Phase 2 Open Label Study of Durvalumab with Neoadjuvant Chemotherapy in Variant Histology Bladder Cancer

Coordinating Center
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305

Protocol Director:
Sandy Srinivas, MD
875 Blake Wilbur Dr, Stanford, CA 94305
Telephone: 650-725-2078
Fax: [redacted]
e-mail: sandysri@stanford.edu

Sub-Investigators:

Alice Fan, MD
875 Blake Wilbur Dr, Stanford, CA 94305
e-mail: [redacted]

Sumit Shah, MD
875 Blake Wilbur Dr, Stanford, CA 94305
e-mail: SAS7@stanford.edu

Biostatistician
[redacted]
e-mail: [redacted]

Study Coordinator:
[redacted]
e-mail: [redacted]

Study Coordinator:
Evandro [redacted]
Email: [redacted]

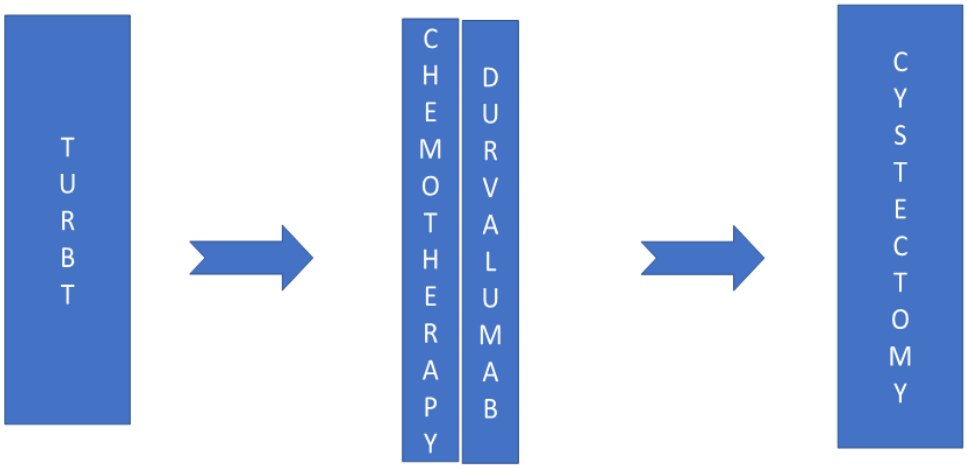
IRB-48062 **OnCore BLDR0028** **NCT03912818**

Amendment 5 dated 31 JAN 2020

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

TITLE	Phase 2 Open Label Study of Durvalumab with Neoadjuvant Chemotherapy in Variant Histology Bladder Cancer
STUDY PHASE	Phase 2
INDICATION	Bladder Cancer with variant histology
STUDY AGENT	**Durvalumab** (MEDI4736), at 750 mg or 1500 mg fixed dose, administered intravenously (IV) over 60 minutes. See Section 4 Treatment Plan for exact dose and schedule by cohort.
OTHER AGENTS	Chemotherapeutic agents will be administered as an IV infusion according to prescribing information or treatment guidance in general use by the Investigating site **Methotrexate** 30 mg/m^2 on Cycle Day 1 **Gemcitabine** 1,000 mg/m^2 on Cycle Day 1 (and Cycle Day 8 for some cohorts) **Carboplatin:** AUC 5 on Cycle Day 1 **Cisplatin** 70 mg/m^2 on Cycle Day 1 or 2 **Vinblastine** 3 mg/m^2 on Cycle Day 2 **Doxorubicin** 30 mg/m^2 on Cycle Day 2 See Section 4 Treatment Plan for the exact agents, dose, and schedule by cohort. Additional supportive care agents, as needed: Filgrastim 5 µg/kg subcutaneous (SC) Pegfilgrastim 6 mg SQ
PRIMARY OBJECTIVE	To assess the safety and tolerability of durvalumab in combination with chemotherapy in subjects with variant histology bladder cancer
SECONDARY OBJECTIVES	To determine the percent of subjects post-neoadjuvant chemo-immunotherapy who achieve tumor stage of pT2 N0 M0 or better (pT1 N0 or pT0) at cystectomy • To assess the response rate (RR) in post-neoadjuvant chemo immunotherapy as assessed by the Investigator using imaging at screening and post treatment • To assess the molecular characterization of tumor tissue pre-neoadjuvant therapy and at post-treatment cystectomy (for subjects who have persistent disease) • To determine cell-free DNA at baseline, during treatment and following post-treatment cystectomy using Natera platform

TREATMENT SUMMARY	This study is designed to evaluate the safety and antitumor activity of the combination of durvalumab and chemotherapy for the treatment of subjects with variant histology bladder cancer in the neoadjuvant setting. All subjects will receive durvalumab, the investigational agent under study, administered as an intravenous (IV) infusion on Day 1 of each cycle for a total of 4 cycles. Standard chemotherapy will be administered as an IV infusion during each of the 4 cycles. Choice of standard chemotherapy is between the following treatments at the discretion of the treating physician: • Dose-Dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin (DD MVAC), in 14-day cycles (2 weeks) • Cisplatin + Gemcitabine (Cis-Gem), in 21-day cycles (3 weeks) • Carboplatin + Gemcitabine (Carbo-Gem), in 21-day cycles (3 weeks) Design  The population to be studied includes subjects with newly-identified bladder cancer with variant histology.
ELIGIBILITY CRITERIA	Eligible participants will be cancer patients with histologically-proven carcinoma of the bladder of variant urothelial carcinoma histology. Due to length, the Eligibility Criteria are only presented in one instance. See Section 3 Participant Selection and Enrollment Procedures
SAMPLE SIZE	24 subjects will be enrolled in this study
STATISTICAL CONSIDERATIONS	**Sample Size Determination:** N = 24. This is a rare population and very limited data are available. The rich correlative study will allow us to design larger trials in the future

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BP	Blood pressure
BSA	Body surface area
CBC	Complete blood count
cfDNA	Circulating free DNA OR cell-free DNA
ctDNA	Circulating tumor DNA
Carbo-Gem	Carboplatin + gemcitabine
CI	Confidence interval
Cis-Gem	Cisplatin + gemcitabine
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DD MVAC	Dose-Dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IDS	Stanford Investigational Drug Service
IRB	Institutional Review Board
IP	Investigational Product
IV	Intravenous
LLN	Lower limit of normal
MIBC	Muscle invasive bladder cancer
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression-free survival
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SC	Subcutaneous
SD	Stable disease
SOC	Standard of care
TTP	Time-to-progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

- To assess the safety and tolerability of durvalumab in combination with chemotherapy in subjects with variant histology bladder cancer

1.2. Secondary Objectives

- To determine the percent of subjects post-neoadjuvant chemo-immunotherapy who achieve tumor stage of pT2 N0 M0 or better (pT1 N0 or pT0) at cystectomy
- To assess the response rate (RR) in post-neoadjuvant chemo immunotherapy as assessed by the Investigator using imaging at screening and post treatment
- To assess the molecular characterization of tumor tissue pre-neoadjuvant therapy and at post-treatment cystectomy (for subject who have persistent disease)
- To determine circulating free DNA (cfDNA) (alternate term “cell-free DNA”) at baseline, during treatment and following post-treatment cystectomy using Natera platform

2. BACKGROUND

2.1. Study Disease

It is estimated that there will be 74,690 new cases and 15,580 deaths from bladder cancer in the United States in 2018. The majority of cases are non-muscle invasive and are treated by cystoscopic resection, with or without intravesical medical therapy instilled directly into the bladder. For those with muscle-invasive disease, therapy consisting of a radical cystectomy or definitive radiation therapy is indicated. Even with these radical treatments, the mortality from muscle- invasive bladder cancer remains high. Despite the survival advantage associated with its use, neoadjuvant chemotherapy remains poorly utilized in general medical practice in the United States. One explanation for the low utilization of neoadjuvant chemotherapy is the concern that some patients with surgically curable disease will become chemotherapy-resistant and may progress during treatment with neoadjuvant chemotherapy, thus be rendered incurable. This protocol will examine the utility of neoadjuvant chemotherapy combined with durvalumab in subjects with variant histology bladder cancer.

Chemotherapy for Bladder Cancer

The mainstay of contemporary, cytotoxic chemotherapy for advanced bladder cancer has been cisplatin-based combination therapy. MVAC chemotherapy was designed in the mid 1980’s and came into general use in the 1990’s. (Sternberg, 1985) When compared to single-agent cisplatin, MVAC was associated with improved response rates and survival, although the regimen produced notable toxicity, mainly hematologic, gastrointestinal and infectious. The doublet of gemcitabine and cisplatin was later recognized to also have significant activity against urothelial cancer. In a randomized, phase 3 study, 405 subjects with Stage IV transitional cell carcinoma were given MVAC vs Cis-Gem. (Von der Maas, 2008) The response rates between the arms were similar (Cis-Gem, 49%; MVAC 45%) as was the overall and

progression-free survival (PFS). The side effects, especially those related to bone marrow suppression (neutropenic fever: 1% for Cis-Gem; 12% for MVAC), were greater in the MVAC arm as compared to Cis-Gem-treated subjects. The long-term results of this study have been reported with a median overall survival (OS) of 14.0 months with Cis-Gem vs 15.2 months with MVAC (p = 0.66).

In the phase 3 trial of Cis-Gem vs MVAC, Cis-Gem was given on a 28-day schedule, the same duration as the traditional MVAC cycle. In regimens utilizing a 28-day cycle of Cis-Gem, gemcitabine is given on Days 1, 8, and 15, although the Day 15 dose is oftentimes delayed or skipped due to bone marrow suppression, notably thrombocytopenia. With this recognition, a 21-day Cis-Gem regimen, with gemcitabine given on Days 1 and 8 only, was investigated. In one retrospective analysis, 212 subjects with Stage IV transitional cell carcinoma were treated with either 21- or 28-day. The response rate between the 2 schedules was similar, with an overall response rate of 59.7% with the 3-week and 55.6 % with the 4-week regimen; the complete response rate was 21% in both arms. Treatment compliance was improved with the 21-day schedule; with only 19% requiring dose modification in the 21-day arm, vs 62% in the 28-day group, with 47% in the latter required to omit Day15 gemcitabine. The rate of febrile neutropenia in the 21-day arm of this study was less than 10%. A smaller, single arm study of 21-day Cis-Gem in 27 bladder cancer patients demonstrated a strong overall response rate of 48% without any Grade 4 toxicity or treatment-related death. In addition, a randomized study of 107 patients with mixed cancer types (predominately lung cancer) examined the safety and efficacy of 21- vs 28-day Cis-Gem. (Soto, Ann Oncol, 2002) The 3-week schedule was better tolerated, with less Grade 3/4 thrombocytopenia (29.5% vs 5.5%) and less delays or dose reductions (51% vs 19%). Only the lung cancer patients were analyzed for response rate, since they represented the majority of the enrolled subjects, and these rates were similar between the arms. In summary, even though the randomized phase 3 trial of Cis-Gem vs MVAC used 28-day Cis-Gem schedule, subsequent studies have reported improved tolerance, dose-density and preserved efficacy with 21-day Cis-Gem.

In a parallel fashion, efforts were undertaken to improve the tolerability and dose-density of MVAC. Early reports of the use of hematologic growth factor support found that dose escalation of MVAC in urothelial carcinoma patients was possible and such an approach was associated with a favorable response rate. With this emerging information, Sternberg, *et al* pursued a randomized phase 3 trial of high-dose intensity MVAC with granulocyte colony-stimulating factor (G-CSF) vs traditional MVAC in 263 advanced urothelial patients. (Sternberg Ann Oncol, 1993) There was a complete response rate (CRR) of 21% and an overall response rate (ORR) of 62% with high-dose MVAC, compared to a CRR or 9% and ORR of 50% with standard-dose MVAC; the p value for the CR difference was 0.009. Neutropenic fever was more common with standard-dose MVAC (26% vs 10%), although this may be attributed to the disproportionate use of GCSF on the high-dose (94%) compared to the standard-dose (19%). In an updated report, with 7 years of follow-up, 24.6% were alive in the high-dose, vs 13.2% in the standard-dose MVAC arms. (Sternberg, Eur J Cancer, 2006) While the median survival was similar between the 2 groups (15.1 vs 14.9 months), the overall mortality hazard ratio (HR) did favor high-dose MVAC (0.76; 95% CI, 0.58 to 0.99). Taken together, high- dose MVAC allows for more dose density, with lower toxicity and improved markers of efficacy.

317 subjects with T2-T4aNxM0 urothelial carcinoma of the bladder were randomized to 3 cycles of cisplatin and methotrexate vs no neoadjuvant chemotherapy. (Grossman NEJM, 2003) The

rate of complete pathologic response (pT0) was higher in the chemotherapy group (26.4%) compared to the non-chemotherapy group (11.5%) (p = 0.001), with the pT0 finding in the control arm likely attributable to complete transurethral resection of the tumor pre-operatively. The 5-year overall survival (OS) was improved in absolute terms by 7%, from 46% to 53%, with neoadjuvant chemotherapy, although this was not statistically significant in this relatively small study. With these and several other small randomized trials available, a meta-analysis of platinum-based neoadjuvant chemotherapy in patients with muscle- invasive bladder cancer was published in 2003. This work found a significant survival benefit with neoadjuvant chemotherapy, yielding a HR of 0.87 (95% CI, 0.78 to 0.98). A second meta- analysis on this topic was performed in 2004 and included 8 randomized trials of cisplatin combination neoadjuvant therapy, with a pooled HR for OS of 0.87 (95% CI, 0.78 to 0.96). This work also noted that a major pathologic response was associated with OS in 4 trials, supporting the use of pT0 rates as a marker of survival.

Two randomized studies were launched in the late 1980's to specifically assess the utility of MVAC and CMV chemotherapy in the neoadjuvant bladder cancer setting, as these regimens emerged as more effective than single-agent cisplatin. SWOG 8710 enrolled 317 subjects with T2-T4aN0M0 bladder cancer, randomizing subjects to 3 cycles of standard-dose (28-day) MVAC vs no chemotherapy before cystectomy. The median survival was improved in the experimental arm (77 vs 44 months) with a p = 0.06, favoring chemotherapy. The proportion of subjects with a pT0 at the time of surgery was also increased in the MVAC arm, 38% vs 15% (p < 0.001). In an important post-hoc analysis of SWOG 8710, the significance of mixed histology (pure urothelial carcinoma versus a proportion of urothelial carcinoma) was analyzed. Among those with mixed tumors, there was a clear survival advantage (HR 0.46; 95% CI, 0.25 to 0.87), supporting the use of neoadjuvant, cisplatin-based chemotherapy in those with a component of squamous or glandular differentiation in addition to urothelial carcinoma in their tumor.

A second, European-led neoadjuvant study was larger and enrolled 976 subjects with T2 (Grade 3), T3-T4a N0M0 urothelial cancer of the bladder in subjects planning for either cystectomy or definitive external beam radiation therapy. (Lancet, 1999) Participants were randomized to a 21-day cycle of cisplatin-methotrexate-vinblastine (CMV) chemotherapy for 3 cycles versus no chemotherapy. For the 417 subjects undergoing cystectomy, the pathologic response rate (pT0 at the time of surgery) was 32.5% with chemotherapy vs 12.3% without. An update of the survival results was subsequently published with 8 years of follow-up. Combining both the radiation and surgery groups, neoadjuvant chemotherapy was associated with a 16% reduction in the risk of death (HR, 0.84; 95% CI, 0.72 to 0.99) and an improvement in the 10-year survival from 30% to 36%. Considering the surgical cystectomy subjects alone, the reduction in the risk of death was 26% (HR, 0.74; 95% CI, 0.57 to 0.96; p = 0.022).

As noted, since the initiation of these phase 3 neoadjuvant studies of MVAC and CMV chemotherapy, Cis-Gem has become a standard approach in advanced urothelial carcinoma, frequently favored over the more toxic MVAC regimen. There is a limited amount of clinical data for the use of Cis-Gem in the neoadjuvant setting. In one report from investigators at Memorial Sloan-Kettering, the results of 42 bladder cancer patients given 21-day neoadjuvant Cis-Gem was reported and compared historical controls given MVAC. The pT0 proportion was 26% with Cis-Gem, compared to 28% with the historical MVAC group. They also assessed < pT2 rate, which was 36% with Cis-Gem, vs 35% with MVAC.

The prognostic importance of the pathologic T staging pT0 at the time of radical cystectomy is associated with long-term and survival outcomes in bladder cancer patients. In the SWOG 8710 trial, regardless of treatment arm, the finding of pT0 at the time of surgery correlated with survival. (Grossman NEJM, 2003) In a subsequent analysis, the impact of pT0 vs < pT2 (pT0, pTa, pTis, and pT1) on survival was analyzed. In the chemotherapy arm, pathologic findings of < pT2 was observed in 44%, with 30% having pT0. The pT0 rate is lower in this analysis compared to the original New England Journal of Medicine publication, as patients who did not actually receive any chemotherapy were also included. Those with pT0 had a median OS of 13.6 years, those with pT1/pTis/pTa had a median OS of 10.6 years, while those with pT2 or great disease at surgery had a median OS of just 3.7 years. (Sonpavade Cancer, 2009) The impact of pathologic stage on long-term outcomes were also evaluated in 2230 patients with radical cystectomy, but no adjuvant chemotherapy. They found 5.1% had pT0 at the time of surgery; with a median follow-up of 48 months, 10.1% of these pT0 patients had recurrent disease. Of note, the recurrence-free outcomes were similar between the pT0 and pTa/pTis patients ($p = 0.557$). Taken together, these data suggest the prognostic significance of both pT0 and < pT2 at the time of cystectomy.

Carboplatin-based chemotherapy has shown to be inferior to cisplatin-based chemotherapy in the metastatic setting. In general, if patients have abnormal creatinine that does not allow cisplatin-based chemotherapy they undergo cystectomy rather than neoadjuvant chemotherapy. Based on the rarity of the data in variant histology we will allow patients to get carboplatin-based chemotherapy if creatinine clearance < 50cc.

2.2 Study Agent Durvalumab

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors. (Dunn, 2004)

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir, *et al*, 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo, 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin, *et al*, 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll, 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T-cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While

functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer, 2012; Hirano, 2005; Iwai, 2002; Okudaira, 2009; Topalian, 2012; Zhang, 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1(Powles, 2014; Rizvi, 2015, Segal, 2015) . In addition, high mutational burden (eg, in bladder carcinoma) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife, 2008). Blockade of CTLA-4 binding to CD80/86 by anti–CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

2.3 Durvalumab Background / Non-Clinical and Clinical Experience

The non-clinical and clinical experience is fully-described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly-owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart, *et al*, 2015). *In vivo*

studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart, *et al*, 2015). Based on these data, durvalumab is expected to stimulate the subject's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

PK/Pharmacodynamic Data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥ 3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥ 3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab.

A population PK model was developed using the data from Study 1108 (doses 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman, 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical Data

The current durvalumab Investigator's Brochure is available for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20 mg/kg Q4W regimen.

Rationale For Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a phase 1 study (study 1108; N = 292; doses 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors).

Population PK analysis indicated only minor impact of body weight (WT) on 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 (Ng, 2006, Wang, 2009, Zhang, 2012, Narwal, 2013). 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 (Wan, 2009)]. 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 (Zhang, 2012).

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. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

Durvalumab is FDA-approved for the treatment of bladder cancer. This study is planned to be conducted as IND-exempt.

2.3 Rationale

Neoadjuvant chemotherapy followed by cystectomy is standard of care in patients with newly-diagnosed urothelial cancer of the bladder; outcome in patients with variant histology is less well known.

Patients achieving a pT0 or < T2 following neoadjuvant chemotherapy have good outcomes with low risk of relapse. The likelihood of achieving > pT2 is 30% with cisplatin-based chemotherapy in patients with classic urothelial cancer and variable with “variant histology” group. Patients with variant histology need better combination therapies to increase the rate of pT0 or < pT2.

Rationale for Dose Selection: The standard dosing chemotherapy regimens that have been well established and described previously along with standard dose of durvalumab will be used in this study. Given that the timing of chemotherapy is variable in the 3 regimens selected durvalumab will be dosed at 750 mg day 1 of each cycle for DD MVAC and 1500 mg in the cis/gem and carbo/gem arms.

2.4 Study Design

This study is designed to evaluate the safety and antitumor activity of the combination of durvalumab and chemotherapy for the treatment of subjects with variant histology bladder cancer in the neoadjuvant setting. Variant bladder cancer histologies include: squamous differentiation; glandular differentiation; nested variant; microcystic variant; micropapillary variant; lymphoepithelioma-like carcinoma; plasmacytoid and lymphoma-like variants;

sarcomatoid variant/carcinosarcoma; giant cell variant; trophoblasitic differenetation; clear cell variant; lipid cell variant; and undifferentiated carcinoma. This is a single arm open label non-randomized trial with the primary objective to assess the safety and tolerability of durvalumab in combination with chemotherapy in subjects with variant histology bladder cancer. Secondary objectives include determining the percent of subjects post-neoadjuvant chemo-immunotherapy who achieve tumor stage of pT2 N0 M0 or better (pT1 N0 or pT0) at cystectomy; assessing the molecular characterization of tumor tissue pre-neoadjuvant therapy and at post-treatment cystectomy (for subjects with have persistent disease); and to determine cell-free DNA at baseline, during treatment and following post-treatment cystectomy using Natera platform.

All subjects will receive durvalumab, the investigational agent under study, administered as an intravenous (IV) infusion on Day 1 of each cycle in combination with neoadjuvant chemotherapy. Subjects will be treated for 4 cycles of durvalumab and chemotherapy followed by cystectomy.

Response will be assessed by pathological staging post-cystectomy.

2.5 Correlative Studies Background

Recent work has suggested that transitional bladder cancer, has a complex mutational signature including on average 300 exonic mutations, 200 segmental alterations, and 22 genomic rearrangements (Nature. 20 March 2014;507:315 to 322). Genomic instability is a hallmark of cancer, with recent studies suggesting that DNA repair pathway dysregulation is common across multiple cancer types (Lawrence, *et al*, Nature, 2014). Germline and / or somatic alterations in pathways controlling homologous recombination, microsatellite instability, and non-homologous end joining have been implicated across multiple cancer types, most notably breast and ovarian cancer (Aleshin, *et al*, Current Breast Cancer Reports, 2017). In urothelial bladder cancer, upwards of 10% of cases have been shown to have defects in homologous recombination pathways (Heeke, *et al*, ASCO, 2017). There is also early evidence to suggest patients with defective DNA repair pathways are most likely to benefit from platinum-based chemotherapy (Bellmunt, *et al*, Ann Onc, 2007, Van Allen, *et al*, Cancer Disco, 2014). However, comprehensive assessment on the genomic landscape of bladder cancer with “variant histology” is lacking, and even less is known about predictive biomarkers associated with treatment response.

Measurement of tumor-specific mutations in plasma and urine is emerging as a powerful tool for cancer treatment and recurrence monitoring. Circulating tumor DNA (ctDNA) is released into circulation and can be recovered from a variety of body fluids, including plasma and urine (Wan, *et al*, Nat Rev Cancer, 2017). Previous work has suggested that ctDNA is detectable in patients with bladder cancer and that rising levels of ctDNA are associated with disease progression and early detection of metastatic relapse (Kirkenkamp, *et al*, Eur Urology, 2017). Furthermore, novel ctDNA measurement techniques allow for creation of personalized probe sets that allow for serial measurement of both clonal and subclonal mutations during and after definitive treatment (abbosh, *et al*, Nature, 2017).

In this study we propose corelative studies including whole exome sequencing on tissue to characterize the genomic landscape of bladder cancer with “variant histology.” Furthermore, sequential plasma collection will be used to characterize the evolution of subject-specific circulating tumor DNA (ctDNA) signatures, as well as, evaluate early plasm- based markers of

disease resistance and relapse. We will also analyze tumor mutational burden and correlate that to response

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Eligibility Criteria and Participant Eligibility Checklist

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist, following, and which may be extracted for use in screening potential subjects.

The following Participant Eligibility Checklist will be completed in its entirety for each subject prior to start of Cycle 1 Day 1. The completed, signed, and dated checklist will be retained in the subject's study file.

Pursuant to Stanford Medicine SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator); the Study Coordinator; and an Independent Reviewer will verify that the subject's eligibility is accurate; complete; and legible in source records. A description of the eligibility verification process will be included in the EPIC or other Electronic Medical Record progress note.

Participant Eligibility Checklist

For each prospective study participant that is screened, this checklist will be printed, the results recorded, and filed in the respective subject binder or file. It is anticipated that not all prospective study participants will be enrolled.

I. Protocol Information

Protocol Title:	Phase 1-2 Open Label Study of Durvalumab with Neoadjuvant Chemotherapy in Variant Histology Bladder Cancer
eProtocol number: **OnCore number:**	IRB-48062 BLDR0028 Amendment 2
Principal Investigator:	Sandy Srinivas, MD

II. Subject Information

Subject ID: SCI - __ __ __			
Regimen Type:	☐ DD MVAC	☐ Cis/Gem	☐ Carbo/Gem
Gender	☐ Male	☐ Female	

III. Study Information

3.2 Inclusion Criteria

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	**Yes**	**No**	**Supporting Documentation ***
1. Signed Informed Consent	☐	☐	
2. Age ≥ 18 years at time of study entry	☐	☐	
3. Eastern Collaborative Oncology Group (ECOG) Performance Status score of 0 or 1	☐	☐	
4. Body weight > 30kg	☐	☐	

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	**Yes**	**No**	**Supporting Documentation ***
5. Adequate hematologic and organ function within 28 days before the first study treatment, defined using the following: • Absolute neutrophil count (ANC) ≥ 1500 mm^3 • Hemoglobin ≥ 9.0 g/dL • Platelet count ≥ 100,000 per mm^3 • Serum bilirubin ≤ 1.5 × upper limit of normal (ULN). Subjects with Glibert's syndrome will be considered after consultation with the PI. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN • For subjects who will be treated with DD MVAC or Cis-Gem, creatinine clearance ≥ 50 mL/min as measured based on Cockroft-Gault glomerular filtration rate estimation • For subjects who will be treated with Carbo-Gem, creatinine clearance ≥ 30 mL/min as measured based on Cockroft-Gault glomerular filtration rate estimation Cockcroft-Gault Equation Males: $\frac{(140 - age) \times (weight\ in\ Kg)}{72 \times (serum\ Creatinine)}$ Females: $\frac{(140 - age) \times (weight\ in\ Kg) \times 85}{72 \times (serum\ Creatinine)}$	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ N/A (Carbo subject) ☐ N/A (Cis subject)
6. Anticipated life expectancy of ≥ 12 weeks as assessed by the Investigator	☐	☐	
7. Histologically-proven carcinoma of the bladder of variant urothelial carcinoma histologies which include squamous, adenocarcinoma, nested, plasmacytoid, micropapillary, glandular differentiation, lipid cell, clear cell, undifferentiated, giant cell, trophoblastic, sarcomatoid, carcinosarcoma; subjects with mixed cell types are eligible	☐	☐	
8. Stage cT2-T4a, N0-N1, M0 disease. Clinical T stage is based on the TURBT sample and imaging studies. Subjects must undergo cystoscopy and TURBT as part of screening within 60 days prior to start of Cycle 1 Day 1	☐	☐	
9. Abdominal/pelvic imaging by CT or MRI scan; chest imaging by CT scan or x-ray (CT/PET) within 30 days prior to start of Cycle 1 Day 1	☐	☐	
10. Resting 12-lead electrocardiogram (ECG) documenting QTcF ≤ 470 ms	☐	☐	
11. Must provide a formalin-fixed paraffin-embedded (FFPE) tissue block and 1 H&E slide (preferred) or one of the following: • 10 unstained slides and 1 H&E slide OR • Tissue block punches and 1 H&E slide, OR • 4 to 6 cores and 1 H&E slide	☐	☐	

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
12. Willing and able to comply with the protocol for the duration of the study including undergoing treatment, scheduled visits and examinations including follow up.	☐	☐	
13. For Female Subjects: • Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). • Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).	☐	☐	☐ N/A (male subject)

3.3 Exclusion Criteria

Prospective Participants Must NOT Match ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
1. Prior treatment with systemic cytotoxic chemotherapy for muscle invasive bladder cancer (MIBC)	☐	☐	
2. *For Carboplatin patients only:* Class III or IV heart failure, according to New York Heart Association Classifications	☐	☐	☐ N/A (non-carbo subject)
3. *For Cisplatin patients only:* Left ventricular ejection fraction of less than normal	☐	☐	☐ N/A (non-cis subject)
4. Administration of an investigational therapeutic agent within 28 days of protocol start of Cycle 1 Day 1	☐	☐	
5. Current participation in a trial using an investigational agent. Subjects may participate in non-interventional, observational studies	☐	☐	
6. Prior treatment with an anti-PD1 or anti-PDL1 inhibitor including durvalumab	☐	☐	
7. Receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent per day within 7 days prior to the first dose of study treatment)	☐	☐	

Prospective Participants Must <u>NOT</u> Match <u>ANY</u> of These Exclusion Criteria	**Yes**	**No**	**Supporting Documentation ***
8. History of another malignancy within 5 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with the following are allowed on study: • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer *in situ*	☐	☐	
9. Immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion: a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection) b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) or anti emetic during chemotherapy	☐	☐	
10. History of allogenic organ transplantation	☐	☐	
11. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease]), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion: a. Subjects with vitiligo or alopecia b. Subjects with hypothyroidism (eg, following Hashimoto Syndrome) stable on hormone replacement c. Any chronic skin condition that does not require systemic therapy d. Subjects with celiac disease controlled by diet alone	☐	☐	
12. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent	☐	☐	
13. History of active primary immunodeficiency	☐	☐	

Prospective Participants Must <u>NOT</u> Match <u>ANY</u> of These Exclusion Criteria	**Yes**	**No**	**Supporting Documentation ***
14. Active infection including: • Tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice) • Hepatitis B (positive HBV surface antigen (HBsAg) result) *Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.* • Hepatitis C *Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA* • Human Immunodeficiency Virus (positive HIV 1/2 antibodies).	☐	☐	
15. Receipt of live attenuated vaccine within 30 days prior to the first dose of Study medication. Note: Subjects, if enrolled, should not receive live vaccine whilst receiving study medication and up to 30 days after the last dose of study medication	☐	☐	
16. Pregnant or lactating	☐	☐	☐ N/A (male subject)
17. Male or female subject of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab	☐	☐	
18. Known allergy or hypersensitivity to any of the study medications or any of the study medication excipients	☐	☐	
19. Judgment by the investigator that the subject is unsuitable to participate in the study and the subject is unlikely to comply with study procedures, restrictions and requirements	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is: ☐ eligible / ☐ ineligible for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the IRB of record, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator printed name:	Date:
Signature:	

Investigator printed name:	Date:
Signature:	

Triple-check reviewer printed name:	Date:
Signature:	

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants or the participant's legally authorized representative must sign the IRB approved informed consent prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

Primary Completion

The study is expected to reach the primary completion date 30 months from the time the first subject is treated on the study.

Study Completion

It is estimated that the study will reach completion 36 months from the time the first subject is treated on the study.

4. TREATMENT PLAN

Screening Visit (Day -30 to Day 1)

The following will be conducted at the screening visit.

- Informed consent
- Medical history and demographics
- Review of prior and concomitant medications
- Initial collection of tumor specimen for genomic sequencing (Natera)
- Blood sample for cell-free DNA (cfDNA)
- CT or MRI abdomen/pelvis preferable. PET-CT for subjects with impaired renal function is an acceptable alternative.
- CT or X-ray of chest
- Bone scan is necessary if bone metastases are suspected (elevated alkaline phosphatase).
- Vital signs, weight and height
- Physical exam
- ECOG performance status
- 12-lead ECG
- CBC with differential

- Comprehensive metabolic panel (Magnesium is to be performed at baseline on Day 1 and as clinically indicated)
- Serology for hepatitis B
- Serology for hepatitis C
- Serology for Human Immunodeficiency Virus
- TSH
- Coagulation (PT, PTT, INR)
- Creatinine clearance
- Urinalysis
- Serum pregnancy test (for women of childbearing potential only)
- Study eligibility per inclusion/exclusion criteria

Treatment Period Assessments, all cohorts, for each cycle (Cycles 1 to 4)

For DD MVAC Cohort ONLY, pre-dose on Day 1, and on Day 2

- Vital signs
- Physical exam (only on Day 1 of each Cycle)
- ECOG performance status (only on Day 1 of each Cycle)
- CBC with differential
- Comprehensive metabolic panel

For Cis-Gem & Carbo-Gem Cohorts ONLY, pre-dose on Day 1, and on Day 8

- Vital signs
- Physical exam (only on Day 1 of each Cycle)
- ECOG performance status (only on Day 1 of each Cycle)
- CBC with differential
- Comprehensive metabolic panel

Treatment Administration per Cycle

- **DD MVAC Cohort: Durvalumab + Dose-dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin (DD MVAC)**

IMPORTANT CLINICAL NOTE:
Durvalumab dose for DD MVAC
DIFFERS from Cis-Gem or Carbo-Gem

Treatment with **Durvalumab plus DD MVAC** is on a 14-day cycle as described below:

On Day 1 of each 14-day cycle, the following treatments will be administered as IV infusions:

- **Durvalumab** at a fixed dose of **750 mg** administered IV over approximately 60 minutes on Day 1 of each cycle

Chemotherapeutic agents will be administered as an IV infusion according to prescribing information or treatment guidance in general use by the Investigating site:

- **Methotrexate** at a fixed dose of 30 mg/m^2 IV on Day 1 of each cycle

On Day 2 of each 14-day cycle. The following treatments will be administered as an IV infusion:

- **Vinblastine** 3 mg/m^2 IV on Day 2 of each cycle
- **Doxorubicin** 30 mg/m^2 IV on Day 2 of each cycle
- **Cisplatin** 70 mg/m^2 IV on Day 2 of each cycle

Additionally, the following supportive care will be administered as needed:

- Filgrastim 5 µg/kg by subcutaneous (SC) administration per institutional SOC (alternative to filgrastim: Pegfilgrastim 6 mg SC per institutional SOC)

- **Cis-Gem Cohort: Durvalumab plus Cisplatin + Gemcitabine**

IMPORTANT CLINICAL NOTE:
Durvalumab dose for Cis-Gem (& Carbo-Gem)
DIFFERS from DD MVAC

Treatment with **Durvalumab plus Cis-Gem** is on a 21-day cycle as described below:

On Day 1 of each 21-day cycle, the following treatments will be administered as an IV infusion:

- **Durvalumab** at a fixed dose of **1500 mg** administered IV over approximately 60 minutes on Day 1 of each cycle

Chemotherapeutic agents will be administered as an IV infusion according to prescribing information or treatment guidance in general use by the Investigating site:

- **Cisplatin** 70 mg/m^2 IV on Day 1 of each cycle
- **Gemcitabine** 1,000 mg/m^2 IV on Day 1 of each cycle

Day 8 of each 21-day cycle. The following treatment will be administered as an IV infusion:

- **Gemcitabine** 1,000 mg/m^2 IV on Day 8 of each cycle

Additionally, the following supportive care will be administered as needed:

- Pegfilgrastim 6 mg SC per institutional SOC
  (alternative to Pegfilgrastim: Filgrastim 5 µg/kg as SC/IV per institutional SOC)

- **Carbo-Gem Cohort: Durvalumab plus Carboplatin + Gemcitabine**

IMPORTANT CLINICAL NOTE:
Durvalumab dose for Carbo-Gem (& Cis-Gem)
DIFFERS from DD MVAC

Treatment with **Durvalumab plus Carbo-Gem** is on a 21-day cycle as described below:

Day 1 of each 21-day cycle, the following treatments will be administered as an IV infusion:

- **Durvalumab** at a fixed dose of **1500 mg** administered IV over approximately 60 minutes on Day 1 of each cycle

Chemotherapeutic agents will be administered as an IV infusion according to prescribing information or treatment guidance in general use by the Investigating site:

- **Carboplatin:** AUC 5 IV on Day 1 of each cycle
- **Gemcitabine** 1,000 mg/m^2 IV on Day 1 of each cycle

Day 8 of each 21-day cycle. The following treatment will be administered as an IV infusion:

- **Gemcitabine** 1,000 mg/m^2 IV on Day 8 of each cycle

Additionally, the following supportive care will be administered as needed:

- Filgrastim 5 µg/kg as SC/IV per institutional SOC
  (alternative to Filgrastim: Pegfilgrastim 6 mg as SC per institutional SOC)

Observation before; during; and after 1st durvalumab infusion

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 during the infusion, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

On the 1st infusion day, subjects will be monitored and vital signs collected/recorded prior to; during; and after infusion of durvalumab.

BP and pulse will be collected from subjects before; during; and after each infusion at the following times (based on a 60-minute infusion):

- Within 30 minutes before the beginning of the infusion
- Every 30 minutes, ie, starting about **halfway** through planned 1-hour infusion period and continuing every 30 minutes until the end of the infusion. 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. If infusion period exceeds 4 hours, see Section 5 Study Agent / See Dose and Route of Administration.

- At the end of the infusion (at 60 minutes ± 5 minutes).
- There should be a 1-hour observation period after the first infusion.

The BP and pulse measurements should be taken more frequently if clinically indicated.

Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. For management of subjects who experience an infusion reaction, please refer to the toxicity and management guidelines in Section 6 Dose and Schedule Modifications.

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, see above) and re-initiated at 50% of the initial rate until completion of the infusion. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.

Observation after subsequent durvalumab infusions

For subjects with a prior ≤ Grade 2 infusion-related reaction to durvalumab, subsequent infusions may be administered at 50% of the initial rate.

BP, pulse and other vital signs should be measured, collected/recorded prior to the start of the infusion. Subjects should be carefully monitored and BP and other vital signs should be measured during and post-infusion as per institution standard and as clinically indicated.

Post-Cycle 4 Procedures/End of Treatment

An **End of Treatment** safety assessment will be obtained in person within 4 weeks ± 2 weeks of completion of neoadjuvant treatment, typically at the subject's cystectomy pre-operative visit. After the completion of the 4 cycles of durvalumab and neoadjuvant chemotherapy, the subjects MUST undergo cystectomy within 6 weeks (on or before 42 days, no grace period). Subjects who complete treatment but fail to undergo cystectomy will be considered inevaluable for endpoint analysis for that reason. The following blood samples will be collected pre- and post-surgery:

ctDNA Collection

- Pre-Initiation of Neoadjuvant Treatment (Whole Exome-Tissue and Target Genes Plasma)
- Upon completion of neoadjuvant treatment and prior to surgical cystectomy (typically at the pre-operative visit)
- 4 weeks post-cystectomy +/-2 weeks
- 12 weeks post-cystectomy +/-2 weeks (at the End of Study visit)

In addition to the blood sample collection, tumor specimen testing will be as follows:

- Tumor specimen for genomic sequencing post-cystectomy
- Tumor specimen PD-L1 testing post-cystectomy

End of Study

The End of Study visit is defined as the last planned visit within 12 weeks (+/- 2 weeks) post cystectomy. All required procedures may be completed within 7 days before the End of Study visit.

Study Assessments

Findings from screening medical history and physical examination will be used as baseline for the assessment of adverse events (AEs).

Medical history

Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations and vital signs

A complete physical examination will be performed on study days noted, and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs. Height will be measured at screening only.

Electrocardiograms

At Screening, a single resting ECG will be obtained, on which QTcF must be ≤ 470 ms.

Resting 12-lead ECGs will be recorded as clinically indicated throughout the study. ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position. In case of clinically-significant ECG abnormalities, including a QTcF value > 470 ms; 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Clinical laboratory tests. The following clinical laboratory tests will be performed.

Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Magnesium[a]
Alanine aminotransferase	Potassium
Aspartate aminotransferase	Sodium
Bicarbonate	Total bilirubin[b]
Calcium	Total protein
Chloride	Blood urea nitrogen
Creatinine[c]	

[a] Magnesium is to be performed at baseline on Day 1 and as clinically indicated

[b] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥ 2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[c] Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

Urinalysis Tests [a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

Samples for Biomarker Studies

Blood samples will be collected for correlative studies (see Section 8) at the following timepoints.

- Pre-initiation of neoadjuvant treatment

- Upon completion of study treatment and prior to surgical removal of bladder (cystectomy).
- 4 weeks subsequent to cystectomy.
- 12 weeks subsequent to cystectomy.

Plasma sample requirements:

A total of minimum 4 mL plasma is required to be submitted per participant per time point. Sample can be batch shipped frozen to Natera.

Tissue Requirements:

Tissue samples may be formalin-fixed, paraffin embedded (FFPE) from primary cancer diagnosis. The tumor content of tissue biopsy shall not be lower than 30%.

Below are the tissue specifications. Natera will conduct a quality assessment of samples to determine if the tissue qualifies for WES. Unqualified samples will be sent back to the Institution.

Sample types for resected tissue:

- Tissue block and 1 H&E slide is preferred, **OR**
- 10 unstained slides and 1 H&E slide **OR**
- Tissue block punches and 1 H&E slides, **OR**
- 4 to 6 cores and 1 H&E slides

Sample size (for slides):

- Surface area of 9 mm^2 is the minimum and 25 mm^2 is ideal
- 5-micron thickness is the minimum and 10-micron thickness is preferred
- Unbaked
- For unstained slides: microdissection will be performed to select tumor rich regions and exclude normal tissue, necrotic areas, and lymphocytes that may decrease the tumor DNA content. To assist in microdissection, site is requester to prepare a minimum of 10 unstained slides by using the H&E to trace tumor regions on adjacent unstained slides.

PD-L1 testing

To ensure comparability of data across all studies of durvalumab and to gain real world experience on the performance of this assay, this study will include PD-L1 testing utilize the Ventana SP263 assay. Testing will be performed at the Stanford Healthcare Clinical Laboratory.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a subject's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at

this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.

- Samples should be collected via tumor biopsy. The following fields of data should be collected from PD-L1 testing laboratory:
- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples that have not been processed will be disposed of or destroyed, and the action documented. As collection of the biological samples is an integral part of the study, the subject is withdrawn from further study participation.

The Principal Investigator will ensure that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented and will ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented. Additionally, the study team will ensure that the subject is informed about the sample disposal.

4.1 General Concomitant Medication and Supportive Care Guidelines

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as “prohibited,” as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted

Prohibited Concomitant Medications

Prohibited medication/ class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day for > 3 days, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Short-term premedication for subjects receiving combination cisplatin agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reaction and nausea is allowed • Use in subjects with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the subject (eg, chronic obstructive pulmonary disease, radiation, nausea, etc) or as anti-nausea premedication for cisplatin chemotherapy
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution during the study

4.2 Criteria for Removal from Study

Permanent discontinuation of study

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. An individual subject will not receive any further durvalumab monotherapy if their weight falls to 30 kg or less
2. Withdrawal of consent or lost to follow-up
3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
4. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
5. A radical cystectomy procedure is not performed (ie, a partial cystectomy or no cystectomy is performed)
6. Pregnancy or intent to become pregnant
7. Any AE that meets criteria for discontinuation
8. Grade ≥ 3 infusion reaction
9. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits
10. Initiation of alternative anticancer therapy including another investigational agent
11. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab

Withdrawal of consent

Subjects are free to withdraw from the study at any time (treatment with durvalumab and assessments) without prejudice to further treatment.

Subjects who withdraw consent for further participation in the study will not receive any further durvalumab or further study observation. Note that the subject may be offered additional tests or tapering of treatment to withdraw safely.

A subject who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

An individual subject will not receive any further treatment with durvalumab if any of the following occur in the subject in question:

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with durvalumab (eg, refusal to adhere to scheduled visits)

- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression, ie, Investigator determination that the subject is no longer benefiting from treatment with durvalumab, with or without radiological progression.

Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (Appendix 1)

If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of any samples

4.3 Alternatives

Subjects may choose not to participate in the trial and get standard of care treatment with either chemotherapy followed by surgery or surgery alone as determined by the treating physician.

5. STUDY AGENT INFORMATION

5.1 Study Agent

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

Formulation; Packaging; and Storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride; 275 mM trehalose dehydrate; and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure

Subjects receiving durvalumab will receive 1500 mg once every 3 weeks or 750 mg once every 2 weeks durvalumab, via IV.

Dosing and Administration:

The investigational agent durvalumab at will be administered by IV infusion at fixed doses of 750 mg (DD MVAC cohort) or 1500 mg (Cis-Gem or Carbo-Gem cohorts), in combination with the investigator's choice of 3 standard therapeutic regimens. The selection is offered for investigator discretion based on renal function. If creatine clearance is > 50 cc, the investigator may choose between DD MVAC or Gemcitabine + Cisplatin. If Cr clearance is less than 50 cc then the Carboplatin + Gemcitabine (Carbo-Gem) regimen may be given.

The therapeutic regimens are described in detail at Section 4 Treatment Plan / Treatment Administration per Cycle.

Allowable Infusion Period and Need for Fresh Preparations of Durvalumab

The target infusion period is 1-hour, but can be extended as needed due to interruptions for up to 4 hours total. In the event that the infusion exceeds 4 hours, the infusion should be terminated. Record the amount not infused, and dispose of the durvalumab per protocol.

Obtain a fresh preparation of durvalumab from the Stanford Investigational Drug Service (IDS, the investigational pharmacy) for the amount not infused, and re-initiate the infusion with freshly-prepared durvalumab.

Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.

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 management of subjects who experience an infusion reaction, please refer to the toxicity and management guidelines in

For any subjects that experienced a prior ≤ Grade 2 infusion-related reaction to durvalumab, subsequent infusions may be administered at 50% of the initial rate. If a infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued for that subject.

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

Observation after subsequent durvalumab infusions

On the 1st infusion day, subjects will be monitored and vital signs collected/recorded prior to; during; and after infusion of durvalumab (1 hour or as clinically indicated). Subsequent observation will be according to institutional standard.

Preparation of durvalumab for administration with an IV bag

The dose of durvalumab for administration will be prepared by the IDS using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 750 mg (DD MVAC cohort) or 1500 mg (Cis-Gem or Carbo-Gem cohorts) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

The standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 4 hours at room temperature. If either the preparation time or projected infusion time exceeds 4 hours, a new dose must be prepared from

new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

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

Accountability and dispensation

Drug accountability records will be kept during the study by the IDS. The IDS will account for all investigational study drug dispensed, and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. DOSE AND SCHEDULE MODIFICATIONS

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab.

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

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 and re-initiated at 50% of the initial rate until completion of the infusion. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.

Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy.

6.1. Dose Modifications for Durvalumab

Dose reductions on durvalumab are not permitted.

Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

All toxicities will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

6.2. Dose Modifications for Gemcitabine and Cisplatin (Cis-Gem)

6.2.1. Hematologic Toxicity

Day 1

For ANC < 1,000 on Day 1, delay treatment until the ANC is > 1000. If delay is 1 week or less, continue at the same dose and consider pegfilgrastim with subsequent cycles, if not receiving. If the delay is for more than a week and pegfilgrastim has not been used, include pegfilgrastim in all subsequent cycles. If there is a dose delay of more than 1 week due to neutropenia despite pegfilgrastim use, reduce cisplatin and gemcitabine by one dose level for this and all subsequent cycles and continue pegfilgrastim.

For platelets < 100,000 on Day 1, delay treatment until platelets are > 100,000. If the delay is 1 week or less, continue at the same dose levels. If the delay is for more than a week, reduce the gemcitabine by one dose level for this and all subsequent cycles.

Day 8

For and ANC < 500, hold gemcitabine and reduce both cisplatin and gemcitabine by one dose level for all subsequent cycles.

For platelets < 50,000, hold gemcitabine and reduce gemcitabine by one does level for all subsequent cycles.

6.2.2. Febrile Neutropenia

Febrile neutropenia is defined as ANC of < 500 and a temperature of 38.3°C orally (101° °C (100.4°F) for more than 1 hour. Add pegfilgrastim if not previously included, continuing at the same dose level. If pegfilgrastim had been utilized, then dose reduce both the gemcitabine and cisplatin by one dose level for all subsequent cycles and continue pegfilgrastim.

6.2.3. Kidney Dysfunction

Calculate the CrCl on Day 1 of each cycle. If CrCl is < 50 mL/min, hold cisplatin for up to 1 week. If Cr cl does not improve to > 50 mL/min in 1 week despite hydration and other supportive measures discontinue the chemotherapy and proceed to surgery. If the CrCl improves to > 50cc proceed with split dose cisplatin administration on Days 1 and 8. If Cr Cl improves to > 60cc on day 1 of subsequent cycle, then split dose not required

If the CrCl is between 50 to 60 mL/min on Day 1 of chemotherapy, administer cisplatin in split dosing, without a dose level reduction. Pegfilgrastim or filgrastim will be given on Day 9 or Days 9 to 13, respectively, when the cisplatin dose is split. With split dosing, if CrCl is < 50 mL/min on Day 8,the cisplatin is to be held for that day.

6.2.4. Liver Dysfunction

For a total bilirubin of > 1.5 × the upper limit of normal (or 3 × ULN in subjects with Gilbert's syndrome), hold therapy until the bilirubin is < 1.6 × ULN (or < 3 × ULN in those with Gilbert's syndrome), and then restart with a one dose level reduction in gemcitabine for this and all remaining cycles.

6.2.5. Neurologic Toxicity

For Grade 3 neuropathy, hold chemotherapy until this resolve to Grade 1 or 2 and then resume with a one dose level reduction in the cisplatin. For Grade 4 neuropathy, remove the subject from protocol treatment.

6.2.6. Gastrointestinal Toxicity

For Grade 3 or 4 vomiting, despite maximal antiemetic medical intervention with aprepitant, corticosteroids, and 5HT-3 antagonists (eg, ondansetron), proceed with a dose reduction for the next cycle in both cisplatin and gemcitabine. If Grade 3 or 4 vomiting occurs despite one dose reduction in chemotherapy and maximal antiemetic therapy, remove the subject from protocol treatment.

6.2.7. Other toxicities

For all other, non-specified adverse events at Grade 2, subjects should be treated symptomatically. For all other Grade 3 or 4 toxicities (excluding alopecia and skin pigment changes), hold cisplatin and gemcitabine and monitor the subject at least weekly. If toxicity resolves to Grade 1 by 1 dose level for this and all subsequent cycles. Any single delay in chemotherapy of more than 3 weeks or cumulative delays of more than 4 weeks will lead to removal from protocol treatment and referral to surgery.

6.3. Dose Modifications for Carboplatin and Gemcitabine (Carbo-Gem)

6.3.1. Hematologic Toxicity

Day 1:

For ANC < 1,000 on Day 1, delay treatment until the ANC is > 1000. If delay is 1 week or less, continue at the same dose and consider pegfilgrastim with subsequent cycles, if not receiving. If the delay is for more than a week and pegfilgrastim has not been used, include pegfilgrastim in all subsequent cycles. If there is a dose delay of more than 1 week due to neutropenia despite pegfilgrastim use, reduce cisplatin and gemcitabine by one dose level for this and all subsequent cycles and continue pegfilgrastim.

For platelets < 100,000 on Day 1, delay treatment until platelets are > 100,000. If the delay is 1 week or less, continue at the same dose levels. If the delay is for more than a week, reduce the gemcitabine by one dose level for this and all subsequent cycles.

Day 8:

For and ANC < 500, hold gemcitabine and reduce both cisplatin and gemcitabine by one dose level for all subsequent cycles.

For platelets < 50,000, hold gemcitabine and reduce gemcitabine by one does level for all subsequent cycles.

6.3.2. Febrile Neutropenia

Febrile neutropenia is defined as ANC of < 500 and a temperature of 38.3°C orally (101° °C (100.4°F) for more than1 hour. Add pegfilgrastim if not previously included, continuing at the same dose level. If pegfilgrastim had been utilized, then dose reduce both the gemcitabine and cisplatin by one dose level for all subsequent cycles and continue pegfilgrastim.

6.3.4. Liver Dysfunction

For a total bilirubin of > 1.5 × the upper limit of normal (or 3 × ULN in subjects with Gilbert's syndrome), hold therapy until the bilirubin is < 1.6 × ULN (or < 3 × ULN in those with Gilbert's syndrome), and then restart with a one dose level reduction in gemcitabine for this and all remaining cycles.

6.3.5. Neurologic Toxicity

For Grade 3 neuropathy, hold chemotherapy until this resolve to Grade 1 or 2 and then resume with a one dose level reduction in the carboplatin. For Grade 4 neuropathy, remove the subject from protocol treatment.

6.3.6. Gastrointestinal Toxicity

For Grade 3 or 4 vomiting, despite maximal antiemetic medical intervention with aprepitant, corticosteroids, and 5HT-3 antagonists (eg, ondansetron), proceed with a dose reduction for the next cycle in both carboplatin and gemcitabine. If Grade 3 or 4 vomiting occurs despite one dose reduction in chemotherapy and maximal antiemetic therapy, remove the subject from protocol treatment.

6.3.7. Other toxicities

For all other, non-specified adverse events at Grade 2, subjects should be treated symptomatically. For all other Grade 3 or 4 toxicities (excluding alopecia and skin pigment changes), hold carboplatin and gemcitabine and monitor the subject at least weekly. If toxicity resolves to Grade 1 by 1 dose level for this and all subsequent cycles. Any single delay in chemotherapy of more than 3 weeks or cumulative delays of more than 4 weeks will lead to removal from protocol treatment and referral to surgery.

6.4. Dose-dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin (DD MVAC)

6.4.1. Hematologic Toxicity

For ANC < 1000 or platelets < 100,000 on Day 1, delay treatment until the ANC is > 1000 and platelets > 100,000. If delay is 1 week or less, continue at the same doses. If the delay is for more than a week, reduce methotrexate, vinblastine, doxorubicin, and cisplatin by one dose level for this and all subsequent cycles.

For febrile neutropenia, defined as ANC of < 500 and a temperature of 38.3 C orally (101 F) dose reduce all chemotherapy agents by one dose level and consider switching to pegfilgrastim (if previously giving filgrastim).

6.4.2. Kidney Dysfunction

Calculate the CrCl on Day 1 of each cycle. If CrCl is < 50 mL/min, hold chemotherapy for up to 1 week. If Cr cl does not improve to > 50mL/min in 1 week despite hydration and other supportive measures discontinue the chemotherapy and proceed to surgery. If the CrCl improves to > 50cc proceed with split dose cisplatin administration on Days 1 and 8. If Cr Cl improves to > 60cc on day 1 of subsequent cycle, then split dose not required

If the CrCl is between 50 to 60 mL/min on Day 1 of chemotherapy, administer cisplatin in split dosing, without a dose level reduction. Pegfilgrastim or filgrastim will be given on Day 9 or

Days 9 to 13, respectively, when the cisplatin dose is split. With split dosing, if CrCl is < 50 mL/min on Day 8,the cisplatin is to be held for that day.

6.4.3. Liver Dysfunction

For a total bilirubin of > 1.5 × the upper limit of normal (or 3 × ULN in subjects with Gilbert's syndrome), hold therapy until the bilirubin is < 1.6 × ULN (or < 3 × ULN in those with Gilbert's syndrome), and then restart with a one dose level reduction in doxorubicin and vinblastine for this and all remaining cycles.

6.4.4. Neurologic Toxicity

For Grade 3 neuropathy, hold chemotherapy until this resolve to Grade 1 or 2 and then resume with a one dose level reduction in the cisplatin and vinblastine. For Grade 4 neuropathy, remove the subject from protocol treatment.

6.4.5. Gastrointestinal Toxicity

For Grade 3 or 4 vomiting, despite maximal antiemetic medical intervention with aprepitant, corticosteroids, and 5HT-3 antagonists (eg, ondansetron), proceed with a dose reduction for the next cycle in both, methotrexate and doxorubicin. If Grade 3 or 4 vomiting occurs despite one dose reduction in chemotherapy and maximal antiemetic therapy, remove the subject from protocol treatment.

6.4.6. Stomatitis

For Grade 2 toxicity, delay infusion until it resolves to Grade 0 or 1. For Grade 3 or 4 toxicity, delay chemotherapy until it resolves to Grade 0 or 1 and reduce doxorubicin, vinblastine and methotrexate by one dose level on all subsequent cycles.

6.4.7. Other Toxicities

For all other, non-specified adverse events at Grade 2, they should be treated symptomatically, as indicated. For all other Grade 3 or 4, hold all chemotherapy and monitor the subject at least weekly. If toxicity resolves vinblastine, doxorubicin, and cisplatin by one dose level for this and all subsequent cycles. Any single delay in chemotherapy of more than 3 weeks or cumulative delays of more than 4 weeks will lead to removal from protocol treatment and referral to surgery.

6.5. Filgrastim (G-CSF) Dose Modifications

Dose adjustments for toxicities associated with filgrastim (G-CSF) (bone pain, splenomegaly, abnormalities in uric acid concentrations, LDH and alkaline phosphatase, transient elevations of serum creatinine and aminotransferase activity) Dose modifications for G-CSF toxicity should only be initiated if symptomatic control of the toxicity fails (ie, analgesics such as acetaminophen or acetaminophen with codeine for myalgias or bone pandect.).

Toxicity Grade	Dose Adjustment
Grade 0 to 1:	No change
Grade 2:	Decrease filgrastim to 3 µg/kg/day
Grade 3 to 4:	Discontinue filgrastim

Cisplatin Dose Level

	Cr Cl > 59	Cr Cl > 50< 60
0	70 mg/m^2	35 mg/m^2 Days 1 and 8 for Cis/Gem; and Days 1 and 2 for DD MVAC
-1	50 mg/m^2	25 mg/m^2 Days 1 and 8 for Cis/Gem; and Days 1 and 2 for DD MVAC

Gemcitabine Dose Level

Level 0	1000 mg/m^2
Level -1	750 mg/m^2
Level -2	500 mg/m^2

Methotrexate Dose Level

Level 0	30 mg/m^2
Level -1	23 mg/m^2
Level -2	15 mg/m^2

Vinblastine Dose Level

Level 0	3 mg/m^2
Level -1	2.3 mg/m^2
Level -2	1.5 mg/m^2

Doxorubicin Dose Level

Level 0	30 mg/m^2
Level -1	23 mg/m^2
Level -2	15 mg/m^2

7. ADVERSE EVENTS AND REPORTING PROCEDURES

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related, including new or aggravated clinically-relevant

abnormal medical findings at physical examination. An adverse event can be any unfavorable and unintended sign or symptom, including abnormal laboratory findings, or disease, that is temporally associated with the use of a drug, and does not imply any judgment about causality. This also includes events of clinical deterioration such as tumor relapse, recurrence, or upstaging, or new cancers. An adverse reaction is any event that is caused by a drug or device, ie, possibly-, probably-, or definitely-related to the use of the drug or device.

7.1 Potential Adverse Events

Adverse events are described in the FDA-approved prescribing information for durvalumab (Imfinzi).

7.2 Adverse Event Reporting

AEs and SAEs will be collected from the time of the subject signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each subject for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the subject has discontinued study drug or the study has completed.

Any AEs that are unresolved at the subject's last visit in the study are followed up by the Investigator for as long as medically indicated. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

In addition, the following variables will be collected for SAEs as applicable:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome
- In addition, the following variables will be collected for SAEs:
- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication

Description of the SAE

The grading scales found in the revised NCI CTCAE version 5 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE v5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab).

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the subject is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Causality collection

The Investigator will assess causal relationship between the IPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent

(ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study subject's medical record.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarize. If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the clinical rather than the laboratory term (eg, anemia vs low hemoglobin value) should be used. In the absence of clinical signs or symptoms, clinically-relevant deteriorations in non-mandated parameters should be reported as AEs.

Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the subject's inclusion in this study.

Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression, or for any unknown cause, should be documented accordingly.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the AstraZeneca Patient Safety as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progressive disease, if appropriate, and should assign main and contributory causes of death.
- Within 24 hours after the Principal Investigator is notified, of a SAE, each such SAE will be reported by Stanford **secure** email to [redacted], using a study-specific CRF or the Stanford Cancer Institute CRF for SAE reporting. In the email, indicate the OnCore or eProtocol number in the subject line. CCTO-Safety will post the report to the OnCore study record, where it will be available for review by the Stanford Data Safety and Monitoring Committee (DSMC).
- In the event of death due to an unknown cause, a post-mortem may be helpful in the assessment of the cause of death. If performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.
- If a death occurs as a result of an event that started after the defined safety follow-up period, and is considered to be due to a late-onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post-study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for subjects treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

Reporting of serious adverse events

All SAEs, whether or not considered causally related to durvalumab, or to the study procedure(s), will be reported to AstraZeneca, as well as the IRB of record according to local requirements. Notifications to AstraZeneca will use a MedWatch/AdEERs form or equivalent. The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator is responsible for informing the IRB of record of the SAE as per local requirements.

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

A cover page should accompany the MedWatch/AdEERs notification to AstraZeneca indicating the following:

- "Notification from an Investigator-sponsored Study"
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-##-#####)

The Investigator must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: [redacted]

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported to AstraZeneca as follows:

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the subject has been

permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

Other events requiring reporting

Overdose

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

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

The investigator will use clinical judgment to treat any overdose.

Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor and AstraZeneca Patient Safety using the designated Safety e-mailbox, unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

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

Pregnancy

Maternal exposure

Female subjects will be advised to use a medically-acceptable method of birth control for 90 days after the last dose of durvalumab. If a subject becomes pregnant during the course of the study, durvalumab should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that durvalumab may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Male subjects will be advised to use a medically-acceptable method of birth control, and should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab.

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong subject received the medication
- Wrong drug administered to subject

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Subject accidentally missed drug dose(s), eg, missed appointment
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

Adverse events will be graded according to CTCAE v5. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

SAEs (per 21CFR§312.32) and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study-specific CRF regardless of the event's relatedness to the investigation.

8. CORRELATIVE/SPECIAL STUDIES

Samples to be collected are defined in Section 4.

- Whole blood or frozen plasma
- Buffy coat (or other germline DNA)

Blood for ctDNA will be drawn at baseline, post-chemotherapy, post-cystectomy at 4 weeks and at 12 weeks

Time Point	Time	Test-Sample
1	Pre-Initiation of Neoadjuvant Treatment	Whole Exome-Tissue
1	Pre-Initiation of Neoadjuvant Treatment	Target Genes [16]-Plasma
2	Upon Completion of Study Treatment / Prior to Surgical Removal of Bladder	Target Genes [16]-Plasma
3	4 weeks Post-surgical Removal of Bladder	Target Genes [16]-Plasma
4	12 weeks Post-surgical Removal of Bladder	Target Genes [16]-Plasma

Natera will provide WES and 4 plasma test time points [1 Signatera test] per study participant . Natera will design custom two-side SNV assays based on SNV's identified in the whole exome sequencing data generated from the tumor tissue. Natera will extract ctDNA from plasma, the ctDNA will be used to prepare Natera libraries. The ctDNA libraries will be analyzed using Natera's custom SNV assays. The ctDNA will be analyzed according to Natera's protocol and SNV calling pipeline.

Natera ctDNA Analysis

Detection and monitoring of tumor-specific mutations in cell-free DNA has great potential to improve patient care by detecting cancer early, assisting adjuvant therapy decision-making, determining treatment effects and assessing the need for follow-up intervention. Existing methodologies for recurrence monitoring (eg, protein biomarkers, CT imaging) have limitations, which may include increased health risk or discomfort for the patient, lower sensitivity and specificity, and/or higher costs.

Natera, Inc., (NASDAQ: NTRA), a leader in non-invasive genetic testing, develops and commercializes non-invasive methods for analyzing circulating free DNA (cfDNA) in plasma. The mission of the company is to transform the diagnosis and management of genetic disease. In pursuit of that mission, Natera operates a CAP-accredited laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) in San Carlos, CA, and it currently offers a host of proprietary genetic testing services primarily to OB/GYN physicians and fertility centers, as well as to genetic laboratories through its cloud-based Constellation™ software system.

Leveraging its unique capabilities in detection of cfDNA, Natera is also applying its proprietary technology for improved treatment of cancer through early detection and recurrence monitoring. Natera aims to create pre-designed or personalized liquid biopsy assays through detection of copy number variants and single nucleotide changes. A recent publication in Nature illustrates Natera's proprietary technology that detected mutations in cfDNA for both clonal and subclonal mutations in early-stage lung cancer patients as part of the TRACERx study. This publication illustrates how Natera's assay identified recurrence 70 days [+/-] before it was identified in a routine clinical setting (Abbosh, *et al*,, 2017, Nature, 545:446).

PD-L1 testing

The Ventana SP263 assay to measure PD-L1 in tumors is fully-analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

9. STUDY CALENDAR BY COHORT (all receive durvalumab)

Dose-Dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin cohort ("DD MVAC" 14-day Cycle)

Procedure	**Screening[a]**	**Cycle 1 Day 1[c]**	**Cycle 1 Day 2[c]**	**Cycle 2 Day 1[c]**	**Cycle 2 Day 2[c]**	**Cycle 3 Day 1[c]**	**Cycle 3 Day 2[c]**	**Cycle 4 Day 1[c]**	**Cycle 4 Day 2[c]**	**EOT Safety Visit**	**Surgery**	**ctDNA Collection**	**End of Study Visit**
Scheduling Window (Days)	**-30 to -1**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	X												
Medical history	X												
Physical exam	X	X		X		X		X					
Vital signs, weight, & height[d]	X	X		X		X		X					
ECOG Performance Status	X	X		X		X		X					
Complete blood count w/differential	X[f]	X		X		X		X					
Comprehensive metabolic panel including Mg[i]	X[f]	X		X		X		X					
Coagulation (PT, PTT, INR)	X												
TSH	X												
Urinalysis	X												
Hepatitis B serology	X												
Hepatitis C serology	X												
HIV serology	X												
Pregnancy test	X												
Biomarkers[k]	X	X								X		X	X
12-lead ECG[g]	X												

ECHO	X												
Tumor specimen testing	X										X		
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												
Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (750mg)		X		X		X		X					
Methotrexate		X		X		X		X					
Vinblastine			X		X		X		X				
Doxorubicin			X		X		X		X				
Cisplatin			X		X		X		X				
Cystectomy[j]											X		

Cisplatin plus Gemcitabine cohort ("Cis-Gem," 21-day cycle)

Procedure	Screening[a]	Cycle 1 Day 1 [b]	Cycle 1 Day 8	Cycle 2 Day 1 [b]	Cycle 2 Day 8	Cycle 3 Day 1 [b]	Cycle 3 Day 8	Cycle 4 Day 1 [b]	Cycle 4 Day 8	EOT Safety Visit	Surgery	ctDNA Collection	End of Study Visit
Scheduling Window (Days)	**-30 to -1**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	X												
Medical history	X												
Physical exam	X	X		X		X		X					
Vital signs, weight, & height[d]	X	X		X		X		X					
ECOG Performance Status	X	X		X		X		X					
Complete blood count w/differential	X[f]	X		X		X		X					
Comprehensive metabolic panel including Mg[i]	X[f]	X		X		X		X					
Coagulation (PT, PTT, INR)	X												
TSH	X												
Hepatitis B serology	X												
Urinalysis	X												
Hepatitis C serology	X												
HIV serology	X												
Pregnancy test	X												
Biomarkers[k]	X	X								X		X	X
12-lead ECG[g]	X												
ECHO	X												
Tumor specimen testing	X										X		
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												

Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (1500mg)		X		X		X		X					
Cisplatin		X		X		X		X					
Gemcitabine		X	X	X	X	X	X	X	X				
Cystectomy[j]											X		

Carboplatin plus Gemcitabine cohort ("Carbo-Gem," 21-day cycle)

Procedure	Screening[a]	Cycle 1 Day 1	Cycle 1 Day 8[b]	Cycle 2 Day 1	Cycle 2 Day 8[b]	Cycle 3 Day 1	Cycle 3 Day 8[b]	Cycle 4 Day 1	Cycle 4 Day 8[b]	EOT Safety Visit	Surgery	ctDNA Collection	End of Study Visit
Scheduling Window (Days)	**-30 to -1**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	X												
Medical history	X												
Physical exam	X	X		X		X		X					
Vital signs, weight, & height[d]	X	X		X		X		X					
ECOG Performance Status	X	X		X		X		X					
Complete blood count w/differential	X[f]	X		X		X		X					
Comprehensive metabolic panel including Magnesium[i]	X[f]	X		X		X		X					
Coagulation (PT, PTT, INR)	X												
TSH	X												
Urinalysis	X												
Hepatitis B serology	X												
Hepatitis C serology	X												
HIV serology	X												
Pregnancy test	X												
Biomarkers[K]	X	X								X		X	X
12-lead ECG[g]	X												
ECHO	X												
Tumor specimen testing	X									X			
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												

Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (1500mg)		X		X		X		X					
Carboplatin		X		X		X		X					
Gemcitabine		X	X	X	X	X	X	X	X				
Cystectomy[j]											X		

a: Subjects must be screened within 30 days prior to Cycle 1 Day 1 with the exception of some labs.
b: For Cis/Gem and Carbo/Gem cohorts there must be at least 7 days between Day 1 and Day 8.
c: Efforts should be made to conduct study visits on the day scheduled (+2 days). Delays in dosing will shift the following cycle so that there are at least 12 days between Day 8 of the previous cycle and Day 1 of the current cycle.
d: Assessments will include vital signs (resting BP HR, RR, and body temperature) and weight. Height will be recorded at screening.
e: PET CT for subjects with impaired renal function is an acceptable alternative.
f: within 28 days of Cycle 1 Day 1
g: ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value > 470 ms; 2 additional 12 lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.
h: Informed consent may be obtained greater than 30 days prior to first dose of study treatment.
i: Magnesium is to be performed at baseline on Day 1 and as clinically indicated
j: Within 6 weeks post completion of 4 cycles
k: Biomarkers sample to be collected at pre-initiation of neoadjuvant treatment, upon completion of neoadjuvant treatment and prior to surgical cystectomy, 4 weeks (+/- 2 weeks) post-cystectomy and 12 weeks (+/- 2 weeks) post cystectomy
L: May be completed within 7 days before the End of Study visit
m: within 4 weeks ± 2 weeks of completion of neoadjuvant treatment, typically at the subject's cystectomy pre-operative visit

10. MEASUREMENTS

10.1 Primary Outcome measures

The safety and tolerability of durvalumab in combination with chemotherapy in subjects with variant histology bladder cancer who initiate study treatment will be assessed as the number, by treatment cohort, of Grade 3, 4, or 5 adverse events, considered probably or definitely related by the investigator. The outcome will be reported as a number.

Time Frame: 120 days

- **Safety Issue**: Is this outcome measure assessing a safety issue? Yes

10.2 Secondary Outcome measures

The number and proportion of subjects who initiate study treatment and achieve tumor stage of pT2 N0 M0 or better (eg, pT0, pT1 N0) at cystectomy.

T0 N0 M0 = No evidence of primary tumor

T1 N0 M0 = Tumor staging by pathological assessment detected in lamina propria (T0), with no tumor-positive nodes (N0).

T2 N0 M0 = Tumor staging by pathological assessment detected in muscularis propria (pT2), with no tumor-positive nodes (N0) or tumor metastases (M0) observed.

Time Frame: 20 weeks

- **Safety Issue**: Is this outcome measure assessing a safety issue? No

See also Appendix 2 National Comprehensive Cancer Network Bladder Cancer Guidelines.

10.2.1 Secondary Outcome Measurement Definition

- Pathological review

10.2.2 Secondary Outcome Measurement Methods

Pathologists standard assessment of cystectomy with pathologic T stage assessment

10.2.3 Secondary Outcome Measurement Time Points:

Post-combination treatment of durvalumab and neoadjuvant chemotherapy for a maximum of four cycles followed by cystectomy

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol and the proposed informed consent will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA

regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

Case Report Forms (CRFs) are printed or electronic documents designed to record all protocol-related information on each trial participant. CRFs should summarize the clinical findings and observations necessary to ensure safety of participants on the study, and to document the study outcomes. CRFs are required by the SRC for all Interventional studies. CRF design and creation must be completed prior to enrollment of the first participant. OnCore will be used for CRF's.

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the Online Collaborative Research Environment (OnCore) database system and will be maintained by study team. CRFs will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 No interim analysis is planned

12.2.1 Analysis Population

Primary

All subjects who initiate study treatment will be included in the safety analysis (primary objective and outcome).

We set the null hypothesis of 1% for the proportion of patients experiencing a grade 3 or greater adverse event. Our sample size has 71% power at the alternative of 10%. Calculation based on binomial probabilities using a one-sided significance level of 5%. The trial will be deemed a success if no more than 2 patients experience a grade 3 or greater immune-related adverse event out of 24.

Precision: A sample of 24 patients will allow proportions to be estimated with a margin of error no larger than plus or minus 21 percentage points. The margin is expected to be smaller. For example if none of the 24 patients experience grade 3 or greater toxicity, we will be able to conclude with 95% confidence that the true rate is not larger than 17%.

Secondary

All subjects undergoing cystectomy will be included for analysis. Subjects who complete treatment but fail to under cystectomy will be considered inevaluable for endpoint analysis for that reason.

12.2.2 Analysis Plan

Primary

Safety data will be collected and assesses by CTCAE v5.

Secondary

Achievement of tumor staging will be determined by pathologist at cystectomy, and reported by treatment cohort. See also Appendix 2 National Comprehensive Cancer Network Bladder Cancer Guidelines.

In addition, molecular characterization of tissue pre- and post-cystectomy will be analyzed. Circulating ctDNA will be collected at baseline and at set time points.

12.3 Sample Size

12.3.1 Accrual estimates

We expect to enroll 12 subjects/year, for a 2 year enrollment of 24 subjects.

12.3.2 Sample size justification

This study will include 24 subjects.

12.3.3 Effect size justification

Variant histology bladder cancer subjects are not a well-studied population and are usually excluded from phase 3 studies. In traditional urothelial cancer, the percent of subjects achieving pT0 is 30%. We hope to improve this level of subjects achieving pT0 with the additional use of immunotherapy.

12.4 Criteria for future studies

If pT0 exceeds 50% we will then pursue a fully-powered study.

13. REFERENCES

Sternberg CN, Yagoda A, Scher HI, *et al*. Preliminary results of M-VAC (methotrexate, vinblastine,doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. JUrol133:403-7, 1985.

von der Maase H, Hansen SW, Roberts JT, *et al*. Gemcitabine and cisplatin versus methotrexate,vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large,randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068-77, 2008.

von der Maase H, Sengelov L, Roberts JT, *et al*. Long-term survival results of a randomized trialcomparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin inpatients with bladder cancer. J Clin Oncol 23:4602-8, 2005.

Als AB, Sengelov L, Von Der Maase H. Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer; 3- or 4-week schedule? Acta Oncol 47:110-9, 2008.

Soto Parra H, Cavina R, Latteri F, *et al*. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. Ann Oncol 13:1080-6, 2002.

Sternberg CN, de Mulder PH, van Oosterom AT, *et al*. Escalated M-VAC chemotherapy andrecombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) in patients with advanced urothelial tract tumors. Ann Oncol 4:403-7, 1993.

Sternberg CN, de Mulder P, Schornagel JH, *et al*. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 42:50-4, 2006.

Grossman HB, Natale RB, Tangen CM, *et al*. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859-66, 2003.

Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 354(9178):533-40, 1999.

Sonpavde G, Goldman BH, Speights VO, *et al*. Quality of pathologic response and surgerycorrelate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer 115:4104-9, 2009.

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, *et al*. Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500:415-21.

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, *et al*. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun;366 (26):2455-65.

Brahmer JR, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, *et al*. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis [ASCO abstract 8112]. J Clin Oncol 2014;32(Suppl).

Butte MJ, Keir ME, Phamduy TB, Freeman GJ, Sharpe AH. PD-L1 interacts specifically with B7-1 to inhibit T cell proliferation. Immunity. 2007;27:111-22.

Drake CG, McDermott DF, Sznol M, Choueiri TK, Kluger HM, Powderly JD, *et al*. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up [abstract 4514]. J Clin Oncol 2013;31(Suppl).

Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials 2008;29(4):456-65.

Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, *et al*. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. Journal of Clinical Oncology, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev. 2008;224:166-82.

Herbst RS, Gordon MS, Fine GD, Sosman JA, Soria JC, Hamid O, *et al*. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumours [abstract 3000]. J Clin Oncol 2013;31(Suppl 15).

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, *et al*. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65(3):1089-96.

Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP, *et al*. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a Phase I trial [ASCO abstract 9002]. J Clin Oncol 2014; 32(Suppl).

Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA. 2002 Sep 17;99:12293-7.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63

Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017–27.

Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, *et al*. Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. Int J Oncol. 2009 Sep;35(4):741-9.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Paterson AM, Brown KE, Keir ME, Vanguri VK, Riella LV, Chandraker A, *et al*. The PD-L1:B7-1 pathway restrains diabetogenic effector T cells in vivo. J Immunol. 2011;187:1097-105.

Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, *et al*. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014 Nov 27;515(7528):558-62.

Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Schadendorf D, Hodi FS, Robert C, *et al*. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma [abstract 24]. Presented at European Cancer Congress 2013 (ECCO-ESMO-ESTRO); 27 September to

Segal NH, Ou S-HI, Balmanoukian AS, Fury mg, Massarelli E, Brahmer JR, *et al*. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, *et al*. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8:1583-93.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.

Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, *et al*. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J

Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol 2014;54(10):1108-16.

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, *et al*. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.

Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, *et al*. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlated with clinical benefit in advanced melanoma patients treated with ipilimumab. Proc Natl Acad Sci U S A 2011;108:16723-8.

Zhang C, Wu S, Xue X, Li M, Qin X, Li W, *et al*. Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy. 2008;10(7):711-9.

Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.

14.1. APPENDIX 1. Dosing Modification and Toxicity Management Guidelines

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (Durvalumab Monotherapy) 1 November 2017 Version.

General Considerations	
Dose Modifications	**Toxicity Management**
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper. Subjects 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 subject is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	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, subjects should be thoroughly evaluated to rule out any alternative etiology (eg, 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, eg, 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 [eg, 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 (eg, infliximab) (also refer to the individual sections of the imAEs for specific type of

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (Durvalumab Monotherapy) 1 November 2017 Version.

General Considerations	
Dose Modifications	**Toxicity Management**
Grade 4 Permanently discontinue study drug/study regimen. **Note**: For Grade ≥ 3 asymptomatic amylase or lipase levels, 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, eg, 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, eg, 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 (ie, 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, eg, 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 (eg, 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 subject.

14.2. APPENDIX 2. National Comprehensive Cancer Network Bladder Cancer Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Bladder Cancer

Table 1. **American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer 8th ed., 2017)**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

N	Regional Lymph Nodes
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Histologic Grade (G)
For urothelial histologies, a low- and high-grade designation is used to match the current World Health Organization/International Society of Urological Pathology (WHO/ISUP) recommended grading system:

LG	Low-grade
HG	High-grade

For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage IIIA	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0

	T	N	M
Stage IIIB	T1-T4a	N2,N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

ST-1