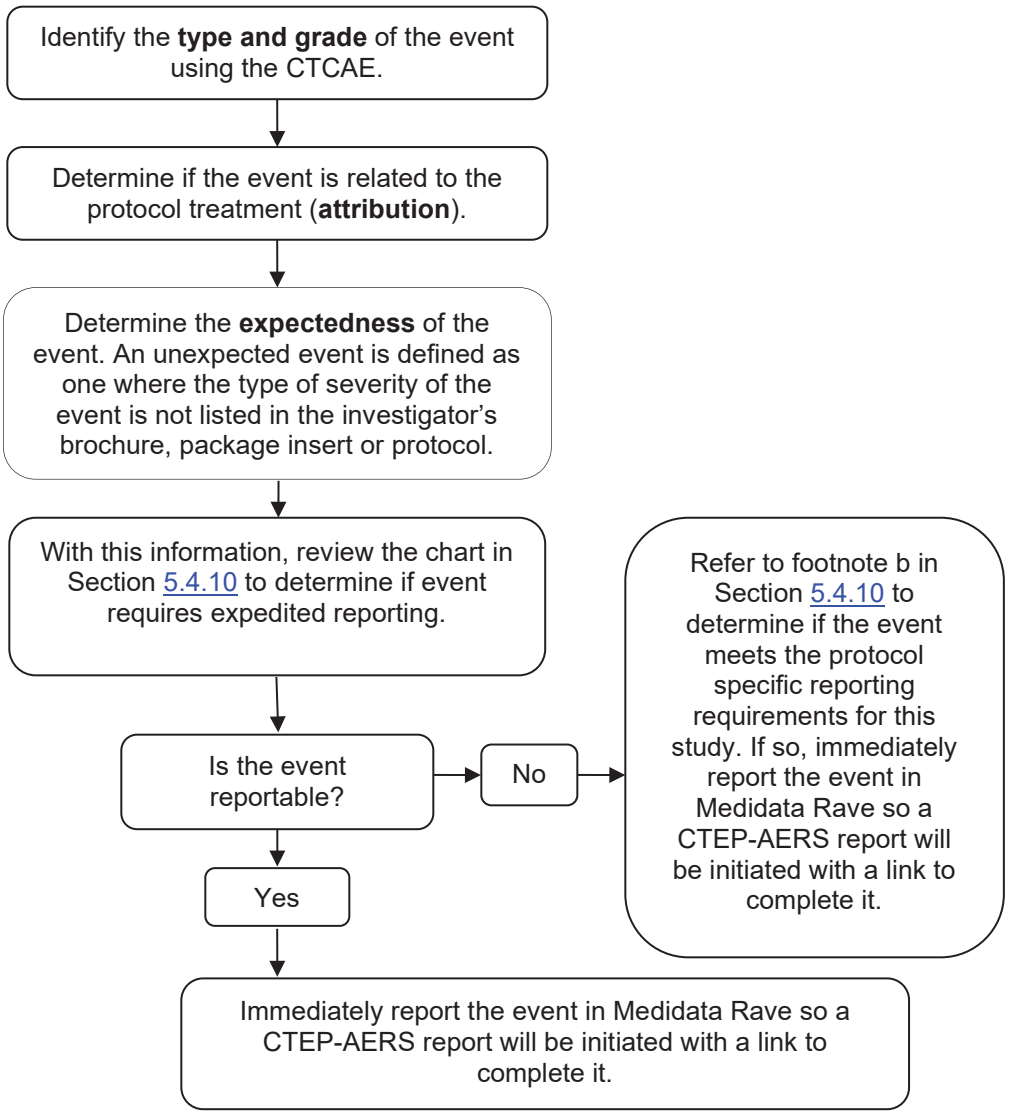
For study Arms C and E, the adverse events listed below **do not** require expedited reporting:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.4.9 Guidelines for determining if an event is to be reported in an expedited manner – Arms D and F

- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.4.10.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS is completed, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

Rev. Add4


Identify the **type and grade** of the event using the CTCAE.
Determine if the event is related to the protocol treatment (**attribution**).
Determine the **expectedness** of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator's brochure, package insert or protocol.
With this information, review the chart in Section 5.4.10 to determine if event requires expedited reporting.
Is the event reportable?
No
Refer to footnote b in Section 5.4.10 to determine if the event meets the protocol specific reporting requirements for this study. If so, immediately report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.
Yes
Immediately report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.

5.4.10 Expedited Reporting Requirements for Arms D and F on protocol EA8185

Commercial Agents: Cisplatin, 5-FU, Mitomycin, Gemcitabine

Other Treatment: Radiation

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only (including Arm F – see footnote c below)

Attribution	**Grade 4**		**Grade 5[a,c]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

Rev. Add3

a A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of protocol treatment and is attributed possibly, probably, or definitely to the protocol treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

c Arm F: The only adverse event requiring expedited reporting on the observation Arm F is a grade 5 death that a) occurred within 30 days of treatment on Arm D regardless of attribution OR b) is EA8185 treatment related, regardless of how long ago the last protocol agent was administered.

5.4.11 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.4.12 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows.

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis expeditiously by initially reporting it PROMPTLY upon learning of the secondary malignancy on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the secondary malignancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

Rev. Add3

NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

NOTE: We encourage all sites to confirm the Rules Engine assessment with the Second Primary reporting requirements outlined in this section.

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.5 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MEDI 4736 (durvalumab, NSC 778709)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3006 patients.* Below is the CAEPR for Durvalumab (MEDI4736).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

NOTE: Any event listed in the EA8185 specific expedited reporting requirements in Section 5.4.8 must be reported in CTEP-AERS, even if the event is listed as exception in the green column below.

Version 2.5, February 29,2024[1]

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes insipidus)	
		Endocrine disorders - Other (diabetes mellitus type 1)[2]	
		Endocrine disorders - Other (thyroiditis)	
	Hyperthyroidism[2]		
		Hypophysitis	
		Hypopituitarism[2]	
	Hypothyroidism[2]		

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
		Keratitis[2]	
		Optic nerve disorder	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
		Gastrointestinal disorders - Other - (gastrointestinal perforation)[2,3]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Immune system disorders - Other (immune related adverse events)[2]	
		Immune system disorders - Other (sarcoidosis)	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Cardiac troponin T increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
		Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
	Back pain		***Back pain (Gr 2)***

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
	Myalgia		***Myalgia (Gr 2)***
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2,5]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (aseptic meningitis)[2]	
		Nervous system disorders - Other (non-infective encephalitis)	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
	Dysuria		***Dysuria (Gr 2)***
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough			***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (dysphonia)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash[2,6]		***Rash[2,6] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (pemphigoid)	
		Skin and subcutaneous tissue disorders - Other (scleroderma)	
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,7]	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***

NOTE: Cardiomyopathy, and graft versus host disease, while not observed on clinical trials of Durvalumab (MEDI4736) at this time, are known events with this class of agent (PD-L1 antagonist).

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions (irAEs) have been reported in patients receiving Durvalumab (MEDI4736). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of Durvalumab (MEDI4736), administration of corticosteroids and supportive care, however, these events can be serious and fatal.

[3]Gastrointestinal perforations have been observed only in patients receiving Durvalumab (MEDI4736) in combination with tremelimumab (CP-675,206).

[4]Infections includes infection in the lungs, upper respiratory tract, dental and oral soft tissues and other organs under the INFECTIONS AND INFESTATIONS SOC. Infections generally are mild (Gr 1-2) but severe infections including sepsis, necrotizing fasciitis, and osteomyelitis have been reported.

[5]Guillain-Barre Syndrome has been reported in patients receiving Durvalumab (MEDI4736) in combination with tremelimumab (CP-675,206) but can potentially occur after durvalumab monotherapy.

[6]Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema.

[7]In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifectations.

Adverse events reported on Durvalumab (MEDI4736) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Durvalumab (MEDI4736) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (coronary artery disease); Cardiac disorders - Other (valvular vegitation); Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Ventricular arrhythmia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired

EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)

GASTROINTESTINAL DISORDERS - Ascites; Colonic obstruction; Colonic stenosis; Constipation; Dental caries; Dry mouth; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Ileal stenosis; Mucositis oral; Proctitis; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema trunk; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (failure to thrive); Hypothermia; Neck edema; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage

IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Immune system disorders - Other (Giany cell arteritis syndrome); Serum sickness

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning, and procedural complications - Other (radiation pneumonitis); Wound complication

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Pain in extremity; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (brain metastasis swelling); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (increase in tumor mass); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Edema cerebral; Encephalopathy; Headache; Ischemia cerebrovascular; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (hypoesthesia); Nervous system disorders - Other (neuropathy peripheral); Paresthesia; Seizure; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Confusion; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Aspiration; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal obstruction; Pleural effusion; Pneumothorax; Pulmonary edema; Pulmonary fistula; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asphyxia); Respiratory, thoracic and mediastinal disorders - Other (granulomatous changes in the lung); Respiratory, thoracic and mediastinal disorders - Other (fungal pneumonia; Phialemonium spp.)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin

VASCULAR DISORDERS - Hypertension; Thromboembolic event

NOTE: Durvalumab (MEDI4736) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.6 Dose Modifications

Rev. Add4

Toxicities related to durvalumab, radiation therapy and concurrent chemotherapy have been described separately below.

5.6.1 Dose-Limiting Toxicities

We will also be evaluating for dose-limiting toxicity (DLTs) for first 6 patients randomized to Arm C (chemoRT+ durvalumab) as described below:

These 6 patients will be monitored for toxicities during the ChemoRT + durvalumab phase. After first 6 patients are randomized to the ChemoRT + durvalumab arm (Arm C), the protocol will be put on hold to new patient registrations until those 6 patients complete the concurrent ChemoRT + durvalumab phase. If 0-1 out of 6 patients have DLTs, the study will be declared safe and the protocol will reopen to new patient registrations. If 2 or more have a dose-limiting toxicity (DLT), the protocol will continue to be suspended and the study team will address safety issues and adjust the ChemoRT+ durvalumab regimen. A modified study will be conducted and again the first 6 patients randomized to the new experimental arm will go through toxicity assessment in the same way.

As standard bladder-sparing combined modality therapy (CMT) is known to produce grade 1-2 treatment-related adverse events (TRAEs) in nearly all patients and grade 3-4 TRAEs in 35% of patients, treatment-related toxicity is expected. With standard CMT, however, immune-related adverse events (IRAEs) are not observed. Therefore, in evaluating the safety of the new durvalumab containing CMT treatment within this protocol, severe IRAEs or non-immune TRAEs which compromise the ability to deliver CMT are of particular interest. Accordingly, DLTs in the first 6 patients in the chemoRT+ durvalumab group (Arm C) will be defined as follows:

i) Any Grade 3 or higher IRAEs including (hypophysitis, uveitis, pneumonitis, myocarditis, hepatitis, and colitis). This would exclude treatment-related hypothyroidism that is successfully treated with levothyroxine oral supplementation and does not cause a treatment delay in radiation by > 21 days (this is not considered a DLT event).

NOTE: When IRAEs are suspected, diagnostic confirmation (supporting labs, imaging, biopsies, etc.) should be provided in all reports.

ii) Any Grade 3 or higher non-immune TRAEs which cause a delay in radiation therapy by > 21 days.

DLTs will be counted based on the number of patients with a DLT, not the absolute number of DLTs. No single patient can trigger more than one DLT event.

Rev. Add4

5.6.2 Durvalumab:

Patients receiving durvalumab will be assessed by their treating physician at the time of each infusion. This evaluation will monitor for adverse events (all grades), serious adverse events, immune related

adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Any toxicity associated or possibly associated with durvalumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Early treatment of immune related AE (IRAE) is advised.

<table>
<tr><th colspan="3">Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 1 October 2019 Version (CTCAE v5.0)</th></tr>
<tr><th colspan="3">General Considerations</th></tr>
<tr><th colspan="2">Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td colspan="2">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 v5.0.
In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTCAE 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 imAE following resumption of dosing</td><td rowspan="5">It is recommended that management of immune-mediated adverse events (imAEs) follows 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, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such 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 (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO 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 specialist consultation.
• If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/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 imAEs for specific type of</td></tr>
<tr><td>Grade 1</td><td>No Dose Modification</td></tr>
<tr><td>Grade 2</td><td>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 regimen 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 Investigator or treating physician’s clinical judgement.
3. Doses of prednisone are at ≤10 mg/day or equivalent.</td></tr>
<tr><td>Grade 3</td><td>Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue study drug/study regimen.</td></tr>
</table>

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 1 October 2019 Version (CTCAE v5.0)		
General Considerations		
Dose Modifications		**Toxicity Management**
	NOTE: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. **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 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).	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/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**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.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• 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 modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** • Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. • Consider Pulmonary and Infectious disease consults.
	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/study 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 to 2 mg/kg/day PO or IV equivalent). • Reimage as clinically indicated. • If no improvement within 3 to 5 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • If still 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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] • Consider pulmonary and infectious disease consult. • Consider, as necessary, discussing with study physician.
	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 study physician. • Hospitalize the patient. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/ Colitis/ 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). • 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			grade event, including perforation. • Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	No dose modifications	**For Grade 1:** • Monitor closely for worsening symptoms. • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	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 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further work-up, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, fever, ileus, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**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 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated		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 the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis.**		**General Guidance**	**For Any Grade:** • Monitor and evaluate liver function test: AST, ALT, ALP, and total bilirubin. • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or total bilirubin >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal	• No dose modifications. • If it worsens, then treat as Grade 2.	**For Grade 1:** • Continue LFT monitoring per protocol.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	Grade 2 AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or total bilirubin >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 Grade ≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** • Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. • If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. • If event is persistent (>3 to 5 days) or worsens, promptly 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 work-up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start further immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil 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-PJP treatment (refer to current NCCN guidelines for treatment of

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			cancer-related infections).[a]
	Grade 3 AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or total bilirubin >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal) **Grade 4** AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or total bilirubin >10×ULN if baseline normal, >10.0×baseline if baseline abnormal	For transaminases elevations ≤8 × ULN, or total bilirubin elevations ≤5 × ULN: • Hold durvalumab until resolution to Grade ≤1. • Resume study drug if LFT elevations resolve to Grade ≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug if the elevations do not downgrade to < Grade 1 within 14 days Permanently discontinue durvalumab for: • Any case meeting Hy's law criteria (AST or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline phosphatase) and in the absence of any alternative cause.[b]	**For Grade 3 or 4:** • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. • If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** • Request hepatology consult, and perform abdominal work-up and imaging as appropriate. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs)	**Any Elevations of AST, ALT, or TB as Described Below**	**General guidance**	For any elevations described: • Monitor and evaluate liver function test: AST, ALT, ALP, and total bilirubin.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
Infliximab should not be used for management of immune-related hepatitis. See instructions at **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** 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**			• 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.
	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	

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
		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 ≤5.0X ULN. • If toxicity worsens, then treat as described for elevations in the row below. If toxicity improves to AST or ALT ≤5.0X, 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 work-up and treatment with IV methylprednisolone 2 to 4 mg/kg/day. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal work-up (including liver biopsy) and imaging (i.e., liver

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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 ≤5.0X ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0X ULN within 14 days and after completion of steroid taper. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	• 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.**

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• 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]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**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).

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• 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 > ULN to 1.5 × ULN)
		No dose modification	**For Grade 1:**
			• Monitor serum creatinine weekly and any accompanying symptoms.
			  ○ 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, electrolyte replacement, and diuretics.
			• If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.

	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study	**For Grade 2:** • Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. • Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. • Consult nephrologist and consider renal biopsy if clinically indicated.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
		regimen after completion of steroid taper.	• If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional work-up should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (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 to 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 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			work-up should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 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 STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**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 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 2:** • Obtain dermatology consult. • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
		• If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	therapy (e.g., urea cream). • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. • Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	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(s). **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** • 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 the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			cancer-related infections).[a] • Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, 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 v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** • Consider consulting an endocrinologist for endocrine events. • Consider, as necessary, discussing with study physician. • 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, polydipsia, 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). • For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			or symptoms of pancreatic inflammation. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**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 consultation of an endocrinologist.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can 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.	**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 isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). • Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] • For patients with normal endocrine work-up (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can 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.	**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 isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV 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 IV corticosteroids with mineralocorticoid activity. • Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
		3. Doses of prednisone are ≤10 mg/day or equivalent.	• 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 (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**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). • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). • Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** • See “Any Grade” recommendations above. • Treat mild signs/symptoms as Grade 1 (e.g., loss of deep

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			tendon reflexes or paresthesia).
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** • Consider, as necessary, discussing with the study physician. • Obtain neurology consult. • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). • Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional work-up and promptly treat with additional immunosuppressive therapy (e.g., 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. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Consider, as necessary, discussing with study physician. • Obtain neurology consult. • Consider hospitalization. • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. • If no improvement within 3 to 5 days despite IV corticosteroids, consider additional work-up and promptly treat with additional immunosuppressants (e.g., IV IG).

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** • The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that 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.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			• 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. • It is 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 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** • Consider, as necessary, discussing with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult.
	Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive	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	**For Grade 2:** • Consider, as necessary, discussing with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	intervention indicated; limiting age-appropriate instrumental ADL)	days or if there are signs of respiratory insufficiency or autonomic instability.	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:* ○ Steroids may be successfully used to treat myasthenia gravis. It is 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. ○ 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. ○ If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			GUILLAIN-BARRE: ○ It is important to consider here 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 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**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 study physician. • Recommend hospitalization. • Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here 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.
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 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,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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 or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	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 (Grade 2: Symptoms with moderate activity or exertion)	• If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to	**For Grade 2-4:** • Monitor symptoms daily, hospitalize. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	(Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	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.	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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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 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,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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. • 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
			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 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening	**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	**For Grade 3 or 4 (severe or life-threatening events):** • Monitor symptoms closely; recommend hospitalization. • Obtain Neurology consult, and complete full evaluation.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**
	consequences; urgent intervention indicated)	≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** • Permanently discontinue study drug/study regimen.	• 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.

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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modification**	**Toxicity Management**

mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	**General Guidance**	**For Any Grade:** • Manage per institutional standard at the discretion of investigator. • Monitor patients 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 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 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 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).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.		
Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	**NOTE**: Dose modifications are not required for AEs 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.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 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.
Grade 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 consultation with the Sponsor.)	Treat accordingly, as per institutional standard.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute

5.6.2.1 <u>During chemoRT+ Durvalumab (Arm C):</u>

Durvalumab would be given for 3 doses of Q3 weekly treatment during concurrent phase.

Treatment may be delayed from the expected date of the next treatment for any reason during concurrent phase.

- If the treatment delay is due to toxicity from durvalumab alone, RT will continue as planned.
- If treatment is delayed ≤ 3 weeks, patients will proceed with the next cycle of treatment.

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- Grade 4 immune related adverse event requires permanent discontinuation of treatment with durvalumab. Please see Section 5.6.2.3 for guidance for discontinuation due to toxicity.

If the dose of Durvalumab is held without a delay in RT, then those doses could be given at a later date of concurrent RT phase. But if Durvalumab and RT are both held for any reason, then the Durvalumab can resume upon re-start of RT.

A new treatment cycle during concurrent phase will only be initiated when blood count shows that platelets ≥ 70000 mcl (or 70K).

5.6.2.2 During adjuvant Durvalumab (Arm E):

Durvalumab would be given Q4 weekly during adjuvant phase. Treatment may be delayed from the expected date of the next treatment for any reason during adjuvant durvalumab, but it cannot be delayed more than 12 weeks. In addition, if treatment was delayed due to an immune related AE and it resolves within 12 weeks and the patient is receiving corticosteroid therapy for the event, Durvalumab may be held for no longer than 16 weeks (up to 4 additional weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Held or missed doses will be made up during adjuvant durvalumab.

A new treatment cycle will only be initiated when the following conditions are met for ANC and platelet:

- ANC ≥ 1,000× 10^9/mcl
- Platelets ≥ 70,000 mcl (or 70K)

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 12 weeks of the planned treatment date during adjuvant durvalumab, the patient will be permanently discontinued from study therapy and will be followed per protocol.

5.6.2.3 For all patients getting Durvalumab:

Following the first dose of durvalumab, subsequent administration of Durvalumab will be managed based on toxicities observed (see tables at the beginning of Section 5.6.2).

Rev. Add4

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

All toxicities will be graded according to the CTCAE. Please also refer to the most current version of the Durvalumab Investigator's Brochure and the FDA product label.

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.
- 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. Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed.

Durvalumab must be permanently discontinued if the patient experiences any of the following events, regardless of benefit:

- Grade 3 or 4 nephritis
- Grade 4 diarrhea or colitis
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 rash
- Grade 4 pneumonitis
- AST or ALT > 5×ULN or total bilirubin > 3×ULN
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Any grade myocarditis

Treatment may be resumed in patients who have recovered (Grade 1 or less) from the following events, but only after consultation with the Study Chair:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions
- Grade 3 immune-related pruritus
- Grade 3 immune-related fatigue
- Grade 3 immune-related hypo/hyperthyroidism

5.6.3 Radiation Therapy

Diarrhea and urinary toxicity are common toxicities of standard chemoradiation, and most patients who undergo this treatment modality will have some element of these symptoms, particularly grades 1 and 2 toxicity. The treating physician must do appropriate work-up to determine the etiology of the toxicity. In patients who have grade ≥ 3 toxicity due to radiation therapy, radiation treatment should be held until the toxicity becomes grade ≤ 2. If the toxicity does not do so within 21 days, radiation treatment on study should be discontinued per the discretion of the treating radiation oncologist.

5.6.4 Concurrent Chemotherapy

Treating oncologist will perform chemotherapy dose modifications and interruptions. Premedications will be delivered per institutional policy and as standard of care.

All patients enrolled on the study will be monitored closely for toxicities with clinical and laboratory tests. All adverse reactions, all grades will be reported at each study visit for the duration of their participation in the study.

We do not expect concurrent chemoRT to cause any immune related adverse events. However if the treating physician believes that an adverse event is immune related, proper work-up and treatment should be considered per medical necessity. Grades 3-4 gastrointestinal or genitourinary side effects could occur during concurrent chemoRT period. We would recommend treatment symptom management per treating physician. Growth factor routine use during chemoRT phase is not allowed. However, use of growth factor for neutropenic complications is appropriate.

Dose modification guidance has been outlined for chemotherapy drugs in the table below.

Chemotherapy	Start dose	Dose level -1	Dose level -2
Gemcitabine	27mg/m^2	21mg/m^2	16mg/m^2
Cisplatin	35 mg/m^2	28mg/m^2	21mg/m^2
5-Fuorouracil	500mg/m^2	400mg/m^2	NA as patient will only have this twice during

Chemotherapy	Start dose	Dose level -1	Dose level -2
			chemoRT in cycles 1,2
Mitomycin	12mg/m^2	NA as patient will only get this once during chemoRT as cycle 1	

5.6.4.1 Treatment-Related Hematological Toxicity

Chemotherapy is known to cause hematological side-effects, thus no dose interruptions should be performed unless it is thought to be medically necessary for patient's health. Please follow guidelines below for dose interruptions.

- Grades 1-2: No dose interruptions
- No dose interruptions for lymphocytopenia
- Dose modifications and/or delays for low Hgb, ANC, and platelets as described below.

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CTCAE Category	Grade 1	Grade 2	≥ Grade 3
Hemoglobin decrease	No dose adjustments	No dose adjustments	Dose level -1 Transfuse to aim for Hgb ≥ 8 g/dL
ANC	Dose level -1	Dose level -2	Hold therapy until it resolves to grade 2, restart at dose level -2. Growth factor use during chemoRT is discouraged. However if needed to manage neutropenic fever or any other life threatening condition, it could be used. Febrile Neutropenia is treated as standard of care and will be considered grade 3. Hold therapy until infection/fever resolves and ANC has resolved to grade 2.
Platelets	Dose level -1 only for Platelets <100k	Dose level -2	Hold therapy until it resolves to grade 2, restart at dose level -2. Platelet transfusion for platelets <10 or bleeding to keep platelets >20. It could also be transfused if needed for any medical necessity-such as procedure to bring platelets >50.

5.6.4.2 Treatment-Related Non-Hematological Toxicity

CTCAE Category	Drug	Event	Dose modification
Hepatitis	Gemcitabine	Grade 1 ALT, AST, or total bilirubin elevation	None
		> Grade 2 ALT, AST, or total bilirubin elevation	Hold all chemotherapy until resolution to ≤ Grade 1 then resume at dose level -1.
Nephrotoxicity	Cisplatin	First event of GFR >45 but <50ml/min	Hold cisplatin. When GFR recovers to ≥ 50 ml/min, resume cisplatin at dose level -1.
		Second event of GFR >45 but < 50 ml/min	Hold cisplatin. When GFR recovers to ≥ 50 ml/min, resume cisplatin at dose level -2.
		Third event of GFR > 45 but < 50ml/min	Permanently discontinue cisplatin. Radiation therapy may continue even without chemotherapy.
		First event GFR ≤ 45 ml/min	Hold cisplatin. When GFR recovers to ≥ 50 ml/min, resume cisplatin at dose level -2.
		Second event GFR ≤ 45 ml/min	Permanently discontinue cisplatin. Radiation therapy may continue even without chemotherapy.
Diarrhea	5-FU and RT	Grade 1	Treat with antidiarrheals.
		Grade 2	Continue with 5-FU and RT, but reduce 5-FU by one dose level.
		≥ Grade 3	Hold 5-FU until diarrhea resolves to ≤ Grade 1. RT should also be stopped until the diarrhea is resolved to ≤ Grade 2 or as considered appropriate by the treating radiation oncologist. Then resume at dose level -1.
Ototoxicity or Neurotoxicity	Cisplatin	Grade 1	None
		Grades 2-4	Physician discretion
Other non-	Gemcitabine, Cisplatin,	Grades 1-3	Physician discretion

CTCAE Category	Drug	Event	Dose modification
hematological toxicity	5-FU, and RT	Grade 4	Hold chemotherapy and RT. RT and chemotherapy together or RT alone can be resumed when the toxicity has resolved to ≤ Grade 2 at the discretion of the treating physician.

Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE)	**Dose Modifications**	**Toxicity Management**
Any Grade	**NOTE:** Dose modifications are not required for AEs 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.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 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.
Grade 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 consultation with the Sponsor.	Treat accordingly, as per institutional standard.

NOTE: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study per Institutional policy. Follow local institutional guidelines.

Refer to Section 8 for individual pharmaceutical agents and potential interactions with other agents and the drug package inserts for specific considerations.

Considerations in agents impacting Cytochrome P450:

5-Fluorouracil: Anticoagulants and CYP 2C9 Substrates Elevated coagulation times have been reported in patients taking fluorouracil concomitantly with warfarin. While pharmacokinetic data are not available to assess the effect of fluorouracil administration on warfarin pharmacokinetics, the elevation of coagulation times that occurs with the fluorouracil prodrug capecitabine is accompanied by an increase in warfarin concentrations. Thus, the interaction may be due to inhibition of cytochrome P450 2C9 by fluorouracil or its metabolites.

5.8 Duration of Therapy

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In addition to discontinuation from therapy related to toxicities as outlined in Section 5.6, a patient 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 appropriate forms in Medidata Rave.

Patients will receive protocol therapy unless:

- Documented disease progression per protocol.
- The treating physician thinks a change of therapy would be in the best interest of the patient.
- The patient requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
- If a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if he or she might still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in on the appropriate forms in Medidata Rave.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA8185 Forms Packet.
- Radiation delay of >21 days or per radiation oncologist judgment.
- Adjuvant durvalumab is delayed for >12 weeks, except when additional steroid tapering is needed for IRAE where it could be delayed up to 16 weeks.
- Radical cystectomy or patients who have no clinical benefit post chemoRT.

5.9 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 4 years from the date of randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response post chemoRT+/- durvalumab at 8 (+/- 2) weeks with imaging and cystoscopy with biopsy.

Cystoscopy to be performed every 3 months during years 1 and 2 post chemoRT treatment and thereafter every 6 months until year 3.

CT scan of the chest/abdomen/pelvis (CT urogram preferred) or MRI to be performed at 8 (+/- 2) weeks, after this, CT abdomen/pelvis (urogram preferred) or MRI abdomen/pelvis along with CXR or CT chest to be performed every 12 weeks (± 14 days) for the 1st year, and thereafter every 6 months (± 14 days) for year 2, then yearly (± 14 days) for years 3 and 4. Additional imaging can be obtained per physician discretion. In addition to a baseline scan, post chemoRT+/- durvalumab imaging, confirmatory scans should also be obtained *(no less than 4 weeks)* following initial documentation of objective response; this would be relevant if the patient is showing concern for progression during adjuvant phase with durvalumab. Additional imaging could be requested per physician discretion.

Response and progression in the lymph node will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the shortest diameter in the malignant lymph nodes are used in RECIST for this study.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden in LN at baseline when possible to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than eight weeks before Step 1 randomization.

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2. Lymph node positivity will be defined based on imaging. This will be used as the baseline measurement. For this study, node positivity will be defined using the definition for non-target nodes per RECIST 1.1. Shortest diameter of LN would be taken into account to define LN positivity and LN >= 1cm will be called radiologically positive. However, if LN <1cm but biopsy proven positive for cancer, they are eligible to be included in the study. See eligibility criteria 3.1.4.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

Post chemoRT+/- durvalumab, clinical outcome will be evaluated based on below.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease in LN (per eligibility definition) present at baseline, and have received non-zero chemoRT+/- durvalumab, will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. To this end, the primary analysis (both interim and final) should include all eligible patients who receive any nonzero amount of chemoRT or chemoRT + Durvalumab.

Related to this, patients who receive at least one dose of treatment and drop out/progress prior to having their disease re-evaluated should be counted as part of the 46 patients necessary to trigger the interim analysis (these patients would be considered non-responders).

NOTE: Patients who exhibit objective disease progression prior to the end of RT, but have also received at least 1 cycle of chemotherapy +/- 1x cycle of durvalumab will also be considered evaluable.

Evaluation of clinical outcome post ChemoRT+/- durvalumab, concurrent phase:

Clinical Response will be defined as a composite of the response to the primary tumor, nodal response, and any potential new metastatic disease as described in Table 6.1.1.

6.1.1.1 Response in the bladder tumor

Responses will be assessed using CT/MRI + cystoscopy

- Imaging response: Imaging could be inaccurate for diagnosing disease in bladder post chemoRT. Thus any imaging finding MUST be confirmed by cystoscopy and biopsy prior to determination of response in bladder. Thickening of the wall will not be counted as residual disease as it could be part of post chemoRT changes, unless it is proven positive by biopsy on cystoscopy.
- Cystoscopy response: Presence or absence of disease in bladder. Biopsies must be performed and disease in bladder will be classified as <T2 or ≥T2 based on biopsy and cystoscopy findings. Biopsy confirmation is required post chemoRT +/- durvalumab and thereafter per physician discretion. However, during the course of treatment on adjuvant vs. observation, biopsy is required to confirm disease recurrence when suspected. Details of evaluation by cystoscopy is described in Section 6.1.3.

6.1.1.2 Response in the nodes

The change in size in short axis of each involved node should be determined, as should the occurrence and size of any new nodes.

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Each initially involved node and any new pelvic nodes should individually be assessed as follows: CR is complete disappearance or decrease in short axis size to <10 mm. [This is based on RECIST 1.1 using non-measurable LN size criteria where CR is defined as size < 10 mm; all LN would need to be < 10 mm to be classified as CR in nodes for this study]. In special circumstances when there is a biopsy proven LN which in short axis is < 10mm, complete disappearance would be defined as CR (rest should be recorded as short axis measurement).

PR is decrease by 30% or more, PD is ≥ 20% increase in size of previously involved nodes + an absolute increase in 5mm in sum or occurrence of a new involved regional nodes (> 1 cm in short axis size). PD must be confirmed with biopsy of LN unless biopsy is contraindicated for medical reason or not feasible based on location of the LN. Confirmatory imaging (no less than 4 weeks) is required during adjuvant durvalumab therapy to document progression but not for primary response. The response in LN should be documented based on report from the radiologist at the treating institution. Please see Section 6.1.3.2 for details in evaluation of response in LNs.

The overall nodal response will incorporate the response to all initially involved nodes and any new nodes that develop on response assessment imaging as documented in table 6.1.1.

6.1.1.3 Distant metastasis

The presence or absence of new distant metastatic disease on imaging will be documented in the response assessment. The distant metastatic lesion should be biopsied for confirmation unless contraindicated for medical reasons.

Table 6.1.1: Definition of Clinical outcome post chemoRT+/- durvalumab:

Primary Outcome	Overall response	Cystoscopy response	Nodal response	Distant metastasis
Clinical Complete response	CR in bladder and nodes with no distant metastases	Negative on exam and negative biopsy of affected area + random biopsies T0	CR	None
Clinical Benefit	PR or SD or CR in nodes but <T2 disease in bladder with no distant metastases	<T2 disease in bladder, biopsy proven (Presence of NMIBC-Ta, T1, CIS would be counted as <T2)	CR, PR or SD	None
No clinical benefit	No evidence of PD in nodes but ≥T2 disease in bladder	≥ T2 in bladder, biopsy proven but surgically	CR, PR or SD	None

Primary Outcome	Overall response	Cystoscopy response	Nodal response	Distant metastasis
	that is resectable with no distant metastases	resectable		
Progressive Disease	PD in either nodes OR bladder that is unresectable OR presence of confirmed distant metastases	≥ T2 in bladder, biopsy proven but surgically unresectable/unfit for surgery	Any response-CR/PR/SD/PD	Positive OR None

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, or ≥ 10 mm by clinical exam (in this case such as cystoscopy). All tumor measurements must be recorded in millimeters.

NOTE: Since the study involves RT to LN, for the purposes of this study, the tumor lesions that are situated in a previously irradiated lymph node would be considered measurable. Post radiation changes are often seen in bladder thus response in bladder must be evaluated by cystoscopy. Bladder wall thickening is NOT considered residual disease post chemoRT unless pathologically proven.

Malignant Lymph Nodes

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To be considered pathologically enlarged and measurable, a lymph node must be ≥ 10 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. In special circumstances when there is a biopsy proven LN which in short axis is <10mm, it would be counted as pathologically involved.

NOTE: At baseline patients must have at least one measurable LN ≥ 10 mm in short axis by CT scan or MRI (CT at baseline and follow-ups are preferred but if MRI has been performed it will be acceptable). In special circumstances where there is a biopsy proven LN which in short axis is <10mm, and no other LN ≥10mm, then that patient would be eligible as well.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with < 10 mm short axis), are considered non-measurable disease.

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All other regional LN <10mm will not be considered as disease unless the LN is pathological AND biopsy proven to be involved with cancer.

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 patient, these are preferred for selection as target lesions.

6.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 8 weeks before Step 1 randomization.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

This study is not enrolling M1 patients, thus this will only be relevant for evaluation of response to treatment. If there is clinical suspicion for PD on skin, then it must be biopsy proven.

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). For purposes of the study for abdominal imaging at baseline and for follow up, CT urogram for abdomen and pelvis is preferred.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Cystoscopy:

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The treating urologist will perform an initial maximal TURBT in all patients no more than 12 weeks prior to initiation of therapy. The goal of the initial resection will be complete resection and maximal debulking of all visible tumor. Additionally, examination under anesthesia should be performed to assess resectability, or confirmation of unresectable disease when applicable. Photographic imaging when possible will be performed to provide a record of baseline local disease. The treating urologist will document whether maximal debulking was successfully performed, or not possible due to risk of bladder perforation. Blue light cystoscopy is allowed and preferred when possible; however the study recommends adhering to the same methodology when evaluating for response and surveillance on all subsequent cystoscopy if possible.

Follow-up cystoscopies: The first cystoscopy after chemoRT+/- durvalumab, will be performed in the operating room with bladder biopsy or transurethral resection of previously affected sites with random mapping biopsies to document response in bladder. The post-chemoRT +/- durvalumab, cystoscopic assessment will be performed approximately 8 weeks (±2 weeks) following the completion of radiotherapy.

Cystoscopy to be performed every 3 months (± 14 days) during year 1 and 2 post chemoRT treatment and thereafter every 6 months (± 14 days) for years 3 and 4.

Subsequent cystoscopy can be performed with flexible cystoscopy in the office, with urine cytology assessment. When there are suspicious findings on cystoscopy or clinical suspicion for recurrence based on

urine cytology or imagine, operative cystoscopy with bladder biopsy or transurethral resection (if appropriate) will be performed to document the presence or absence of tumor or CIS. Photographic imaging when possible will be performed to document progression or lack thereof. If any suspected tumor recurrence or progression is noted on imaging or cystoscopy, a brief cessation of systemic therapy will be recommended 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 would be recorded as PD.

In the event that non-muscle invasive disease (Ta, Ti or CIS) is the only finding, the patient will be deemed a PR but patient may be offered appropriate resection and intravesical therapy for non-muscle invasice disease. Intravesical therapy includes BCG, mitomycin C or gemcitabine therapy at the discretion of treating urologist.

Tumor Markers

Tumor markers alone cannot be used to assess response for this study. There are no established tumor markers for bladder.

Cytology, Histology

Urine cytology would be performed during surveillance period post completion of treatment on the study. However suspicious or positive urine cytology cannot be used alone, as the criteria for progression. Pathological confirmation on cystoscopy or biopsy of LN or any other area that is demonstrative of recurrence is required.

6.1.3.1 Evaluation by Cystoscopy

Efficacy by cystoscopy:

The first post treatment cystoscopy will be performed in the operating room with bladder biopsy or transurethral resection of previously affected sites with random mapping biopsies to document response in bladder. At each subsequent 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 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. **Pathologically downstaged recurrences of NMIBC such as Ta, CIS, or T1 disease 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 when possible.**

If a CR is suspected, confirmatory directed and random biopsies will be performed to rule out residual papillary tumor or CIS. In the event that non-muscle invasive disease (Ta, T1, CIS) is the only finding, the patient will be deemed a PR and may be offered appropriate intravesical chemotherapy (mitomycin or gemcitabine) or intravesical BCG per discretion of treating urologist in addition to ongoing treatment per protocol.

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

6.1.3.2 Evaluation of Target Lesions per RECIST (minor modification for exceptional circumstances for the purposes of the study)

The overall response post chemoRT+/- durvalumab will be evaluated per details provided in the Section 6.1.1. For follow-up evaluation of response, please see below.

Complete Response (CR)

Disappearance of all target lesions by cystoscopy and by imaging.

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All clinically suspicious lymph nodes must have reduction in short axis to < 10 mm. If any lymph node was <10mm at baseline, with high suspicion on imaging or pathologically, biopsy proven to be positive , it must resolve completely.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. Cystoscopy should be negative for cancer in bladder or < T2. These patients will be classified into clinical benefit group as detailed in the Section 6.1.

Progressive Disease (PD)

Patients with evidence of progression in the bladder or lymph nodes that are unresectable, or with a presence of distant metastasis.

For PD in bladder: cystoscopy will be performed and documentation of T2 disease is needed either by pathology or by treating urologist (this is to incorporate circumstances such – when T2 is suspected by urologist but adequate TURBT could not be done for concerns of perforating the bladder). Pathological confirmation is preferred. Please see Section 6.1.3.1.

For response evaluation by imaging: 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 progression, see Section 6.1.3.4. Since the study involves Immunotherapy, the patients who are receiving durvalumab should get a confirmatory CT scan no less than 4 weeks to document progression. Biopsy if possible should be considered.

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. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease.)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.1.3.3 Evaluation of Non-Target Lesions except bladder that is defined above in Section 6.1.3.1.

This study does not involve metastatic patients. Thus this criteria will be used for follow ups to capture progression.

Complete Response (CR)

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Disappearance of all non-target lesions. All clinically suspicious lymph nodes must be non-pathological in size (< 10 mm short axis). If there is any <10mm at baseline, with high suspicion on imaging or pathologically positive, it should disappear in order to be called as complete response. As mentioned before patients must have at least one target LN for the study.

Non-CR/Non-PD

Persistence of one or more non-target lesions.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.3.5). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Since the study involves Immunotherapy, the patients who are receiving durvalumab should get a confirmatory CT scan no less than 4 weeks to

document progression. Biopsy if possible should be considered.

6.1.3.4 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) Increases in size to ≥ 10 mm in the short axis, or

b) There is new pathological confirmation that it is disease (regardless of size).

New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

New Bladder lesion must be evaluated by cystoscopy and should be biopsy proven.

6.1.3.5 Evaluation of Best Overall Response in adjuvant vs. observation phase

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response post chemoRT+/- durvalumab will be defined as mentioned above in beginning of Section 6.1.

In general, the subject's best response assignment during adjuvant treatment vs. observation will depend on the achievement of both measurement and confirmation criteria.

Table: Response assessment in the adjuvant phase for Arms E and F					
Target Lesions	**Non-Target Lesions**	**Cystoscopy**	**New Lesions***	**Overall Response**	**Best Overall Response when Confirmation is Required**
CR	CR	CR	No	CR	≥ 4 weeks. Confirmation
CR	Non-CR**/Non-PD OR Not evaluated	NMIBC or not evaluated	No	PR	≥ 4 weeks. Confirmation
PR	Non-PD**/not evaluated	NMIBC or not evaluated	No	PR	
SD	Non-PD**/not evaluated	NMIBC or not evaluated	No	SD	Documented at least once ≥ 4 weeks from study entry
PD	Any	Any	Yes or No	PD	Progression by imaging alone must be confirmed by repeat imaging ≥ 4 weeks apart
Any	PD**	Any	Yes or No	PD**	
Any	Any	MIBC	Yes or NO	PD	
Any	Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.					
** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.					

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.

6.1.3.6 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for clinical until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Clinical Benefit

Clinical benefit is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of clinical benefit measurements must have met the criteria at post chemoRT +/- Durvalumab.

7. Study Parameters

For all patients in Steps 1

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- Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 8 weeks prior to Step 1 randomization.
- Prestudy CBC (with differential and platelet count) must be done within 14 days before Step 1 randomization.
- All required prestudy chemistries, as outlined in Section 3.1, must be done within 14 days before Step 1 randomization – unless specifically required on Day 1 as per protocol.
- Radiation therapy must start within 20 business days of Step 1 randomization.

For patients in Step 2

- CT scan and cystoscopy to be done at 8 weeks (+/- 2 weeks) after completion of chemoRT (Step 1).
- Prestudy CBC (with differential and platelet count) must be done within ≤ 28 days before Step 2 registration

7.1 Arm C and Arm E:

Arm C and Arm E: Treatment Calendar for ChemoRT+ durvalumab followed by adjuvant durvalumab									
	Screen prior to Step 1 Randomi -zation	**ChemoRT+ durvalumab (±4d)**				**Post chemo RT + durvalumab Prior to Step 2 Registration**	**Adjuvant durvalumab for total of 6 Q4W doses**		**Follow up[Q]**
	-28 d	**W1**	**W4**	**W7**	**W8**	**W16 (±14d)**	**Q4W while on adjuvant durvalumab(±5d)**	**Q12W for Year 1 (±14d)**	**Year 2 Q6 monthly; then years 3 and 4 annually (±14d)**
Chemotherapy Administration[O]		Will vary per regimen. Please see Section 5.1							
Radiation Therapy[M]		RT per protocol- will vary 6.5-8 weeks							
Durvalumab[N]		Starting Day 1 q3 weekly x 3 doses					Q4 weeks for 6 doses		
REQUIRED ASSESSMENTS									
History and Physical Exam	X	Per institutional policy				X			
ECOG Performance Status	X					X			
Vital signs (temperature, blood pressure, heart rate)	X	X	X	X		X	X		
EKG[R]	X								
Toxicity assessment[A]	X	X	X	X		X	X		X[P]
Concomitant Medications[B]	X	X	X	X		X	X		
DLTs only[S]		Only for 1st 6 patients on chemoRT+ durvalumab							
LABORATORY ASSESSMENTS									
Complete Blood Cell Count with diff (CBC)[C]	X	Per Institutional policy[C]				X	X	X	
Comprehensive Metabolic Profile (CMP)[D]	X	Per Institutional policy[D]				X	X	X	
GGT, Mg, Phos, Uric Acid, LDH	X	Per Institutional policy							

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Arm C and Arm E: Treatment Calendar for ChemoRT+ durvalumab followed by adjuvant durvalumab									
	Screen prior to Step 1 Randomi-zation	ChemoRT+ durvalumab (±4d)				Post chemo RT + durvalumab Prior to Step 2 Registration	Adjuvant durvalumab for total of 6 Q4W doses		Follow up[Q]
	-28 d	W1	W4	W7	W8	W16 (±14d)	Q4W while on adjuvant durvalumab(±5d)	Q12W for Year 1 (±14d)	Year 2 Q6 monthly; then years 3 and 4 annually (±14d)
TSH (free T3, free T4 if TSH abnormal)[E]	X				X		X		
Pregnancy test (serum or urine)[F]	X								
Hepatitis serologies; HIV testing[G]	X								
Coagulation panel[H]	X								
DISEASE ASSESSMENT									
Exam under anesthesia and TURBT[I]	Within 12 weeks prior to Step 1 randomization								
Bladder biopsy[J]						X			
Cystoscopy[J]						X		X	Every 12 weeks for year 2, then every 6 months for year 3
Urine Cytology[K]	X					X		X	Every 12 weeks for year 2, then every 6 months for year 3

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Arm C and Arm E: Treatment Calendar for ChemoRT+ durvalumab followed by adjuvant durvalumab									
	Screen prior to Step 1 Randomi -zation	ChemoRT+ durvalumab (±4d)				Post chemo RT + durvalumab Prior to Step 2 Registration	Adjuvant durvalumab for total of 6 Q4W doses		Follow up[Q]
	-28 d	W1	W4	W7	W8	W16 (±14d)	Q4W while on adjuvant durvalum ab(±5d)	Q12W for Year 1 (±14d)	Year 2 Q6 monthly; then years 3 and 4 annually (±14d)
Rev. Add4 CT or MRI[L]	Within 8 weeks prior to Step 1 randomiz ation					X		X	X
SPECIMEN COLLECTION See Sections 7.3 and 10									

A Arm C: Toxicities must be assessed weekly throughout the first six weeks, then until toxicities resolve or decrease to grade 1. Arm E: Toxicities must be assessed prior to each durvalumab infusion. Follow-up toxicity assessments are also required at 30 days after last dose of protocol treatment. Thereafter the frequency is determined per physician discretion.

B Concomitant medications to be assessed on each clinic visit.

C For screening labs, these must be completed within 14 days prior to Step 1 randomization and within 28 days prior to Step 2 registration. During chemoradiation, time points should follow institutional practices. However, at a minimum, obtain WBC, ANC, platelets, hemoglobin prior to durvalumab infusions +/- 4 days.

D For screening labs, these must be completed within 14 days prior to Step 1 randomization. During chemoradiation, time points should follow institutional practices. However, at a minimum, obtain CMP basic metabolic panel (creatinine, potassium, AST/ALT, bilirubin, albumin) prior to durvalumab infusion +/- 4 days.

E Thyroid stimulating hormone- (TSH) to be performed at screening per physician discretion. Free T3 and free T4 will only be measured if TSH is abnormal, or as clinically indicated by the treating physician. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

F All patients of childbearing potential must have a negative [blood test or urine test] within 14 days prior to Step 1 randomization to rule out pregnancy.

G Hepatitis serologies and HIV- if applicable, per physician discretion. Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.

H Coagulation panel - to include prothrombin time (PT), and INR. aPTT is to be performed at screening as clinically indicated by the treating physician.

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I Cytoscopy and Maximal TURBT- within 12 weeks prior to Step 1 randomization. The treating urologist would determine extent of maximal TURBT. Attempt should be made for maximal TURBT unless it is contraindicated for safety reasons, in which case the case must be discussed and approved with the study chair prior to enrollment. Documentation of correspondence with the study chair must be kept on file. Documentation whether there is presence or absence of residual disease is required for the study. Please note for patients who have no residual disease upon cystoscopy post induction chemotherapy by urologist, i.e., not ideal for TURBT, would be classified as no residual disease. Please note those patients who had induction chemotherapy before randomization would need cystoscopy and attempt for repeat TURBT post chemotherapy and prior to Step 1 randomization.

J Cystoscopy and biopsy- (post chemoRT+ durvalumab); biopsy of affected site in bladder and random biopsies should be performed. Thereafter, cystoscopy is performed Q12 weekly (biopsy only if clinically indicated) for years 1 and 2, and then every 6 months for year 3.

K Urine cytology- to be performed for disease status evaluation at the same time points as imaging.

L Baseline: CT scan (IV contrast with urogram preferred) or MRI of chest and abdomen and pelvis are required within 8 weeks prior to Step 1 randomization. Note: Baseline CT is preferred but MRI of abdomen and pelvis are acceptable Thereafter, CT scans to be performed at 8 weeks (+/- 2 week) post chemoRT+ durvalumab. Timing of the CT imaging once adjuvant durvalumab starts is every 12 weeks (± 14 days) for year 1, every 6 months (± 14 days) for year 2, then annually for years 3-4. Follow up imaging of chest: CT chest preferred but CXR is allowed. The confirmatory scan are needed and is acquired preferably at the next regularly scheduled imaging visit (could be requested earlier if there is suspicion for PD) and no earlier than 4 weeks after the prior assessment of disease status. CR, PR, SD need to be confirmed with another scan on next clinic visit and no sooner than 4 weeks. Additional imaging could be done per physician discretion. Please not that PET/CT post chemoRT + durvalumab is not encouraged. However, if PET/CT scan is done at baseline or any other time, CT portion of the scan could be used if there are financial restraints from insurance to get CT urogram (provided safe for patient). When possible, advise to maintain the use of the same modality for follow-up.

M Radiation therapy per treatment by Radiation Oncologist. Radiation therapy should start within 20 business days of Step 1 randomization.

N Durvalumab needs to be given Q3 weekly during chemoRT phase and in adjuvant phase it will be Q4 weekly. D1 durvalumab during chemoRT+ durvalumab phase to start +/- 4 days (before or after) the start of radiation therapy.

O Chemotherapy – frequency and dosing per treatment Section 5.1 and physician discretion. C1D1 chemo during chemoRT phase to start +/- 4 days (before or after) the start of radiation therapy.

P Safety follow up visit – The safety follow-up visit should occur when patient permanently stops 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. Patients 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.

Q Long-term follow up- Long-term follow up will occur in all patients until documented disease progression. Patients who discontinue treatment for any reason without documented disease progression will be followed every 12 weeks for year 1, then Q6 months years 2, then annually for years 3 and 4 until confirmed PD. Once disease progression is documented, patients will enter a survival follow-up period every 3 months for 4 years from Step 1 randomization. For patients who achieve disease control after adjuvant durvalumab treatment or discontinue due to toxicity or symptomatic deterioration, tumor assessments should be performed every 12 weeks (± 14 days) for year 1, followed by every 6 months for year 2, then annually for years 3 and 4 from the date of Step 1 randomization until confirmed PD. After confirmed PD, scans should be conducted according to local practice.

R EKG is to be done at baseline as clinically indicated and then throughout treatment as clinically indicated by the treating physician.
S Refer to Section 5.6.1.

7.2 Arm D and Arm F:

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NOTE: For patients who come off the study post chemoRT with no clinical benefit (even if they have salvage cystectomy) would be followed only for overall survival.[Q]

Arm D and Arm F: Treatment Calendar for ChemoRT followed by observation								
	Screen prior to Step 1 Randomization	**ChemoRT (±4d)**				**Post chemoRT prior to Step 2 registration**	**Follow up**	**Follow up[Q]**
	-28 d	**W1**	**W4**	**W7**	**W8**	**W16 (±14d)**	**Q12W for Year 1 (±14d)**	**Year 2 Every 6 months, years 3 and 4 annually (±14d)**
Chemotherapy Administration[O]		Will vary per regimen selection. Please see Section 5.1						
Radiation Therapy[M]		RT per protocol- will vary 6.5-8 weeks						
REQUIRED ASSESSMENTS								
History and Physical Exam	X	Per institutional policy				X		
ECOG Performance Status	X					X		
Vital signs (temp, blood pressure, heart rate)	X	X	X	X		X	X	
EKG[R]	X							
Toxicity assessment [A]	X	X	X	X		X		X[P]
Concomitant Medications[B]	X	X	X	X		X	X	
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)[C]	X	Per institutional policy[C]				X	X	
Comprehensive Metabolic Profile (CMP)[D]	X	Per institutional policy[D]				X	X	
GGT, Mg, Phos, Uric Acid, LDH	X	Per Institutional policy						
TSH (free T3, free T4 if TSH abnormal) [E]	X				X		As clinically indicated	
Pregnancy test (serum or urine)[F]	X							

Arm D and Arm F: Treatment Calendar for ChemoRT followed by observation								
	Screen prior to Step 1 Randomization	**ChemoRT (±4d)**				**Post chemoRT prior to Step 2 registration**	**Follow up**	**Follow up[Q]**
	-28 d	**W1**	**W4**	**W7**	**W8**	**W16 (±14d)**	**Q12W for Year 1 (±14d)**	**Year 2 Every 6 months, years 3 and 4 annually (±14d)**
Hepatitis serologies; HIV testing[G]	X							
Coagulation panel[H]	X							
DISEASE ASSESSMENT								
Rev. Add4 Exam under anesthesia and TURBT[I]	X Within 12 weeks prior to Step 1 randomization							
Bladder biopsy[J]						X		
Cystoscopy[J]	X					X	X	Every 12 weeks for year 2, then every 6 months for years 3 and 4
Urine Cytology[K]	X					X	X	Every 12 weeks for year 2, then every 6 months for year 3s and 4
CT or MRI [L]	Within 8 weeks prior to Step 1 randomization					X	X	X

Arm D and Arm F: Treatment Calendar for ChemoRT followed by observation								
	Screen prior to Step 1 Randomization	ChemoRT (±4d)				Post chemoRT prior to Step 2 registration	Follow up	Follow up[Q]
	-28 d	W1	W4	W7	W8	W16 (±14d)	Q12W for Year 1 (±14d)	Year 2 Every 6 months, years 3 and 4 annually (±14d)
SPECIMEN COLLECTION See Sections 7.3 and 10								

A Arm D: Toxicities must be assessed weekly throughout the first six weeks, then until toxicities resolve or decrease to grade 1. Follow-up toxicity assessments are also required at 30 days after last dose of protocol treatment. Thereafter the frequency is determined per physician.

B Concomitant medications to be assessed on each clinic visit. For those patients on Arm F, who did not received any induction chemotherapy prior to Step 1 randomization, and their physician is giving them adjuvant chemotherapy on Arm F, information regarding this treatment must be captured in Medidata Rave (i.e.: dates and type of adjuvant chemotherapy, number of cycles). Any adverse events related to adjuvant chemotherapy while on Arm F do not need to be reported in Medidata Rave. NOTE: Patient cannot receive any checkpoint inhibitors while on Arm F.

C For screening labs, these must be completed within 14 days prior to Step 1 randomization and within 28 days prior to Step 2 registration. During chemoradiation, time points should follow institutional practices. However, at a minimum, obtain WBC, ANC, platelets, hemoglobin weekly for gemcitabine and cisplatin regimens (prior to infusion) and every three weeks for 5-FU regimen (prior to infusion).

Rev. Add4 D For screening labs, these must be completed within 14 days prior to Step 1 randomization. During chemoradiation, time points should follow institutional practices. However, at a minimum, obtain CMP basic metabolic panel (creatinine, potassium, AST/ALT, bilirubin, albumin) weekly for gemcitabine and cisplatin regimens (prior to infusion) and every three weeks for 5-FU regimen (prior to infusion).

E Thyroid stimulating hormone (TSH) to be performed at screening per physician discretion. Free T3 and free T4 will only be measured if TSH is abnormal or as clinically indicated by the treating physician. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

F All patients of childbearing potential must have a negative [blood test or urine test] within 14 days prior to Step 1 randomization to rule out pregnancy.

G Hepatitis serologies and HIV - if applicable, per physician discretion. Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.

H Coagulation panel -to include prothrombin time (PT), and INR. aPTT to be performed at screening, per physician discretion, and as clinically indicated per the treating physician.

Rev. Add3 I Cytoscopy and Maximum TURBT- within 12 weeks prior to starting Step 1 randomization. The treating urologist would determine extent of maximal TURBT. Attempt should be made for maximal TURBT unless it is contraindicated for safety reasons, in which case the case must be discussed and approved with the study chair prior to enrollment. Documentation of correspondence with the study chair must be kept on file.

Documentation whether there is presence or absence of residual disease is required for the study. Please note for patients who have no residual disease upon cystoscopy post induction chemotherapy by urologist, i.e., not ideal for TURBT, would be classified as no residual disease. Please note those patients who had induction chemotherapy before randomization would need cystoscopy and attempt for repeat TURBT post chemotherapy prior to Step 1 randomization.

J Cystoscopy and biopsy- (post chemoRT+ durvalumab); biopsy of affected site in bladder and random biopsies should be performed. Thereafter cystoscopy is performed Q12 weekly (biopsy when clinically indicated) for year 1, then every 6 months for years 2 and 3.

K Urine cytology- to be performed for disease status evaluation at the same time points as cystoscopy.

L Baseline: CT scan (IV contrast with urogram preferred) or MRI of chest and abdomen and pelvis are required within 8 weeks of Step 1 randomization Note: Baseline CT is preferred but MRI of abdomen and pelvis are acceptable Thereafter, CT scans to be performed at 8 weeks (+/- 2 week) post chemoRT+ durvalumab. Timing of the CT imaging once adjuvant durvalumab starts is every 12 weeks (± 14 days) for year 1, every 6 months (± 14 days) for year 2, then annually for years 3-4. Follow up imaging of chest: CT chest preferred but CXR is allowed. The confirmatory scan are needed and is acquired preferably at the next regularly scheduled imaging visit (could be requested earlier if there is suspicion for PD) and no earlier than 4 weeks after the prior assessment of disease status. CR, PR, SD need to be confirmed with another scan on next clinic visit and no sooner than 4 weeks. Additional imaging could be done per physician discretion. Please not that PET/CT post chemoRT + durvalumab is not encouraged. However, if PET/CT scan is done at baseline or any other time, CT portion of the scan could be used if there are financial restraints from insurance to get CT urogram (provided safe for patient). When possible, advise to maintain the use of the same modality for follow-up.

M Radiation therapy per treatment by Radiation Oncologist. Radiation therapy should start within 20 business days of randomization.

Rev. Add4 N Durvalumab needs to be given Q3 weekly during chemoRT phase and in adjuvant phase it will be Q4 weekly. D1 durvalumab during chemoRT+ durvalumab phase to start +/- 4 days (before or after) the start of radiation therapy.

O Chemotherapy – frequency and dosing per treatment Section 5.1 and physician discretion. C1D1 chemo during chemoRT phase to start +/- 4 days (before or after) the start of radiation therapy.

P Safety follow up visit- The safety follow-up visit should occur when patients 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. Patients 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.

Q Long-term follow up- Long-term follow up will occur in all patients until documented disease progression. Patients who discontinue treatment for any reason without documented disease progression will be followed every 12 weeks for year 1, then every 6 months for years 2, and annually for years 3 and 4 until confirmed PD. Once disease progression is documented, patients will enter a survival follow up period every 3 months for year 1, every 6 months for year 2, and annually for years 3 and 4 from the time of Step 1 randomization. For patient who achieve disease control after treatment or discontinue due to toxicity or symptomatic deterioration, tumor assessments should be performed every 12 weeks (± 14 days) for the first year, then every 6 months for years 2, 3, and 4 from the date of Step 1 randomization until confirmed PD for at least 4 years. After confirmed PD, scans should be conducted according to local practice. Please note that for those patients who did not get induction chemotherapy, and treating physician decides to give adjuvant chemotherapy, details of chemotherapy regimen needs to be captured (dates of cycle of chemotherapy, number of cycles, treatment regimen).

R EKG is to be done at baseline as clinically indicated and then throughout treatment as clinically indicated by the treating physician.

7.3 Biological Specimen Submissions

Specimens are to be submitted as outlined in Section 10.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

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Biological Materials	Prior to Start of Treatment (Step 1)[3]	Post chemoRT at Restaging [week 16][4]	Submit to:
For patients who answer "Yes" to "My samples and related information may be kept in a Biobank for use in future health research".			
Tumor Tissue[1]	X	X[2]	EA CBPF
Peripheral Blood (one 10mL EDTA purple top tube)	X[5]		
Peripheral Blood (two 10mL Streck Cell-Free DNA tubes)[6]	X	X	
Peripheral Blood (one 10mL SST red top tube)[6]	X	X	

[1] Baseline prior to starting chemoRT +/- durva. TURBT specimen within 12 weeks of starting treatment preferred, if not available, previous TURBT specimen is acceptable.

[2] If residual disease, prior to starting adjuvant durvalumab or surveillance.

[3] Pre-chemoRT +/- durva, prior to week one (1)/ day one (1).

[4] +/- four (4) weeks

[5] If baseline collection is missed, please collect at any other time during the study, if necessary.

[6] Kits are being provided for the collection and shipment of peripheral blood. See Appendix VI for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Sites may order initial agent supplies when a subject has been randomized.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record Form (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

8.1 Durvalumab (NSC 778709)

8.1.1 Other Names

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Durvalumab, MEDI4736 (durvalumab)

8.1.2 Classification

Anti-PD-L1 MAb

8.1.3 Molecular Weight

149 kDa

8.1.4 Mode of Action

Durvalumab inhibits binding of programmed cell death ligand 1 (PD-L1) to PD-1 and CD80. In-vitro studies demonstrate that durvalumab relieves PD-L1-mediated suppression of human T-cell activation. durvalumab does not trigger antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity in cell-based functional assays.

8.1.5 Description

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody.

8.1.6 How Supplied

Durvalumab is supplied by AstraZeneca/MedImmune, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 500 mg/vial solution for infusion (50 mg/mL). Durvalumab solution for infusion is formulated in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0. Durvalumab is supplied in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal.

8.1.7 Preparation

Durvalumab solution for infusion must be diluted prior to administration. To prepare the infusion solution add the dose volume of durvalumab to an infusion bag containing 0.9% Sodium Chloride Injection or Dextrose 5% in Water Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between 1 mg/mL to 15 mg/mL. Infusion bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.

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8.1.8 Storage

Store intact vials between 2-8°C (36-46°F). Do not freeze.

If a storage temperature excursion is identified, promptly return durvalumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of

temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

8.1.9 Stability

Stability testing of the intact vials is on-going.

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). Prior to the start of the infusion, ensure that the bag contents are at room temperature (approximately 25°C) to avoid an infusion reaction due to the administration of the solution at low temperatures. If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

8.1.10 Route of Administration

IV infusion. Infuse over approximately 60 minutes using an infusion set containing a 0.22 or 0.2 µm in-line filter. No incompatibilities between durvalumab and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Flush the IV line with a volume of IV bag diluent equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

8.1.11 Patient Care Implications

Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

NOTE: Patients, if enrolled, should not receive live vaccine whilst receiving durvalumab and up to 30 days after the last dose of durvalumab.

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NOTE: Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily in order to minimize an overlap of adverse events).

Review with the patient acceptable and effective methods of contraception to use while on durvalumab, including:

- Copper T intrauterine device
- Levonorgestrel-releasing intrauterine system (e.g., Mirena®)
- Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant®
- Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing®
- Injection: Medroxyprogesterone injection: e.g. Depo-Provera®
- Combined Pill: Normal and low dose combined oral contraceptive pill

- Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra®
- Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based contraceptive pill.

8.1.12 Side Effects

See Section 5.5 for the Comprehensive Adverse Event and Potential Risks (CAEPR) list.

Rev. Add4

8.2 Cisplatin (CDDP, Platinol®, Platinol-AQ) (NSC119875)

8.2.1 Pharmacology

Mechanism of Action:

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

Pharmacokinetics

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of total platinum increase gradually during the infusion and peak immediately following the end of the infusion.
2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.
3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.
4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m^2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum-containing molecules are actively

secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

8.2.2 Side Effects

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

8.2.3 Drug Interactions

During cisplatin therapy, plasma levels of anticonvulsant agents may become sub-therapeutic and should be monitored. For complete information refer to the current FDA-approved package insert.

8.2.4 Dosing & Administration

Dosing – See Section 5 for Treatment Plan

Refer to the current FDA-approved package insert for drug administration.

8.2.5 Preparation, Storage & Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information.

8.2.6 How Supplied

Cisplatin is commercially available and will not be supplied.

8.2.7 Nursing Implications

8.2.7.1 Prior to administration, assess:

- Labs: CBC, platelet count, BUN, creatinine
- Urine Output: 100-150 ml/hr for at least 4-6 hours
- Signs of ototoxicity or neurotoxicity

8.2.7.2 Administer supportive medications

- Antiemetic's: 5HT antagonists and dexamethasone combinations can usually be 3 given once daily
- Hydration
- Diuretics

8.2.7.3 Observe for signs of allegic reaction

Rev. Add4

8.3 Fluorouracil (5-FU, Adrucil ®) (NSC19893)

8.3.1 Pharmacology

Mechanism of Action: Fluorouracil is a pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis in the S phase of cell division. After activation, the active metabolite F-UMP is incorporated into RNA to replace uracil and inhibit cell growth. The active metabolite, F-dUMP, inhibits thymidylate synthetase and depletes thymidine triphosphate

8.3.2 Pharmacokinetics

1. Absorption: Rapid intravenous injection of fluorouracil results in high early levels of drug achieved both in plasma and bone marrow with a rapid fall afterwards. Prolonged infusions of fluorouracil show constant levels of the drug in plasma and significantly less in bone marrow.
2. Distribution: Fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver, third space fluids and other tissues. Fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.
3. Metabolism: Fluorouracil is primarily metabolized in the liver via dihydropyrimidine dehydrogenase (DPD) to the active metabolites 5-fluoroxyuridine monophosphate (F-UMP) and 5-5-fluoro-2'-deoxyuridine-5'-O-monophosphate (F-dUMP).
4. Elimination: The mean elimination half-life of fluorouracil from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. Seven to 20% of fluorouracil is excreted unchanged in the urine.

8.3.3 Side Effects

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

8.3.4 Drug Interactions

Fluorouracil is a strong inhibitor of CYP2C9. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including fluorouracil, should be screened prior to initiation of and during treatment with fluorouracil.

8.3.5 Dosing & Administration

See Section 5 for Treatment Plan

8.3.6 How Supplied

Fluorouracil is commercially available and will not be supplied.

8.3.7 Nursing Implications

- Monitor CBC, platelet counts.
- Administer antiemetics as indicated.
- Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose-limiting.
- Assess for stomatitis - oral care recommendations as indicated.
- Monitor for neurologic symptoms (headache, ataxia).
- Patients on continuous infusions may need instruction regarding central IV catheters and portable IV infusion devices.
- Inform patient of potential alopecia.

Rev. Add4

8.4 Mitomycin (systemic) (Mitomycin-C, Mutamycin ®) (NSC 26980)

8.4.1 Pharmacology

Mechanism of Action: Mitomycin (also known as mitomycin-C) is an antibiotic isolated from the broth of Streptomyces caespitosus with antimetabolite activity. It is an alkylating agent, which requires activation by reduction of its quinone group and loss of the methoxy group. Mitomycin causes cross-linking DNA and selectively inhibits DNA synthesis. The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations, cellular RNA and protein synthesis are also suppressed.

8.4.2 Pharmacokinetics

1. Absorption: mitomycin is administered intravenously.
2. Distribution: The volume of distribution of mitomycin is 11 to 48 L/m^2. After injection of 30 mg, 20 mg, or 10 mg intravenously, the maximal serum concentrations were 2.4 mcg/mL, 1.7 mcg/mL, and 0.52 mcg/mL, respectively.
3. Metabolism: The liver is the primary site for mitomycin metabolism but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because of saturation of the degradative pathways.
4. Elimination: In humans, mitomycin is rapidly cleared from the serum after intravenous administration. The time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. Approximately 10% of a dose of mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose.

8.4.3 Side Effects

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

8.4.4 Drug Interactions

Mitomycin is a substrate of P-glycoprotein and may interact with P-glycoprotein inhibitors and inducers. Mitomycin level may be increased by vinca alkaloids and P-Glycoprotein inhibitors. Mitomycin level may be decreased by P-glycoprotein inducers.

8.4.5 Dosing & Administration

See Section 5 for Treatment Plan.

Mitomycin is a hazardous agent. Appropriate precautions for receiving, handling, administration and disposal must be used.

8.4.6 Nursing/ Patient Implications

Mitomycin is a potent vesicant. Proper needle or catheter placement must be ensured prior and during infusion to avoid extravasation.

Monitor CBC for anemia, neutropenia, and thrombocytopenia.

8.4.7 How Supplied

Mitomycin is commercially available and will not be supplied.

Rev. Add4

8.5 Gemcitabine hydrochloride (Gemzar®) (NSC 613327)

Refer to the current FDA-approved package insert.

8.5.1 Side Effects

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Drug Interactions:

Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with carboplatin or paclitaxel there was minimal or no effect on the pharmacokinetics of the studied drugs.

8.5.2 Dosing & Administration

See Section 5 for Treatment Plan.

8.5.3 How Supplied

Gemcitabine is commercially available and will not be supplied.

8.5.4 Nursing/ Patient Implications

Refer to package insert

- If the patient report burning at the injection site, slow down the rate to allow the dose to run in over 1 hour.
- Rash can be treated with topical therapy or the administration of diphenhydramine and dexamethasone prior to administration.

Rev. Add4

- Flu like symptoms can be treated with acetaminophen.

9. Statistical Considerations

Rev. Add4

Patients will be randomized 1:1 to chemoradiation with or without durvalumab. Simon Pocock minimization will be used to balance the following four stratification factors between arms:

- Induction Chemotherapy prior to randomization: Yes vs. No
- Cisplatin vs. non-cisplatin regimen during RT
- Stage of Lymph node (N1 vs. N2-3)
- Extent of TURBT (no residual disease vs. residual disease after TURBT)

Given the paucity of data predicting outcomes with chemoradiotherapy in node-positive bladder cancer, these stratification factors were selected because they have impacted patient outcomes in other settings and may be associated with clinical outcomes with chemoradiotherapy +/- durvalumab. With the large number of stratification factors relative to the sample size, Simon-Pocock minimization will help ensure that these patient characteristics are similar between arms.

9.1 Sample size justification

The primary endpoint is clinical CR. While there are no prospective studies demonstrating efficacy of chemoRT in node positive patients, Coen *et al*. showed in their retrospective review that the response rate to chemoRT was about 70% in node-negative patients. In addition, presence of incomplete TURBT, hydronephrosis, and higher T stage were negative predictors for response to chemoradiation.[13] We assume that node positive patients are likely to have higher T stage, hydronephrosis, and higher incidences of incomplete TURBT and thus, a lower response rate. The phase Ib part of the DUART study demonstrated a promising efficacy signal post- durvalumab + RT. Other studies have shown response rates of 17-24% with CPI alone. We assume that the addition of chemoRT to durvalumab will further increase the response rate. This study is designed to detect an improvement in clinical CR rate from 37.5% on the chemoRT arm to 62.5% on the chemoRT + durvalumab arm. With a one-sided type I error rate of 0.1, a total of 92 evaluable patients will provide 81% power to detect this difference using a Fisher's exact test.

The total accrual goal will be 95 accounting for the three patients that never got randomized.

Patients who receive any chemoRT +/- durvalumab will be included in the interim and final analyses. Those who are unevaluable post chemoRT +/- durvalumab, such as those patients who drop out before completing treatment post randomization or drop out prior to evaluation of first response or those patients who cannot get CT scan and or cystoscopy to evaluate for response will be considered non-responders.

9.2 Safety Monitoring

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The first 6 patients randomized to the chemoRT + durvalumab arm will be monitored for dose-limiting toxicities (DLTs), as defined in Section 5.6.1. If fewer than 2 of these 6 patients experience a DLT the regimen will be considered safe and enrollment will continue. If 2 or more patients experience DLTs during this period the trial will be suspended for review. These 6 patients will be included in the primary analysis.

In addition to above, we will do close monitoring on immune related AEs for subsequent patients. Toxicity comparison will be done after 20 patients are randomized to each arm. The first 20 patients on the experimental arm will be evaluated more intensively for adverse events. Assessment will be done Q3weekly for the chemoRT+/- durvalumab during concurrent phase and thereafter Q4 weekly during the adjuvant phase. Although there will be a global approach to AE assessment, we will focus particularly on immune related adverse events. In addition to evaluating the rate and severity of toxicities on the experimental arm, the first 20 patients on the standard arm of chemoRT will also be assessed as a comparator and to provide context for the background rate of toxicity without durvalumab.

If 25% or more of these patients on experimental arm experience grade 3 or higher immunologic toxicities a safety review will be conducted to evaluate the experimental design. In addition, the radiation related toxicity rates on the two arms will be compared during the concurrent phase. If the toxicity rate of grade 3 or higher on the combination arm exceeds ***1.5x of that on the control*** arm then the study would be suspended for review.

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We will also closely monitor the adverse events among the N3 patients and this will be reviewed by the DSMC twice a year. If there are any concerns, N3 accruals can be suspended.

Additionally, interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.4.

9.3 Interim Monitoring

At 50% information time (46 patients evaluable for CR) a futility analysis will be performed. If at this time the one-sided p-value for the comparison of CR rates between arms using a Fisher's exact test exceeds 0.5 we will consider termination for inefficacy.

A subgroup analysis in the hydronephrosis cohort at the time of enrollment will also occur at this time. Hydronephrosis will be evaluated from eCRF response data. If the upper bound of the 90% confidence interval on the clinical CR rate does not exceed 35% then no additional hydronephrosis patients will be enrolled.

9.4 Secondary Endpoints

Metastasis-free survival is defined as the time from randomization to first evidence of metastatic disease or death from any cause. Patients who are alive and metastasis-free will be censored at date of last assessment.

Events of interest for bladder-intact event-free survival are presence of muscle-invasive bladder cancer, clinical evidence of progression of nodal involvement or development of metastatic disease, radical cystectomy, or death due to any cause. BI-EFS is the time from randomization to the first BI-EFS event. Patients last known to be BI-EFS event-free will be censored at the date of last assessment. Patients alive without disease assessment will be censored at randomization.

Bladder cancer specific survival is the time from randomization to death from bladder cancer. Deaths due to other causes will be considered competing events and patients known to be alive will be censored at the date of last contact.

Overall survival is defined as the time from randomization to death from any cause. Patients still alive will be censored at date of last contact.

Progression-free survival is defined as the time from randomization to first of local progression, nodal or distant metastasis, or death from any cause. Patients last known to be alive and progression-free will be censored at the date of last contact.

For the subset of patients who achieve a clinical complete response during the primary endpoint assessment, complete response duration is defined from the date of the biopsy documenting the complete response to the time of muscle invasive recurrence, local progression, evidence of metastatic disease or death due to any cause. Patients will be censored at the date of last disease assessment.

The salvage cystectomy rate will be reported as a proportion of patients who do not experience clinical benefit and undergo salvage cystectomy after chemoRT +/- durvalumab along with a 90% confidence interval.

The Kaplan-Meier method will be used to estimate time-to-event endpoints and stratified Cox proportional hazards models will be used to estimate hazard ratios in all eligible patients.

Toxicity will be evaluated in all treated patients, regardless of eligibility.

Subset analysis on clinical outcomes by the stratification factors will also be performed.

9.5 Gender and Ethnicity

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Patients of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Based on data from Haque et al. the anticipated accrual in subgroups defined by gender and race is:

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	3	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	7	0	0	**9**
White	22	55	1	1	**79**
More Than One Race	0	1	0	1	**2**
Total	**26**	**66**	**1**	**2**	**95**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Statistical analyses for exploratory objective would be provided in near future and the protocol would be amended to include it. We currently are only collecting samples for analyses in future. We do plan to submit an application to NIH and also seek funds from AZ if needed to perform correlative tests. More details on statistical analyses would be provided in near future.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

10. Specimen Submissions

Diagnostic TURBT tissue, restaging TURBT tissue and peripheral blood specimens are to be submitted per patient consent for future undefined research studies.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number EA8185, the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type. For pathology materials, it is strongly recommended that full patient names be provided.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) Section 10.5. An STS shipping manifest form is to be included with every submission.

10.1 Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

If you have any questions concerning tumor tissue and peripheral blood submissions please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org.

10.1.1 Pathology Material Submissions

Guidelines for pathologists are provided in Appendix I.

Diagnostic TURBT tissue and restaging TUBRT tissue are to be submitted within one month of randomization or collection.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID# as well as the information above.

10.1.1.1 Required Material

Forms: Must be submitted with all pathology submissions.

- STS generated shipping manifest form
- Copy of the institutional diagnostic and surgical pathology report
- Immunological study reports, if available

Tumor Tissue Submissions:

- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks and three (3) H&E stained slides from the pretreatment TURBT biopsy (prior to starting chemoRT +/- durva within eight (8) weeks of starting treatment preferred, if not available, previous TURBT specimen is acceptable)
- Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks and three (3) H&E slides from TURBT biopsy at the time of restaging (prior to starting adjuvant radiation or surveillance)

  NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All

cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- Three (3) H&E slides
- Ten (10) 10 µm and five (5) 4 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor (Superfrost Plus recommended). After cutting, the slides should be kept refrigerated (2-5°C) until shipment or dried overnight between ambient temperature and 37°C.
- Two (2) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.2 Peripheral Blood Submissions

Kits for the collection and shipment of the peripheral blood specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VI. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

10.2.1 Peripheral Blood [EDTA Purple Top Tube]

10.2.1.1 Collection Time Point:

- Prior to Start of Treatment [if baseline collection is missed please collect at any other time during the study, if necessary]

10.2.1.2 Preparation Guidelines

- Collect 10mL of whole blood into one (1) EDTA purple top tube
- Invert tube gently 8-10 times to ensure proper mixing.
- Package and ship the day of collection at ambient temperature (no wet or dry ice and no cool packs).

10.2.2 Peripheral Blood [Streck Cell-Free DNA Tubes]

10.2.2.1 Collection Time Points:

- Prior to Start of Treatment [Step 2 pre-chemoRT/prior to week one (1)/day one (1)]

- Post-chemoRT at Restaging [week 16]

10.2.2.2 Preparation Guidelines

- Collect 10mL of whole blood into two (2) Streck Cell-Free DNA BCT tubes at each time point. Fill each tube completely
- Ensure at least 10mL of whole blood is drawn in each tube. Avoid low volume to minimize agitation during shipping
- Immediately after collection, gently invert tubes 180 degrees and back 10 times to ensure adequate mixing
- Maintain blood at room temperature (6ºC to 37ºC) until shipping. **Do Not** place Streck tubes in refrigerator. Ship the day of collection.

10.2.3 Peripheral Blood [SST Red Top Tube]

10.2.3.1 Collection Time Points:

- Start of treatment [Step 2 pre-chemoRT/prior to week one (1)/day one (1)]
- Post-chemoRT at Restaging [week 16]

10.2.3.2 Preparation Guidelines

- Collect 10mL of whole blood into one (1) SST red top tube.
- Invert tube gently 8-10 times to ensure proper mixing
- Package and ship the day of collection at ambient temperature (no wet or dry ice and no cool packs).

10.3 Shipping Procedures

Pathology materials from diagnostic and restaging TURBT biopsies are to be shipped at ambient temperature (cool pack in warm weather) within one month following randomization or collection.

Fresh cut tissue slides must be shipped overnight within one (1) week of sectioning on refrigerated gel packs.

Whole blood is to be shipped day of collection at ambient temperature Monday-Thursday via overnight courier.

Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the specimens.

Access to the FedEx shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your institution needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

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MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713)-563-6506

10.4 Use of Specimens in Research

EA8185 has several proposed correlative objectives, including PD-L1, MRE11, and ctDNA. Specimens are being collected to determine potential predictive and prognostic markers.

An amendment or proposal for any additional correlative science studies to be performed on biological specimens will be submitted to CTEP/NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological specimens will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Specimens for testing will not be released until the appropriate NCI approvals have been obtained.

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de–identified prior to distribution for any approved research projects.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the institution. All other specimens will be destroyed per guidelines of the respective repository.

10.5 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu .

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.6 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Electronic Data Capture

Please refer to the EA8185 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave

11.1 Data Mapping Utility (DMU) Monitoring

DMU Monitoring is performed by ECOG-ACRIN.

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.html).

NOTE: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

11.2 The Data Quality Portal (DQP)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

11.3 ECOG-ACRIN Radiation Oncology Quality Assurance Materials

Summary of the Required Dosimetry Digital Data Submission to TRIAD

Within 7 days of the initiation of treatment, the following data must be submitted to TRIAD unless the case requires a Pre-Treatment review.

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Required Submission to TRIAD		Cases Requiring Pre-Treatment Review	Cases Requiring Post-Treatment Review
DICOM DIGITAL DATA	DICOM CT Data Set DICOM RT Structure DICOM RT Dose (1-3 files*) DICOM RT Plan *A composite dose file is required for submission, if the data can be exported from planning system **NOTE: Digital Data for all treatment fields must be included in one TRIAD submission only.**	***Due within 7 days of Step 1 Randomization*** **TRIAD submission time point =** ***RT DIGITAL PLAN*** **Pre-Treatment Review Cases** First case registered by each Institution requires a Pre-Treatment Review	***Due within 7 days of the start of RT*** **TRIAD submission time point =** ***RT DIGITAL PLAN*** **Post Treatment Review Cases** All cases which do not require Pre-Treatment Review
All required structures MUST be labeled per the table in Section 5.3.5 and 5.3.8.			
Digital Data Submission Information Form (DDSI) Upon submission of the digital data via TRIAD, complete an online Digital Data Submission form https://www.irocqa.org/Resources/TRIAD-for-RT-QA.			
NOTE: All Simulation/DRR and Portal Images will be archived at the Institution and only submitted, if requested			

Within 7 days of RT End Date the following RT data is required in Rave:

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- Upload a copy of the anonymized RT Treatment Record with documentation of the Daily Date, Fraction #, Daily Dose column and the Treatment Prescription page which has the Radiation Oncologist's treatment prescription for the case PRIOR to the start of RT included.
- Complete Radiation Treatment Summary Form.
- Complete Protocol Specific Form.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

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Journal of Clinical Oncology 2021 39:6_suppl, 398-398

Rev. Add3 **Phase II Study of Bladder-Sparing ChemoradiatioN with Durvalumab in Clinical Stage III, Node Positive bladdeR CancEr (INSPIRE)**

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

Guidelines for Submission of Pathology Materials

The following pathology materials are to be submitted within one (1) month of randomization or collection.

1. Pathology Submissions
   - Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks and three (3) H&E stained slides from the pretreatment diagnostic TURBT biopsy (prior to starting chemoRT +/- durvalumab within eight (8) weeks of starting treatment preferred, if not available, previous TURBT specimen is acceptable)
   - Representative formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks and three (3) H&E slides from TURBT biopsy at the time of restaging (prior to starting adjuvant radiation or surveillance)

   NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:
   - Three (3) H&E slides
   - Ten (10) 10 µm and five (5) 4 µm unstained, positively charged, air-dried plus slides from the thickest part of the tumor (Superfrost Plus recommended). After cutting, the slides should be kept refrigerated (2-5°C) until shipment or dried overnight between ambient temperature and 37°C.
   - Two (2) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

   If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.
2. Forms and Reports

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including pathologists).

   The following items are to be included with the pathology materials:
   - Institutional Diagnostic and Surgical Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981v3) [If STS is unavailable]
   - Sample Tracking System (STS) Shipping Manifest Form
   - Immunological study reports, if available
3. Mail pathology materials to:

   MD Anderson Cancer Center CBPF
   Mike Balco
   Life Science Plaza - Suite 910
   2130 West Holcombe Boulevard, LSP9.4227
   Houston, TX 77030
   Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)

Fax: (713)-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions, contact the pathology coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

ECOG-ACRIN cancer research group
Reshaping the future of patient care
Operations Office

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA8185: Phase 2 Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage 3, node PosItive BladdeR CancEr (INSPIRE)

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requests the submission of pathology materials for future undefined research studies.

Please return the diagnostic and surgical pathology reports, the slides and/or blocks and any other required materials to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

Appendix III

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.”):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on durvalumab or within 28 days of the female patient's last dose of durvalumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm the pregnancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave.

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERS accessed via Medidata Rave.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female patient be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* and separate CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

For this study, it must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm the pregnancy loss requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to durvalumab must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm the neonatal death requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any

additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

Phase II Study of Bladder-SparIng ChemoradiatioN with Durvalumab in Clinical Stage III, Node PosItive bladdeR CancEr (INSPIRE)

Appendix VI

EA8185 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. It is preferred that baseline kit requests are made after patient consent, at a minimum the patient must be considered a candidate for consent and randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact
  - Protocol Number (REQUIRED): EA8185
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): Type in the kit type needed
  - EA8185 Collection Kit
  - Quantity: 1
  - Comments: Provide EA8185 Patient Case ID# and full shipping address
  - Patient Case ID =' #####
  - *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
  - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.