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Randomized Phase I/II study of AVB-S6-500 in Combination with Durvalumab (MEDI4736) in Patients with Platinum-resistant, Recurrent Epithelial Ovarian Cancer

MD Anderson Protocol Number: 2019-0149

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TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BLQ	Below level of quantification
CBC	Complete blood count
CI	Confidence interval
CL	Clearance
C_{max}	Peak concentration
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DLS	Discovery Life Sciences
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
EGFR	Epidermal growth factor receptor
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBsAb, HBcAb	Hepatitis B surface antibody, Hepatitis B core antibody
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IP	Investigational product(s)
irAE	Immune-related adverse event

IRB	Institutional Review Board
IV	Intravenous(ly)
MAb	Monoclonal antibody
MDACC	MD Anderson Cancer Center
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	Renal cell carcinoma
RD	Repeat dosing
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dosing
SAD	Single ascending dose
SAE	Serious adverse event
SD	Stable disease
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
TMG	Toxicity Management Guidelines
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time to peak concentration
TMDD	Target mediated drug disposition
TMG	Toxicity Management Guidelines
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

1. INTRODUCTION

1.1 DISEASE BACKGROUND

1.1.1 EPITHELIAL OVARIAN CANCER

Each year in the United States, over 22,000 women develop ovarian cancer and there are approximately 14,240 attributed deaths annually, making ovarian cancer the deadliest of gynecologic malignancies [1]. Despite high rates of complete response to the combination of tumor reductive surgery and adjuvant platinum-taxane based chemotherapy, the vast majority of patients with stage III/IV EOC recur with a median progression free survival (PFS) of approximately 18 months. In those who recur, despite decades of clinical investigations, most cytotoxic and biological agents result in only modest rates of response and have a typical median PFS of 3 months [2], [3]. Therefore, a crucial unmet need is the development of new strategies that will ultimately improve the overall survival (OS) of patients with EOC.

1.1.2 IMMUNOTHERAPIES

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 [4].

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 [5]. It has two known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) [6]. 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. Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment[7]. 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 [8]–[11]. 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 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-L1 class showing clinical activity in a wide range of tumor types.

1.1.3 POTENTIAL UTILITY OF IMMUNE CHECKPOINT INHIBITORS IN OVARIAN CANCER

Immunogenicity of EOC has been well-documented, and there is extensive literature demonstrating the presence of clonally activated CD3+CD8+ TCRαβ+ T-cells in ovarian tumors and their prognostic significance[12]–[18]. Tumor infiltrating lymphocytes (TIL) derived from patients with EOC demonstrate tumor specificity by a) clonal proliferation in response to low concentrations of IL2 in the presence of autologous tumor cells [19] and b) exhibit MHC restricted killing of EOC tumor cell lines as well as cloned autologous tumor cells [18] and c) cytokine production [12], [14], [20]. However, there is also strong evidence that EOC harbors an immune-suppressor environment that includes the presence of regulatory T Cells, CTLA4-positive TILs, monocyte/macrophages, and elevated intratumoral and plasma levels of immunosuppressive cytokines such as IL10, IL6 and TGFβ [21]–[26]. Indeed, expression of PDL1 and PDL2 in EOC was shown to correlate with poorer OS[24], and both ascites and peripheral blood derived monocytes from patients with EOC showed upregulated PDL1 expression [26].

1.1.4 POTENTIAL UTILITY OF AXL INHIBITION IN OVARIAN CANCER

As a novel treatment, checkpoint blockade and immune modulation have demonstrated efficacy in heavily pretreated tumors with some durable responses, but only in a small fraction of patients. The emerging data on anti-PD1 / anti-PDL-1 therapies in ovarian cancer demonstrates response rates of 10-15%[8], [27]–[29].

While the mechanism for immune resistance to checkpoint inhibition remains poorly understood, a predictor of response to anti-PD1 therapy is the extent of CD8+ infiltration within the pretreated tumor [30]–[33]. Factors which contribute to T-cell exclusion, and thus resistance, within the tumor microenvironment include immune cell suppression via cytokines, aberrations in antigen presentation, or microenvironmental factors such as hypoxia. The receptor tyrosine kinase AXL has recently been identified as a possible mediator of T-cell exclusion and therapeutic resistance. In multiple tumor types, including uterine serous cancer, head and neck malignancy, and non-small cell lung cancers, AXL expression correlated with poor survival [34]–[37]. In ovarian cancer specifically, a meta-analysis of DNA microarray data and confirmatory cohort demonstrated that AXL ligand GAS6 was highly expressed and correlated to poor survival [38]–[40].

An increasing body of evidence suggests that this survival difference may be due to AXL's suppressive effect on the innate immune response by supporting maturation of natural killer cells and inhibiting macrophage-driven inflammation. AXL has been shown to redirect downstream signaling via STAT1 to result in activation of suppression cytokine signaling proteins [41], and activation of AXL in macrophages leads to a switch from M1 to M2 phenotype resulting in inability to activate CD8 T-cells [42]. Interestingly, AXL has been demonstrated to be induced together with the appearance of drug resistance to both targeted and conventional chemotherapy [34]–[37], [43]–[45]. Therefore, clinical trials utilizing AXL inhibition have been launched for both liquid and solid tumors (NCT02488408, NCT02729298, NCT03454243, NCT02424617).

However, while this signaling axis represents an attractive target for therapeutic intervention, the strong picomolar binding affinity (~14-33 pM) between endogenous GAS6 and AXL and the promiscuity of

small molecule AXL inhibitors has historically presented a barrier to specific and potent inhibition of AXL. AVB-S6-500 is a highly sensitive and specific inhibitor of AXL, with apparent affinity of 93-324 femtomolar to G AS6, which is approximately 200-fold higher affinity than wild-type (WT) AXL. AVB-S6-500 binds GAS6, the sole ligand of AXL, inhibiting its interaction with AXL, thereby dramatically reducing AXL signaled invasion and migration of highly metastatic cells *in vitro* and inhibiting metastatic disease in nonclinical models of aggressive human cancers.

1.1.5 COMBINATION OF IMMUNE CHECKPOINT AND AXL INHIBITION

There is the expectation of synergy between AXL and immune targeting agents[46]. A recent study investigated the genomic profile of anti-PD1 checkpoint-resistant melanoma, and demonstrated that AXL transcript levels were significantly correlated to resistance [47]. Subsequent literature further investigated the role of AXL in checkpoint sensitive and resistant clones and demonstrated that loss of AXL resulted in significantly greater TIL population and subsequent response to radiotherapy and checkpoint immunotherapy[43]. These findings have now been supported with translational mouse models of colon and breast cancer, with markedly decreased tumor growth with dual inhibition of AXL and immune checkpoint inhibition[48]–[50]. Trials utilizing this combination of immune checkpoint inhibition and AXL inhibitor have begun in other solid tumor types, including lung and breast cancer (NCT03184571, NCT03184558).

1.2 DURVALUMAB: 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 [51]. *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism[51]. Based on these data, durvalumab is expected to stimulate the patient'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 8000 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.

1.3 AVB-S6-500: NON-CLINICAL AND CLINICAL EXPERIENCE

AVB-S6-500, a GAS6-AXL pathway inhibitor, is an engineered receptor-Fc fusion protein therapeutic and is being developed by Aravive for use in the treatment of cancer. The proposed MOA for AVB-S6-500 is the high affinity and highly specific binding to GAS6, the sole ligand for AXL, with 200 fold greater affinity compared to native AXL receptor. In vitro studies demonstrate that AVB-S6-500 has single agent efficacy in metastatic ovarian cancer models, decreasing both number of metastases and

tumor weight. While the exact mechanism requires further elucidation, prior data suggests that AXL inhibition stimulates a patient's antitumor immune response by decreasing suppressive cytokine signaling and preventing the AXL mediating macrophage switch from the M1 to the M2 phenotype. Additionally, AVB-S6-500 proposed anti-fibrotic effects may benefit desmoplasia and drug penetrance.

When directly compared in nonclinical models with the most advanced selective anti-AXL small molecules currently in clinical development, AVB-S6-500 achieved superior antitumor efficacy while displaying no toxicity in pharmacology studies [52]. AVB-S6-500 causes regression of tumor cells in vivo when dosing in these models commenced 4-7 days after tumor inoculation and establishment of small tumors in the mouse. However, AVB-S6-500 is not directly cytotoxic in vitro and under normal physiological (nonstressed) conditions, as the in vitro IC50 in cancer cells (with high levels of AXL on the cell surface) is > 100 μM. Modulation of AXL signaling by a predecessor AXL decoy receptor protein, MYD1 Fc (AXL-S6-1 hIgG), increased expression of the epithelial marker E-cadherin, consistent with the AXL decoy protein causing a mesenchymal to epithelial phenotype transition in vivo [52]. Reversal of the mesenchymal phenotype has been reported to cause growth inhibition, suppression of spheroid forming capacity and induction of apoptosis[53], [54]. This is consistent with the combination treatment studies conducted with predecessor proteins, which demonstrated a relationship between AXL signaling and the cellular response to DNA damage in breast, pancreatic and ovarian cancer models. The damage was observed more so in combination with cytotoxic chemotherapies such as doxorubicin and gemcitabine[52]. Thus, inhibiting the AXL/GAS6 pathway in stressed cells (due to transition from mesenchymal to epithelial phenotype and/or in combination with cytotoxic agents) appears to lead to cell death in vivo.

Safety data from the Phase 1 first-in-human study in healthy volunteers indicate that AVB-S6-500 was very well tolerated across all administered doses and a MTD was not reached. In addition to safety and tolerability, serum levels of AVB-S6-500 (pharmacokinetic [PK] data) and serum GAS6 levels (pharmacodynamics data) were used to identify the active doses of AVB-S6-500 that fully suppress serum GAS6 and guided selection of doses to be tested in combination with the standard-of-care (SOC) therapies in Phase 1b/2 studies in cancer patients. Refer to Investigational Brochure for complete details.

1.4 RESEARCH HYPOTHESIS

Our overarching hypothesis is that the addition of AXL inhibition via the novel agent AVB-S6-500 to durvalumab (MEDI4736) therapy will produce clinically significant improvement in response rate compared to the currently achievable response rate with programmed cell death protein 1 (PD1) immune inhibition alone in patients with platinum resistant epithelial ovarian, fallopian tube and primary peritoneal cancers (that will be collectively referred to as EOC). We hypothesize that this combination will be associated with an acceptable toxicity profile. Additionally, dual targeting of programmed cell death protein ligand 1 (PDL1) and AXL in combination may synergistically prolong time to progression. In an exploratory analysis we will also compare translational objectives, to investigate molecular and immunologic changes associated with the combination of AVB-S6-500 and durvalumab.

1.5 RATIONALE FOR CONDUCTING THIS STUDY

1.5.1 AVB-S6-500 DOSE

Based on available data from a recently completed First-in-Human, Phase 1 study in healthy volunteers (AVB500-HV-001), PK and pharmacodynamics data for AVB-S6-500 were evaluated in real time using validated enzyme linked immunosorbent assays (ELISA) in each cohort. As expected with an IV administered drug, Cmax increased proportionally to dose and Tmax was 1 h (the earliest time point

collected) for all doses. Consistent with target mediated drug disposition (TMDD), the area under the curve (AUC) increased more than proportionally across doses and the half-life increased across doses. At the lowest dose tested, 1 mg/kg, serum GAS6 levels were suppressed (below level of quantitation [BLQ] of 2 ng/mL) for one-week post-dose in 4 out of 6 subjects. All 6 subjects in the 2.5 and 5 mg/kg groups had serum GAS6 levels BLQ 1-week post dose. All 6 subjects in the 5 mg/kg had serum GAS6 levels BLQ 2 weeks post dose. A single 10 mg/kg dose suppressed serum GAS6 for at least 3 weeks. Thus, all single doses tested had the desired pharmacological activity. In addition, GAS6 levels were suppressed for 3 weeks after the 4th dose of 5 mg/kg in the RD portion of the study.

The dosing regimen that will be tested in the current trial is therefore 10 mg/kg every other week. The AVB-S6-500 concentrations vs the serum GAS6 levels are shown in the **Figure 1** for this recommended dosing. This dose is anticipated to provide abrogation of serum GAS6 for at least 14 days and maintain the AVB-S6-500 levels in blood above those needed for 90% saturation of GAS6. Additionally, as above, subjects in the 5 mg/kg dosing also had serum GAS6 levels BLQ at 2 weeks post-dose. Thus, all doses intended during the current study, including dose de-escalation, had the desired pharmacological activity.

In terms of safety, review of safety data from first-in-human study suggests that IV doses of up to 10 mg/kg of AVB-S6-500 have been well tolerated. No serious adverse events (SAEs), deaths or withdrawals from study due to AEs have been reported. The incidence of treatment-emergent AEs (TEAE) does not appear to increase with dose.

However, if tolerability issues unexpectedly arise for the AVB-S6-500 combination with Durvalumab, there is opportunity to adjust the AVB-S6-500 dose prior to enrolling the combination cohort. If, after review of the first cycle safety data from 3 subjects, the regimen of 10 mg/kg AVB-S6-500 every 2 weeks (Q2W) is deemed not well-tolerated in combination with Durvalumab, 3 new subjects will be enrolled into a cohort with a lower AVB-S6-500 dose of 5 mg/kg with weekly dosing (the durvalumab dose would remain unchanged).

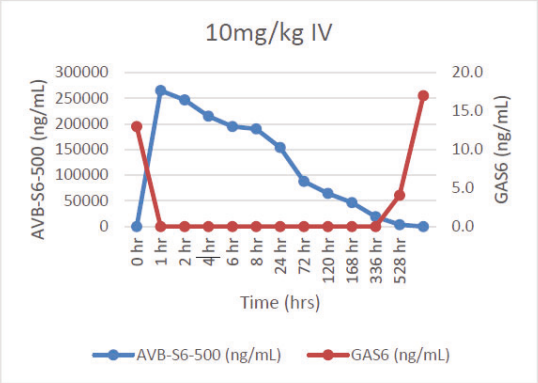

Figure 1. PK/PD for the 10 mg/kg Cohort

1.5.2 DURVALUMAB DOSE

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

Similar findings have been reported by others[55]–[58]. 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 [56]. 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 [57].

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 combination therapy phases of the current study. Weight based dosing at 20 mg/kg will be utilized for any patient whose body weight drops below 30 kg while on the combination treatment.

For the monotherapy phase, Q3W dosing will be employed with fixed dose of 1120 mg, in order to accommodate the 6 week monotherapy lead-in timing. Patients randomized to durvalumab monotherapy will then transition to the Q4W dosing at initiation of combination phase, as above.

1.6 BENEFIT/RISK AND ETHICAL ASSESSMENT

1.6.1 POTENTIAL BENEFITS

Patients with platinum resistant ovarian cancer have a poor prognosis with typical response rates of 0-20% and median PFS of approximately 3 months and OS ranging between 8 and 17 months across a large number of clinical trials employing cytotoxic and biological antineoplastic therapies[2], [3]. Emerging data from clinical trials investigating immune checkpoint inhibitors targeting PD1 pathways reveal that approximately 10-15% of patients with platinum resistant ovarian cancer respond to checkpoint inhibitor monotherapy[8]. Furthermore, many of the responses are durable in nature lasting many months. However, ongoing trials reveal that combination therapies are required in order to improve this low response rate. The expected synergy with AXL inhibition represents a valuable and important avenue of investigation in this patient population with no better alternative treatment options.

1.6.2 OVERALL RISKS

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

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

1.6.2.1 AVB-S6-500

AVB-S6-500 has been well tolerated across all doses trialed in initial healthy volunteer single ascending dose and repeat dose trial. There were no serious adverse events. There were no treatment-related changes noted in physical examinations or vital signs. None of the AEs based on laboratory values were deemed clinically significant, none required treatment, and all were asymptomatic. As per protocol, all laboratory values that met CTCAE v 4.03 criteria for subjects given active drug were considered possibly related. None were considered probably/likely or certainly related. Further information can be found in the Investigator's Brochure.

However, the combination of AXL inhibition with durvalumab may result in exacerbation of immune-related adverse effects. Therefore, the risks with the combination include, but are not limited to, the categories as listed within **Section 1.6.2.2**.

1.6.2.2 DURVALUMAB

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

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated adverse events (**Section 6.3.1**).

1.6.3 OVERALL BENEFIT-RISK

Ovarian cancer is the deadliest gynecologic malignancy, with a short progression free interval and limited treatment options at time of recurrence. While checkpoint inhibition has showed exciting initial activity, the rates of response remain low. Therefore, further investigation of novel combinations where synergy is expected, such as with AXL inhibition, represents an essential approach to advancing the care of these women. Additionally, rapid expansion of the use of immunotherapies have demonstrated that the majority of immune-related adverse events are manageable and acceptable in such a patient group with few alternatives. Thus, overall, the risks-benefit ratio is in favor of further investigations to refine checkpoint and AXL inhibitor therapy combinations and their associated toxicities in this population.

2. STUDY OBJECTIVES

2.1 PRIMARY

To determine toxicity profile of the combination of AVB-S6-500 and durvalumab therapy

2.2 SECONDARY

1. To estimate objective response rate to combination AVB-S6-500 and durvalumab therapy
2. To estimate the median immune-related progression free survival (irPFS) as well as overall survival OS by RECIST 1.1 after treatment with combination durvalumab and AVB-S6-500
3. To investigate molecular and immunological changes associated with the combination of AVB-S6-500 and durvalumab; specifically to describe changes in T cell populations (including but not limited to CD3, CD8, CD4, FOXP3) and cell proliferation, as well as report changes in the proportion of macrophage phenotypes M1 and M2 (with phenotypic markers potentially including arginase1, CD11b, PDL-1, and CD206)

2.3 EXPLORATORY

1. To evaluate blood and tissue-based biomarkers for immune related adverse events and disease progression
2. To investigate impact and possible sensitization of pretreatment with AVB-S6-500 monotherapy on subsequent combination of durvalumab and AVB-S6-500
3. To evaluate for molecular and immunologic differences between pre-treatment with single agent AVB-S6-500 as compared to durvalumab

3. ORIGINAL STUDY DESIGN

This is a randomized phase I/II trial of the combination of immune checkpoint inhibitor therapy and AXL inhibition in patients with recurrent platinum resistant EOC. The design is based on the clinical rationale that the combination of durvalumab and AVB-S6-500 may have increased efficacy but at the risk of potentially greater toxicity. This trial will determine appropriate combination dosing and then, based on efficacy and safety assessments, allow for development of a superior suitable regimen for a follow-up phase III investigation based on these efficacy and toxicity tradeoffs. It will also be informative regarding response rates associated with this combination regimen and will generate key preliminary data to determine impact on irPFS and if pretreatment with either durvalumab or AVB-S6-500 impacts subsequent response to the combination of both therapies. Furthermore, translational correlative studies will include immune profiling and ribonucleic acid (RNA) expression analysis of tumor at enrollment, following monotherapy, and on combination treatment to investigate biological correlates for response, possible sensitization of immune microenvironment, and any indication of adverse event. Progression during investigational agent treatment cycles will be defined based on immune-related response criteria (irRC; including computed tomography (CT) confirmation at least 5 weeks apart to determine progression).

3.1 END OF STUDY ENROLLMENT

In the first quarter of 2021, study supporters Aravive and AstraZeneca made the decision to end enrollment based on available data after the 5th evaluable subjected completed treatment on the safety lead-in.

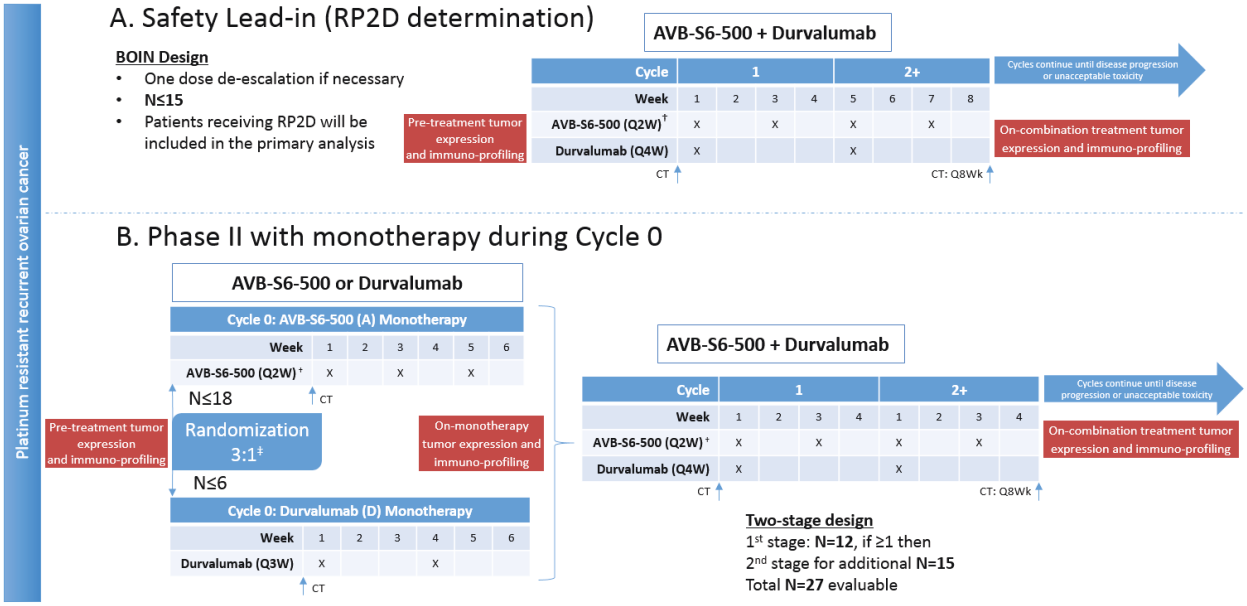

Figure 2. Study Schema

Dosing schedule as above demonstrates investigational product at week of administration, where A = AVB-S6-500 monotherapy, D= durvalumab monotherapy, and A+D = AVB-S6-500 + durvalumab combination therapy

* Patients receiving the recommended Phase 2 dose (RP2D) will then be included in the primary analysis of the combination therapy. However, these patients will continue on the Safety Lead-in dosing schedule and will not participate in the Phase 2 monotherapy. See de-escalation dosing regimens below.

‡ Sample size calculations account for predicted 8% dropout rate due to toxicity.

† Dosing schedule shown reflects the starting dose for the dose escalation. This may be adjusted for the de-escalation schedule below and determination of the RP2D.

Table 1. Dosing for Dose Escalation

Dose Level	Durvalumab + AVB-S6-500
Dose Level 0 (Initial dose)	durvalumab (1500mg Q4W), AVB-S6-500 (10mg/kg Q2W)
Dose level 1	durvalumab (1500mg Q4W), AVB-S6-500 (15mg/kg Q2W)
Dose level 2	durvalumab (1500mg Q4W), AVB-S6-500 (20mg/kg Q2W)

3.2 SAFETY LEAD-IN

The trial will begin with a dose escalation phase to determine the recommended Phase 2 dose (RP2D). The design for dose escalation is provided in **Section 9**. The dose level established in the dose escalation phase will define the recommended dosing for subsequent combination treatment. Those patients treated at the RP2D will continue on treatment and will contribute to primary analysis of combination therapy.

Of note, prior to receipt of any treatment, all patients will undergo a computed tomography (CT) scan to determine baseline volume of disease. An initial pre-treatment biopsy and blood samples will be obtained to measure immune function in both the pretreated tumor environment and systemically.

To investigate translational aims, all patients participating in safety lead-in cohorts will undergo a biopsy and blood sampling after receiving 6 weeks of treatment.

Refer to the Schedule of Assessments in **Table 6** for complete details (**Section 6.5**).

3.3 PHASE II

The Phase II portion of the study will begin after the RP2D is established in the Safety Lead-in. In Phase II, eligible subjects first will participate in a 6-week monotherapy cycle (Cycle 0) with either AVB-S6-50 (ARM I) or durvalumab (ARM II) before proceeding to receive the combination therapy at the RP2D. We will randomize 3:1 to AVB-S6-500 and durvalumab monotherapy arms, respectively. Subjects randomized to Arm 1 will receive single agent AVB-S6-500 (Q2W), and subjects randomized to Arm 2 will receive durvalumab (fixed Q3W dosing) during the monotherapy cycle. The monotherapy dose for each agent will be based on the combination RP2D established in the Safety Lead-in. Prior to receiving monotherapy treatment, all subjects will undergo a CT scan to determine initial volume of disease. An initial pre-treatment biopsy and blood samples will be obtained to measure immune function in both the pretreated tumor environment and systemically.

Following 6 weeks of monotherapy treatment, a repeat CT scan will be performed and an additional biopsy will be obtained. Of note, this CT scan serves as the new baseline imaging from which response to combination will be compared.

All patients who have completed monotherapy treatment without limiting toxicity will then be treated with combination therapy at the RP2D. Patients will receive treatment until progression or unacceptable toxicity with combination therapy. An additional biopsy will be obtained after 2 cycles of therapy, and CT scans will be performed every 8 weeks.

Refer to the Schedules of Assessments in **Table 7** and **Table 8** for complete details (**Section 6.5**).

4. PATIENT SELECTION

4.1 INCLUSION CRITERIA

Inclusion criteria will be assessed within 28 days of starting study treatment:

1. Ability to provide signed informed consent.
2. Age ≥ 18 years at time of study entry.
3. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
4. Histology (reviewed at MDACC) showing recurrent high grade epithelial ovarian, peritoneal, or fallopian tube cancer.
5. Platinum resistant or refractory disease as defined by progression of disease on a platinum-containing regimen or recurrence of disease within 180 days of previous platinum treatment.
6. Have measurable disease based on modified RECIST 1.1. For the purposes of this study measurable disease is defined at least one "target lesion" that can be accurately measured in at least one dimension (longest dimension to be recorded). Each target lesion must be >20 mm when measured by conventional techniques, including palpation, plain x-ray, computed tomography (CT), and magnetic resonance imaging (MRI), or >10 mm when measured by spiral CT. The

target lesion must be distinct from other tumor areas selected for pre-treatment biopsies. Pre-treatment imaging must be performed within 4 weeks of starting therapy.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Life expectancy of ≥12 weeks.
9. Body weight >30 kg. Note: if subject's weight falls below 30 kg during study but the patient is otherwise eligible to continue investigational therapy the dose of durvalumab will be modified to be weight-based (20 mg/kg for the 1500 mg dose; modification is not required for 1120 mg dose). Refer to **Section 5.1.2** and **Appendix C** for complete details.
10. Adequate normal organ and marrow function as defined below.
    a. Hemoglobin ≥9.0 g/dL.
    b. Absolute neutrophil count (ANC) > 1500/mm^3.
    c. Platelet count ≥100 x 10^9/L (>75,000/mm^3).
    d. Serum bilirubin ≤1.5 x ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
    e. AST (SGOT)/ALT (SGPT) ≤2.5 x ULN unless liver metastases are present, in which case it must be ≤5x ULN.
    f. Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

11. Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. 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).
    b. 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).
12. Patients must have no currently available standard of care treatment options

4.2 EXCLUSION CRITERIA

Exclusion criteria will be assessed within 28 days of starting study treatment:

1. Participation in another clinical study with an investigational product during the last 28 days.
2. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
3. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤28 days prior to

the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca, Aravive, and the investigator.

4. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the primary investigator.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the primary investigator.
5. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
6. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
7. History of allogenic organ transplantation.
8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., 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. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
    c. Any chronic skin condition that does not require systemic therapy.
    d. Patients without active disease in the last 5 years may be included but only after consultation with the primary investigator.
    e. Patients with celiac disease controlled by diet alone.
9. 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 patient to give written informed consent.
10. Any medical, social, or psychological condition that would interfere with evaluation of study treatment or interpretation of patient safety or study results.
11. 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 (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
12. History of another primary malignancy except for the following histories.
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease.
13. History of leptomeningeal carcinomatosis.

14. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have a MRI (preferred) or CT each preferably with intravenous (IV) contrast of the brain prior to study entry.
15. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms.
16. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or AVB-S6-500. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., 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 (e.g., CT scan premedication).
17. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 90 days after the last dose of IP.
18. Female patients who are pregnant or breastfeeding or of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + AVB-S6-500 combination therapy.
19. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
20. Unresolved partial or complete small or large bowel obstruction
21. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

4.3 WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT AND/OR STUDY

4.3.1 PERMANENT DISCONTINUATION OF DURVALUMAB + AVB-S6-500

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

1. Withdrawal of consent or lost to follow-up.
2. Adverse event that, in the opinion of the investigator, contraindicates further dosing.
3. Patient 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.
4. Pregnancy or intent to become pregnant.
5. Any AE that meets criteria for discontinuation as defined in **Section 6.3**.
6. Clinically significant dose-limiting toxicity (DLT) that is attributable to both drugs. Durvalumab or AVB-S6-500 may be held individually due to a DLT while dosing with the other drug continues if the DLT is attributable to only one drug (See **Section 6.2** for definition of DLT and **Section 6.3** for individual drug dose holds).
7. Grade ≥3 infusion reaction.
8. Patient noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Confirmation, per irRC, of PD and investigator determination that the patient is no longer benefiting from treatment with durvalumab and AVB-S6-500. See **Section 7.2**.
11. Subjects who are discontinued from further receipt of both investigational products, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Patients who are permanently discontinued from receiving investigational product will be followed for safety per Schedule of Assessments, including the collection of any protocol-specified blood specimens, unless consent is withdrawn, or the patient is lost to follow-

up or enrolled in another clinical study. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 6 months as an alternative.

4.3.2 WITHDRAWAL OF CONSENT

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

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient 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.

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

- all further participation in the study including any further follow up (e.g., survival contact telephone calls),
- withdrawal of consent to the use of their study generated data, and/or
- withdrawal to the use of any samples.

4.3.3 REPLACEMENT OF PATIENTS

Subjects who withdraw consent or otherwise become ineligible prior to receiving the first dose of investigational regimen will be replaced.

5. INVESTIGATIONAL PRODUCTS

5.1 DURVALUMAB

5.1.1 FORMULATION/PACKAGING/STORAGE

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/ histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. 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 original packaging until use to prevent prolonged light exposure.

5.1.2 PRODUCT PREPARATION AND DOSE ADMINISTRATION

Patients in the durvalumab monotherapy treatment group will receive Q3W dosing of 1120 mg durvalumab during the monotherapy cycle (Cycle 0).

In the Safety Lead-in Phase and during the combination treatments in Phase II, subjects will receive Q4W dosing of 1500 mg durvalumab (for patients >30kg in weight). Weight based dosing at 20 mg/kg will be utilized for any patient whose body weight drops below 30 kg while on the combination treatment.

The dose of durvalumab (MEDI4736) for administration must be handled and prepared by the Investigator's or site's designated IP manager using aseptic technique according to institutional guidelines. 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

A dose of 1500 mg (for patients >30kg in weight) or 1120 mg will be administered using an intravenous (IV) bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500 mg of durvalumab [MEDI4736]) or 22.4 mL (i.e., 1120 mg of durvalumab [MEDI4736]) 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.

If patient weight falls to < 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is 1 hour, however if there are interruptions during infusion, the total and allowed infusion time should not exceed 8 hours at room temperature. If preparation time or infusion time exceeds the time limits 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.

During combination treatment, durvalumab will be administered prior to AVB-S6-500. IV line flushing in between IP treatments will be performed per institutional policy.

5.1.3 MONITORING OF DOSE ADMINISTRATION

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

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. However, a single occurrence of a Grade 3 reaction that resolves within 6 hours is permitted in the absence of prophylaxis. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Section 6.3**.

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 patients to an intensive care unit if necessary.

5.2 AVB-S6-500

The AVB-S6-500 is an Fc fusion protein of the extracellular portion of the AXL receptor that has been engineered to have higher affinity to GAS6 by the substitution of five amino acids in the AXL extracellular domain. The molecule consists of one of the genetically modified AXL receptors fused to each arm of a human Fc molecule (CH2 & CH3), thereby creating a dimer of the genetically modified AXL receptor.

5.2.1 FORMULATION/PACKAGING/STORAGE

AVB-S6-500 will be supplied by Aravive as a solution for injection with the composition of the formulated drug product (DP) shown in Table 1. AVB-S6-500 should be diluted in normal saline prior to infusion.

AVB-S6-500 DP vials are filled with 10 mL at 20 mg /mL (±2 mg/mL) for a total of approximately 200 mg/vial into 20 mL Schott USP Type I glass vials with rubber stoppers and aluminum-plastic flip caps. Vials are filled on an automated aseptic filling line and stored at -20°C.

Vials of AVB-S6-500 drug product should be refrigerated in their box at 2-8℃ until ready to use. Refer to Investigator's brochure and pharmacy manual for additional details.

Table 2. Formulation of AVB-S6-500 Drug Product

Components	Function	Amount
AVB-S6-500	Active	20 mg/ml ± 2 mg/mL
Polysorbate-80	Stabilizer	0.01%
Mono and disodium phosphate	Buffer to pH 7.0	10 mM
Sucrose	Stabilizer	9%

5.2.2 PRODUCT PREPARATION AND DOSE ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. AVB-S6-500 should be diluted in normal saline to a total volume of 150 mL (to achieve the desired dose in mg/kg) and administered as an i.v. infusion over 60 minutes.

During combination treatment, durvalumab will be administered prior to AVB-S6-500. IV line flushing in between IP treatments will be performed per institutional policy.

5.2.3 PRE-MEDICATION FOR AVB-S6-500 DOSING

All patients must be premedicated with anti-H1 and anti-H2 prior to first administration of AVB-S6-500 (Cycle 0 in the AVB-S6-500 monotherapy group; Cycle 1 in the Safety Lead-In and durvalumab monotherapy groups) to reduce the risk and severity of infusion reaction.

Premedication (or components thereof) could be optionally omitted for future cycles, if no infusion reaction was observed during or after the first AVB-S6-500 infusion.

Steroids can be optionally included at the discretion of the treating physician, ideally administered the evening before and again the morning of dosing (for example, dexamethasone 12 mg PO the evening prior and 12 mg PO in the morning prior to dosing). If IV steroids are utilized on the morning of dosing, they should be administered at least 1 hour prior to dosing.

Most infusion reactions occur toward the end of the infusion, or after the infusion has been completed, and patients must be observed for at least 45 minutes after their first AVB-S6-500 infusion.

Any patient who experiences a reaction DURING the infusion and is deemed by the Investigator to be acceptable for same day rechallenge, should be premedicated prior to rechallenge, and the remainder of the infusion should be administered at one-half of the previous infusion rate.

Any patient who experiences a reaction AFTER the infusion and is deemed by the Investigator to be acceptable for rechallenge with the next dose, should be premedicated with an anti-H1, anti-H2, and steroid-containing regimen prior to rechallenge, and the duration of AVB-S6-500 at rechallenge should be 2 hours (instead of 1 hour).

If the patient tolerates AVB-S6-500 upon rechallenge, the premedication regimen and infusion duration should remain the same for subsequent dosing.

Infusion reactions should be managed symptomatically. Meperidine should be considered for treatment of rigors.

5.2.4 MONITORING OF DOSE ADMINISTRATION

Patients will be monitored before, during, and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment and as per **Section 5.1.3**. After the first AVB-S6-500 infusion, a 45-minute observation will be required for all patients (Cycle 0 in the AVB-S6-500 monotherapy group; Cycle 1 in the Safety Lead-In and durvalumab monotherapy groups). After the first infusion, observation will only be needed as clinically indicated.

5.3 ACCOUNTABILITY AND DISPENSATION

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent. The Velos IData System will be utilized by the MD Anderson Investigational Pharmacy services for accountability.

5.4 DISPOSITION OF UNUSED INVESTIGATIONAL STUDY DRUG

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. TREATMENT PLAN

6.1 PROCEDURES FOR RANDOMIZATION

Subjects will be recruited from the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. Patients with platinum resistant high grade ovarian, primary peritoneal, or fallopian tube cancers will be screened by the designated research staff and/or study investigators for eligibility. Interested patients will be approached and provided information regarding the study and potential eligibility and participation. After informed consent, screening evaluation will be performed to determine eligibility. Patients may elect to leave the study at any time.

We will enroll up to 30 evaluable subjects with platinum-resistant EOC at an expected rate of 3 subjects per month. Subjects will be evaluable for the primary objective once they have completed one cycle of combination therapy at the RP2D. Up to 12 evaluable subjects will be enrolled into the dose de-escalation combination phase (Safety Lead-in) to determine the RP2D. Once the RP2D is determined, subsequent subjects will be randomized to monotherapy arms as described below. To replace patients that are registered but do not proceed to treatment (e.g. screen failures), an additional 15 patients may be

registered; however, a maximum of 30 evaluable patients will be treated as per the protocol. Subjects will be treated until disease progression or until unacceptable toxicity. We will follow all patients for at least 12 months, and we will employ safety and efficacy monitoring rules as described in **Section 9.2.1** and **Section 9.2.2.**

Following RP2D determination, we will randomly assign patients to one of two monotherapy treatment arms (durvalumab or AVB-S6-500) at a ratio of 1 (durvalumab) to 3 (AVB-S6-500). All patients, with the exception of any who meet discontinuation criteria, will then receive combination treatment regimen.

Randomization will be carried out using CORe.

Subjects who are incorrectly enrolled but have not been initiated on treatment will be withdrawn from the study. Such subjects will be replaced. Any subjects who are incorrectly enrolled and randomized and initiated on therapy will be reported to the IRB as a protocol violation. Such subjects will be evaluated on an individual basis by the PI and the decision to continue treatment or withdraw will be based on an analysis of risk/benefit for the subject.

6.2 DEFINITION OF DOSE-LIMITING TOXICITIES

DLTs will be evaluated during the safety lead-in (dose de-escalation phase) of the trial. The period for evaluating DLTs will be from the time of first administration of study drug until 6 weeks (1.5 cycles). Any treatment-related toxicities that first occurred during the DLT period must be followed for resolution to determine if the event qualifies as a DLT as specified in the DLT criteria below. Patients who do not remain on the study up to this time for reasons other than DLT will be replaced with another patient at the same dose level. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

To be considered a DLT, an AE must be at least possibly related to the investigational product or regimen and meet the criteria listed below. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The DLT criteria are specified in the following lists.

Hematologic toxicity:

- Grade ≥3 neutropenia complicated by fever >38.3°C
- Grade ≥3 neutropenia that does not improve ≤Grade 1 within 7 days
- Grade 4 neutropenia (lasting more than 7 days)
- Grade ≥3 thrombocytopenia with significant bleeding
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding and does not improve by at least 1 grade within 7 days
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

Non-hematologic toxicity:

- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE, including fatigue, that does not resolve to ≤Grade 1 or baseline within 30 days with optimal medical management
- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to ≤Grade 2 or baseline within 15 days and to ≤Grade 1 within 30 days after onset of the event, despite optimal medical management including systemic corticosteroids

- Grade 3 diarrhea or colitis
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- **Aspartate** aminotransferase (AST) or **alanine** aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., "Hy's Law")
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN

The DLT definition excludes the conditions listed below.

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 lymphopenia
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 14 days

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

6.3 TOXICITY MANAGEMENT GUIDELINES

It is possible only one of the investigational agents is deemed attributed to causality of an AE, in this instance, only the attributed study drug may be held. Per principal investigator discretion, the treating investigator may elect to hold the study drug they deem attributable to the experienced AE.

6.3.1 DURVALUMAB

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab Toxicity Management Guidelines (TMGs). Please see **Section 6.3** and **Appendix A**.

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

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (**Appendix A**). Following the first dose of investigational product, subsequent administration of durvalumab and AVB-S6-500 can be modified based on toxicities observed. 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 and the durvalumab + AVB-S6-500 regimen by the reporting investigator

Following determination of RP2D, **dose reductions are not permitted**.

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

All toxicities will be graded according to NCI CTCAE, Version 5.0.

6.3.2 AVB-S6-500

The safety, pharmacokinetic and pharmacodynamic profile of AVB-S6-500 has been evaluated in healthy volunteers in a single-ascending dose (SAD) and repeat-dose (RD) Phase 1 clinical study (AVB500-HV-001). AVB-S6-500 was well tolerated at all doses evaluated in healthy volunteers.

Following the establishment of RP2D, **dose reductions are not permitted**. In addition, there are certain circumstances in which AVB-S6-500 should be permanently discontinued (see **Appendix A**).

6.3.3 COMBINATION TREATMENT REGIMEN

In addition to the individual toxicity management guidelines for durvalumab and AVB-S6-500 described above management of any potential overlapping toxicities that may occur following treatment with this combination must be considered. For AEs that are considered at least partly due to administration of durvalumab or AVB-S6-500, treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required). If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or AVB-S6-500 along with appropriate continuing supportive care.

For these subjects, once the AE resolves to permit resumption of the investigational combination, if the AE recurs at a dose-limiting severity, AVB-S6-500 and durvalumab dosing should be held until the recurrence until the AE resolves to Grade 1 or baseline. The AE should resolve to Grade 1 or baseline within 21 days for the subject to be considered for continued treatment. If the AE does not resolve to Grade 1 or baseline within 21 days, the investigator should consult the MDACC IND Office to determine feasibility of continued treatment with AVB-S6-500 and durvalumab.

6.4 RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

6.4.1 SUBJECTS OF CHILD-BEARING POTENTIAL

Female subjects of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (**Table 3**) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of study drug). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- 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.
- 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.

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly are described in **Table 3**. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 3. Highly Effective Methods of Contraception (<1% Failure Rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

6.4.2 BLOOD DONATION

Patients should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab or AVB-S6-500.

6.4.3 CONCOMITANT TREATMENT(S)

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary, as briefly listed in **Table 3**, to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Table 4. The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the medical record.

Table 4. Permitted Supportive Medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., 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 or alternate treating physician in consultation with Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

Table 5. 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 patient 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 patient 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 patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Prohibited medication/class of drug:	Usage:
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Use in patients 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 patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of durvalumab during the study
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 90 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by Aravive and AstraZeneca

6.5 SCHEDULES OF STUDY ASSESSMENTS AND PROCEDURES

Table 6. Schedule of Assessments and Procedures: Safety Lead-in

			Cycle 1 (4 weeks)		Cycle 2 (4 weeks)		Cycle 3+[a] (4 weeks)		EOT[b]	Follow-up[c]	
	Screening 1	Screening 2	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	N/A	30 Days	90 Days
Assessment/Procedure	Days -28 to -1	Days -28 to -1	N/A	±7 Days						±3 Days	±7 Days
Written Informed Consent	X[d]										
Medical History	X										
Physical Exam[e]	X		X	X	X	X	X	X	X	X	X
Vital Signs[f]	X		X[g]	X	X	X	X	X	X	X	X
ECOG PS	X		X	X	X	X	X	X	X	X	X
Adverse Event Evaluation	X		X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X
CBC w/Diff[h]	X		X	X	X	X	X	X	X	X	X
Chemistry Panel[i]	X		X	X	X	X	X	X	X	X	X
Beta hCG[j]	X		X		X		X		X		
Thyroid Function[k]	X		X		X		X		X		
Urinalysis[l]	X		X		X		X		X	X	X
Coagulation[m]	X										
Hepatitis/HIV Screening[n]	X										
ECG[o]	X										
Tumor Imaging[p]	X[q]					X[r]					
RECIST[s]	X					X					
Biopsy[t]	X[u]	X[v]				X[w]					
CA125			X		X		X		X		
Research Blood[x]			X[y]		X		X[z]				X
AVB-S6-500 dosing[aa]			X	X	X	X	X	X			
Durvalumab dosing[bb]			X		X		X				

[a] The procedures/assessments including treatment will continue until intolerable toxicity or confirmed progression.
[b] End of treatment (EOT) is defined as the last visit where the decision is made to discontinue protocol directed treatment, including confirmed progression of disease. All required procedure may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 35 days prior to the EOT visit.
[c] For subjects who end treatment de to progression, follow-up visits will occur every 6 weeks for at least 90 days or until initiation of subsequent treatment or alternative trial. For subjects who are no longer receiving study drug(s) but have not had confirmed progression, follow-up with clinical and laboratory evaluation will occur every 6 weeks with imaging assessment every 12 weeks (unless more frequent assessment is clinically indicated) for at least 90 days or until progression, whichever occurs later. All patients should have further chemistry profiles performed at 30 days (±3 days) and 90 days (±1 week) after permanent discontinuation of IP. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 6 months as an alternative.
[d] Informed consent of study procedures and pretreatment tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent,

these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

[e] Full physical exam will be performed at screening, with targeted physical exam at all other time points. Body weight is recorded at each visit. Height to be performed at screening only.

[f] Routine vital signs to be performed at each visit, and these should occur prior to infusion on treatment days. On treatment days, BP and pulse will be collected from patients prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ±5 minutes). If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

[g] A 1-hour observation period is recommended after the first dose of combination therapy.

[h] May be performed more frequently than noted in the schedule if clinically indicated. CBC with differential includes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, and total white cell count.

[i] May be performed more frequently than noted in the schedule if clinically indicated. Chemistry Panel includes: albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyltransferase, glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin total protein, BUN, and uric acid. If total bilirubin is ≥2 × ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Amylase and lipase are to be performed at screening, Day 1 of each cycle, and at EOT. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable. Bicarbonate, chloride, creatinine clearance, and magnesium testing are to be performed at screening, on Day 0 (if required), and if clinically indicated. If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Section 6.3** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. Gamma glutamyltransferase may be included at any time if clinically indicated.

[j] Serum B-HCG within 72 hours prior to the first dose of therapy and as clinically indicated prior to day 1 of each subsequent cycle and at end of treatment only in women of childbearing potential (women who are not surgically-sterile or post-menopausal).

[k] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

[l] Urinalysis includes: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color, and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

[m] May be performed more frequently than noted in the schedule if clinically indicated. Coagulation testing includes: PT, aPTT, and INR.

[n] Hepatitis screening tests include: HCV-Ab, HBsAg, HBcAb, and HBsAb.

[o] Resting 12-lead ECG on which QTcF must be <470 ms. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient 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 (e.g., 30 minutes) to confirm the finding. ECGs may be performed more frequently than noted in the schedule if clinically indicated.

[p] Imaging to occur Q8W (±7 days) and should continue unless the subject has confirmed progression, death or unacceptable toxicity. If progression is identified, then a confirmatory scan should be obtained 6 weeks (±7 days) after the first positive scan. As long as treatment is being well-tolerated and the investigator believes that the patient may derive benefit, the patient should continue regularly scheduled visits and receive additional treatment until the confirmatory scan results have been reviewed.

[q] Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with intravenous (IV) contrast of the brain.

[r] To occur during the final week of the marked Cycle, prior to initiating treatment in the following Cycle.
[s] RECIST measurements will be performed in line with imaging. Refer to **Section 7.1.**
[t] Refer to **Section 6.6.2** for details regarding Tumor sample.
[u] Biopsy can be newly acquired or archival ≤3 years old. Refer to **Section 6.6.2** for details regarding tumor sample.
[v] If subjects are not required to have a diagnostic biopsy (i.e. tumor recurrence/progression has been already histologically confirmed), tissue acquisition will occur during a research-only biopsy procedure. Refer to **Section 6.6.2** for details regarding tumor sample.
[w] To occur immediately prior to Cycle 3 where possible. Refer to **Section 6.6.2** for details regarding tumor sample.
[x] Sample will be taken within 45 minutes before dosing. Additional post-dose time points will be collected only on Day 1 of Cycle 1. See note "y" below. Refer to **Section 6.6.1**. A blood sample will be collected and processed for serum at the 90-day follow up visit to analyze for the presence of anti-drug antibodies for AVB-S6-500.
[y] Samples will be taken within 45 minutes before dosing begins and at 1 and 4 hours after the completion of treatment. Refer to **Section 6.6.1**.
[z] Cycles 3 and 4 only.
[aa] Refer to **Section 5.2**.
[bb] Refer to **Section 5.1**.

Table 7. Schedule of Assessments and Procedures: Phase II, Durvalumab Monotherapy Cohort

			Cycle 0 (6 Weeks)			Cycle 1 (4 Weeks)		Cycle 2 (4 Weeks)		Cycle 3+[a] (4 Weeks)		EOT[b]	Follow-up[c]	
	Screening 1	Screening 2	Day 1	Day 22	Day 29	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	N/A	30 Days	90 Days
Assessment/Procedure	**Days -28 to -1**	**Days -28 to -1**	**N/A**	**±7 Days**									**±3 Days**	**±7 Days**
Written Informed Consent	X[d]													
Medical History	X													
Physical Exam[e]	X		X	X		X	X	X	X	X	X	X	X	X
Vital Signs[f]	X		X[g]	X		X[h]	X	X	X	X	X	X	X	X
ECOG PS	X		X	X		X	X	X	X	X	X	X	X	X
Adverse Event Evaluation	X		X	X		X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X		X	X	X	X	X	X	X	X	X
CBC w/Diff[i]	X		X	X		X	X	X	X	X	X	X	X	X
Chemistry Panel[j]	X		X	X		X	X	X	X	X	X	X	X	X
Beta hCG[k]	X		X			X		X		X		X		
Thyroid Function[l]	X					X		X		X		X		
Urinalysis[m]	X		X			X		X		X		X	X	X
Coagulation[n]	X													
Hepatitis/HIV Screening[o]	X													
ECG[p]	X													
Tumor Imaging[q]	X[r]				X[s]				X[s]					
RECIST[t]	X				X				X					
Biopsy[u]	X[v]	X[w]			X[x]				X[y]					
CA125			X			X		X		X		X		
Research Blood[z]			X			X		X		X[aa]				X
AVB-S6-500 dosing[bb]						X	X	X	X	X	X			
Durvalumab dosing[cc]			X	X		X		X		X				

[a] The procedures/assessments including treatment will continue until intolerable toxicity or confirmed progression.
[b] End of treatment (EOT) is defined as the last visit where the decision is made to discontinue protocol directed treatment, including confirmed progression of disease. All required procedure may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 35 days prior to the EOT visit.
[c] For subjects who end treatment due to progression, follow-up visits will occur every 6 weeks for at least 90 days or until initiation of subsequent treatment or alternative trial. For subjects who are no longer receiving study drug(s) but have not had confirmed progression, follow-up with clinical and laboratory evaluation will occur every 6 weeks with imaging assessment every 12 weeks (unless more frequent assessment is clinically indicated) for at least 90 days or until progression, whichever occurs later. All patients should have further chemistry profiles performed at 30 days (±3 days) and 90 days (±1 week) after permanent discontinuation of IP. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 6 months as an alternative.
[d] Informed consent of study procedures and pretreatment tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to

randomization. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

[e] Full physical exam will be performed at screening, with targeted physical exam at all other time points. Body weight is recorded at each visit. Height to be performed at screening only.

[f] Routine vital signs at each visit and should occur prior to infusion on treatment days. On treatment days, BP and pulse will be collected from patients prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ±5 minutes). If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

[g] A 1-hour observation period is recommended after the first infusion of durvalumab.

[h] A 1-hour observation period is recommended after the first dose of combination therapy.

[i] May be performed more frequently than noted in the schedule if clinically indicated. CBC with differential includes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, and total white cell count.

[j] May be performed more frequently than noted in the schedule if clinically indicated. Chemistry Panel includes: albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyltransferase, glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin total protein, BUN, and uric acid. If total bilirubin is ≥2 × ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Amylase and lipase are to be performed at screening, Day 1 of each cycle, and at EOT. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable. Bicarbonate, chloride, creatinine clearance, and magnesium testing are to be performed at screening, on Day 0 (if required), and if clinically indicated. If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Section 6.3** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. Gamma glutamyltransferase may be included at any time if clinically indicated.

[k] Serum B-HCG within 72 hours prior to the first dose of therapy and as clinically indicated prior to day 1 of each subsequent cycle and at end of treatment only in women of childbearing potential (women who are not surgically-sterile or post-menopausal).

[l] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

[m] Urinalysis includes: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color, and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells.

[n] May be performed more frequently than noted in the schedule if clinically indicated. Coagulation testing includes: PT, aPTT, and INR.

[o] Hepatitis screening tests include: HCV-Ab, HBsAg, HBcAb, and HBsAb.

[p] Resting 12-lead ECG on which QTcF must be <470 ms. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient 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 (e.g., 30 minutes) to confirm the finding. ECGs may be performed more frequently than noted in the schedule if clinically indicated.

[q] Imaging to occur Q8W (±7 days) and should continue as long as the subject has not had confirmed progression, death or unacceptable toxicity. If progression is identified, then a confirmatory scan should be obtained 6 weeks (±7 days) after the first positive scan. As long as treatment is being well-tolerated and the investigator believes patient may derive benefit, the patient should continue regularly scheduled visits and receive additional treatment until the confirmatory scan results have been reviewed.

[r] Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with intravenous (IV) contrast of the brain.
[s] To occur during the final week of the marked Cycle, prior to initiating treatment in the following Cycle.
[t] RECIST measurements will be performed in line with imaging. Refer to **Section 7.1.**
[u] Refer to **Section 6.6.2**.
[v] Biopsy can be newly acquired (standard-of-care) or archival ≤3 years old. Refer to **Section 6.6.2** for details regarding tumor sample.
[w] If subjects are not required to have a diagnostic biopsy (i.e. tumor recurrence/progression has been already histologically confirmed), tissue acquisition will occur during a research-only biopsy procedure. Refer to **Section 6.6.2** for details regarding tumor sample.
[x] To occur immediately prior to initiation of combination therapy. Refer to **Section 6.6.2** for details regarding tumor sample.
[y] To occur immediately prior to initiation of Cycle 3 where possible. Refer to **Section 6.6.2** for details regarding Tumor sample.
[z] Sample will be taken within 45 minutes before dosing. Refer to **Section 6.6.1**. A blood sample will be collected and processed for serum at the 90-day follow up visit to analyze for the presence of anti-drug antibodies for AVB-S6-500.
[aa] Cycles 3 and 4 only.
[bb] Refer to **Section 5.2**.
[cc] Refer to **Section 5.1**.

Table 8. Schedule of Assessments and Procedures: Phase II, AVB-S6-500 Monotherapy Cohort

			Cycle 0 (6 Weeks)			Cycle 1 (4 Weeks)		Cycle 2 (4 Weeks)		Cycle 3+[a] (4 Weeks)		EOT[b]	Follow-up[c]	
	Screening 1	Screening 2	Day 1	Day 15	Day 29	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	N/A	30 Days	90 Days
Assessment/Procedure	**Days -28 to -1**	**Days -28 to -1**	**N/A**	**±7 Days**									**±3 Days**	**±7 Days**
Written Informed Consent	X[d]													
Medical History	X													
Physical Exam[e]	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X		X[g]	X[g]	X[g]	X[h]	X[o]	X[o]	X[o]	X[o]	X[o]	X	X	X
ECOG PS	X		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X
CBC w/Diff[i]	X		X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel[j]	X		X	X	X	X	X	X	X	X	X	X	X	X
Beta hCG[k]	X		X			X		X		X		X		
Thyroid Function[l]	X					X		X		X		X		
Urinalysis[m]	X		X			X		X		X		X	X	X
Coagulation[n]	X													
Hepatitis/HIV Screening[o]	X													
ECG[p]	X													
Tumor Imaging[q]	X[r]				X[s]				X[s]					
RECIST[t]	X				X				X					
Biopsy[u]	X[v]	X[w]			X[x]				X[y]					
CA125			X			X		X		X		X		
Research Blood[z]			X			X		X		X[aa]				X
AVB-S6-500 dosing[bb]			X	X	X	X	X	X	X	X	X			
Durvalumab dosing[cc]						X		X		X				

[a] The procedures/assessments including treatment will continue until intolerable toxicity or confirmed progression.
[b] End of treatment (EOT) is defined as the last visit where the decision is made to discontinue protocol directed treatment, including confirmed progression of disease. All required procedure may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 35 days prior to the EOT visit.
[c] For subjects who end treatment due to progression, follow-up visits will occur every 6 weeks for at least 90 days or until initiation of subsequent treatment or alternative trial. For subjects who are no longer receiving study drug(s) but have not had confirmed progression, follow-up with clinical and laboratory evaluation will occur every 6 weeks with imaging assessment every 12 weeks (unless more frequent assessment is clinically indicated) for at least 90 days or until progression, whichever occurs later. All patients should have further chemistry profiles performed at 30 days (±3 days) and 90 days (±1 week) after permanent discontinuation of IP. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 6 months as an alternative.
[d] Informed consent of study procedures and pretreatment tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent,

these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

[e] Full physical exam will be performed at screening, with targeted physical exam at all other time points. Body weight is recorded at each visit. Height to be performed at screening only.

[f] Routine vital signs to be performed at each visit, and these should occur prior to infusion on treatment days.

[g] During administration of monotherapy AVB-S6-500: BP and pulse will be collected from patients prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]), approximately 15 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 30 minutes ±5 minutes). If the infusion takes longer than 30 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of AVB-S6-500.

[h] During administration of combination therapy: BP and pulse will be collected from patients prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ±5 minutes). If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first dose of combination therapy.

[i] May be performed more frequently than noted in the schedule if clinically indicated. CBC with differential includes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, and total white cell count.

[j] May be performed more frequently than noted in the schedule if clinically indicated. Chemistry Panel includes: albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyltransferase, glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin total protein, BUN, and uric acid. If total bilirubin is ≥2 × ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Amylase and lipase are to be performed at screening, Day 1 of each cycle, and at EOT. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable. Bicarbonate, chloride, creatinine clearance, and magnesium testing are to be performed at screening, on Day 0 (if required), and if clinically indicated. If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Section 6.3** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. Gamma glutamyltransferase may be included at any time if clinically indicated.

[k] Serum B-HCG within 72 hours prior to the first dose of therapy and as clinically indicated prior to day 1 of each subsequent cycle and at end of treatment only in women of childbearing potential (women who are not surgically-sterile or post-menopausal).

[l] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

[m] Urinalysis includes: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color, and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

[n] May be performed more frequently than noted in the schedule if clinically indicated. Coagulation testing includes: PT, aPTT, and INR.

[o] Hepatitis screening tests include: HCV-Ab, HBsAg, HBcAb, and HBsAb.

[p] Resting 12-lead ECG on which QTcF must be <470 ms. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient 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 (e.g., 30 minutes) to confirm the finding. ECGs may be performed more frequently than noted in the schedule if clinically indicated.

[q] Imaging to occur Q8W (±7 days) and should continue as long as the subject has confirmed progression, death or

acceptable toxicity. If progression is identified, then a confirmatory scan should be obtained 5 weeks (±7 days) after the first positive scan. As long as treatment is being well-tolerated and the investigator believes patient may derive benefit, the patient should continue regularly scheduled visits and receive additional treatment until the confirmatory scan results have been reviewed.

[r] Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with intravenous (IV) contrast of the brain.

[s] To occur during the final week of the marked Cycle, prior to initiating treatment in the following Cycle.

[t] RECIST measurements will be performed in line with imaging. Refer to **Section 7.1.**

[u] Refer to **Section 6.6.2**.

[v] Biopsy can be newly acquired or archival ≤3 years old. If subjects are not required to have a diagnostic biopsy (i.e. tumor recurrence/progression has been already histologically confirmed), tissue acquisition will occur during a research-only biopsy procedure. Refer to **Section 6.6.2** for details regarding tumor sample.

[w] If subjects are not required to have a diagnostic biopsy (i.e. tumor recurrence/progression has been already histologically confirmed), tissue acquisition will occur during a research-only biopsy procedure. Refer to **Section 6.6.2** for details regarding tumor sample.

[x] To occur immediately prior to initiation of combination therapy. Refer to **Section 6.6.2** for details regarding tumor sample.

[y] To occur immediately prior to initiation of Cycle 3 where possible. Refer to **Section 6.6.2** for details regarding tumor sample.

[z] Samples will be taken within 45 minutes before dosing. Refer to **Section 6.6.1**. A blood sample will be collected and processed for serum at the 90-day follow up visit to analyze for the presence of anti-drug antibodies for AVB-S6-500.

[aa] Cycles 3 and 4 only.

[bb] Refer to **Section 5.2**.

[cc] Refer to **Section 5.1**.

6.6 BIOLOGICAL SAMPLING PROCEDURES

6.6.1 RESEARCH BLOOD

A pharmacokinetics/pharmacodynamics (AVB-S6-500 plasma concentration/GAS6 suppression) model was developed from non-human primate (monkey) data, scaled to humans, and used to predict human AVB-S6-500 exposure and GAS6 suppression (refer to AVB-S6-500 Investigator Brochure for more complete details). In healthy volunteer studies, GAS6 was demonstrated to be suppressed for at least 3 weeks post-dose administration. Therefore, in the current study we will collect blood to evaluate GAS6 levels as a relevant biomarker at cycles 1 and 2, immediately prior to dose administration.

Blood will be collected on the days noted in the Schedules of Assessments in **Section 6.5**. Sample collection specifics are detailed below.

Table 9. Detailed Research Blood Collection Schedule

Phase of Study	**Safety Lead-in**		**Phase II: Durvalumab**		**Phase II: AVB-S6-500**	
Time point	**Serum**	**Plasma/ PBMC**	**Serum**	**Plasma/ PBMC**	**Serum**	**Plasma/ PBMC**
Cycle 0 Day 1: Pre-treatment	N/A			X	X	X
Cycle 1 Day 1: Pre-treatment	X	X	X	X	X	X
Cycle 1 Day 1: 1 hour after treatment	X					
Cycle 1 Day 1: 4 hours after treatment	X					
Cycle 2 Day 1: Pre-treatment	X	X	X	X	X	X
Cycle 3 Day 1: Pre-treatment		X		X		X
Cycle 4 Day 1: Pre-treatment		X		X		X
90-day Follow-Up	X		X[a]		X	

[a] Only for patients who have received at least one dose of AVB-S6-500.

Serum fractions will be isolated from blood samples collected in EDTA-free tubes and will be used to measure 1) PK: AVB-S6-500 concentrations in serum, 2) Pharmacodynamics: GAS6 suppression, which will be analyzed by Altasciences, and 3) Anti-drug Antibody (ADA): immunogenicity of AVB-S6-500, which will be analyzed by Charles River Labs. Blood will be collected and processed for serum for analysis of AVB-S6-500 ADA at the 90 day Follow Up visit.

Plasma and PBMCs will be extracted from blood samples collected in EDTA-containing tubes and will be used for planned translational analysis, including gene expression analysis, functional proteomics, and immune profiling using a variety of complementary platforms. It is important to note that assays available for analysis of trial specimens are continuously evolving, thus the final method/platform used will be selected by primary investigators and translational collaborators at the time of specimen analysis.

6.6.2 TUMOR BIOPSIES

Pre- and on-treatment biopsies will be performed as part of this clinical investigation. To avoid putting patients in undue risk, procedures more invasive than a core biopsy will not be used. Pretreatment biopsies will be collected prior to the first dose of study drug regimen. On-treatment biopsies include sampling after monotherapy treatment and then after combination treatment with Durvalumab and AVB-

S6-500 when there is a lesion amenable to biopsy as assessed by imaging study by MDACC Radiologist. The time points for each Phase and Arm are noted in the Schedules of Assessments in **Section 6.5**.

When possible, on-treatment biopsies will be obtained from the same area of tumor as the pre-treatment biopsy.

At all biopsy time points and when deemed clinically safe, up to 10 core biopsies will be collected by Radiology faculty through an image-guided procedure. When feasible and depending on the tumor volume, 1-3 cores will be processed as formalin-fixed, paraffin-embedded blocks (FFPE) and 1-3 cores will be flash frozen, and remaining cores will be kept fresh in media. In cases where only limited amounts of tumor can be obtained, the FFPE samples will be prioritized. Samples will be collected, labeled, processed, and stored by the MDACC Gynecologic Oncology Tumor Bank. Sample identification and associated collection data will be entered into a secure database.

Translational studies including tumor immune and gene expression profiling will be performed with collaborators at MD Anderson group and Discovery Life Sciences (DLS). This assessment may include, but is not limited to, fresh flow cytometry, tissue cyTOF, and multiplex immunofluorescence. Exploratory analyses may include sequencing platforms and, given that assays for these evaluations are rapidly evolving in the laboratories at MDACC, other assays will be performed with the current state of the art technology available at the time of analysis. Aliquots may be stored and used for exploratory and future translational immunology research.

6.6.3 WITHDRAWAL OF INFORMED CONSENT FOR DONATED BIOLOGICAL SAMPLES

If a patient withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. However, any data that was previously generated from the sample will be retained. Such subjects may still continue with the therapeutic portion of the investigation.

The Principal Investigator:

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient is informed about the sample disposal

7. DISEASE EVALUATION AND METHODS

7.1 MODIFIED RECIST V1.1

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy. These difference include the following [59], [60]:

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

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

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 5 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab and AVB-S6-500 would continue between the initial assessment of progression and confirmation for progression.
- In addition, patients may continue to receive durvalumab and AVB-S6-500 beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and AVB-S6-500 and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

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

7.1.1 PHYSICAL EXAMINATION

Lesions detected by physical examination will only be considered measurable if superficial, e.g., skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

7.1.2 CT SCAN WITH CONTRAST OF THE CHEST, ABDOMEN, AND PELVIS

CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

7.1.3 MRI SCANS

MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weight

7.1.4 MEASURABILITY OF TUMOR LESIONS

Tumor lesions will be categorized as follows.

7.1.4.1 MEASURABLE LESIONS

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).

Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

7.1.4.2 NONMEASURABLE LESIONS

Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal or organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

7.1.4.3 TARGET LESIONS

All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

7.1.4.4 NON-TARGET LESIONS

It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from durvalumab + AVB-S6-500 treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Schedule of Assessments).

7.2 RESPONSE CRITERIA

7.2.1 EVALUATION OF TARGET LESIONS

- **Complete Response** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

7.2.2 EVALUATION OF NON-TARGET LESIONS

- **Complete Response** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for

measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

7.2.3 APPEARANCE OF NEW LESIONS

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. However, considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive the study regimen if investigators consider that subjects continue to benefit from treatment. A confirmatory radiologic assessment should be performed at least 5 weeks from the original study suggesting PD.

7.2.4 EVALUATION OF OVERALL RESPONSE WITH MODIFICATIONS

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 5 weeks from the date of first documentation. Treatment with study regimen will continue between the initial assessment of PD and confirmation for PD. If PD is confirmed by the second confirmatory scan, the associated time of progression will be reported as that of the initial imaging study revealing progression. In the absence of clinical deterioration, such modifications to the RECIST criteria may discourage the early discontinuation of the study regimens and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria.

Table 10 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 10. Overall Responses for All Possible Combinations of Tumor Responses

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
Complete response	Not evaluable[a]	No	Partial response
Complete response	Non-complete response/non-progressive	No	Partial response
Partial response	Non-progressive and non-evaluable[a]	No	Partial response
Stable disease	Non-progressive and non-evaluable[a]	No	Stable disease
Not all evaluated	Non-progressive	No	Not evaluable
Progressive disease	Any	Yes/No	Progressive disease[b]
Any	Progressive disease	Yes/No	Progressive disease[b]
Any	Any	Yes	Progressive disease[b]

[a] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment

[b] Disease progression requires confirmatory radiologic assessment

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions and
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression.

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 5 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point), and/or
- additional new unequivocal lesions at the confirmatory scan time-point.

To have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Following confirmed progression, patients should continue to be followed up for survival as outlined in the follow-up schedules of assessments.

8. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff members involved in the study are familiar with the content of this section.

8.1 SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS

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

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

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

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, MDACC IND Office, or supporting companies, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

1. Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office. All AEs that do not meet any of the criteria for serious will be regarded as non-serious AEs.
2. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The

University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of relatedness to study drug (within 5 working days of knowledge of the event).

3. **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
4. Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
5. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
6. Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the IND sponsor's guidelines, and Institutional Review Board policy.

8.1.3 DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

If the treatment team has any questions in regards to an event being an irAE, the primary investigator should promptly contacted.

AESIs for this study include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current versions of the durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (TMG, please see **Appendix A**). These guidelines have been prepared by AstraZeneca and agreed upon by Aravive 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 the study drug/study regimen by the reporting investigator.

8.1.3.1 INFUSION REACTIONS

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and Aravive and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. All infusion reactions should be reported to AstraZeneca Patient safety and to Aravive as AESI's. The electronic SAE application (eSAE) will be utilized for reporting to the IND Office and MDACC IRB, as well as AstraZeneca Patient safety and Aravive. If the AESI does not meet the criteria of an SAE, this should be clearly indicated on the eSAE form. These AESI's should be reported to all parties within five working days. If an AESI also meets the criteria of an SAE, then they should be reported as an SAE as described in **Section 8.1.2**.

8.1.3.2 HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PDL1 and anti-PD-1 therapy. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines on management can be found in **Appendix A.**

8.1.3.3 PNEUMONITIS

AEs of pneumonitis are also of interest for AstraZeneca and Aravive, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PDL1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and TMG will be applied. Refer to **Appendix A** for details.

8.1.3.4 HEPATIC FUNCTION ABNORMALITIES (HEPATOTOXICITY)

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

8.1.3.5 GASTROINTESTINAL DISORDERS

Diarrhea/colitis is a commonly observed treatment emergent SAE when durvalumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management can be found in **Appendix A**.

8.1.3.6 ENDOCRINE DISORDERS

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events can be found in **Appendix A**.

8.1.3.7 PANCREATIC DISORDERS

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

8.1.3.8 NEUROTOXICITY

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

8.1.3.9 NEPHRITIS

Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc). Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) and consultation with nephrologist is recommended. Guidelines for the management of patients with immune-mediated renal events are provided in **Appendix A**.

8.2 ASSESSMENT OF SAFETY PARAMETERS

8.2.1 ASSESSMENT OF SEVERITY

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

- Grade 1 (mild): An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate): An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
- Grade 4 (life-threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal): Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in **Section 8.1.2**. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

8.2.2 ASSESSMENT OF RELATIONSHIP

The investigator (or physician designee) will provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met.

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (e.g., the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related).
- A causal relationship between the investigational product and the event is biologically implausible (e.g., death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

8.3 RECORDING AND REPORTING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs and SAEs will be recorded according to the NCI suggested criteria as listed below.

Table 11. NCI Suggested AE recording criteria.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.3.1 STUDY RECORDING PERIOD AND FOLLOW-UP FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs and SAEs will be collected from the time of the first protocol-specific procedure until the follow-up period is completed (30 days after the last dose of durvalumab ±AVB-S6-500). 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. Investigator will instruct subjects to report to the investigator any subsequent SAEs; these events' relatedness to investigational regimen will be determined by the investigator and if felt to be related will be reported to the IND office as per **Section 8.3** Definition of Serious Adverse Events.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient 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 patient has discontinued study drug or the study has completed.

8.3.2 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

Any AEs that are unresolved at the patient'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. AstraZeneca and Aravive shall retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 INVESTIGATOR COMMUNICATIONS WITH ASTRAZENECA AND ARAVIVE

SAE report forms should be forwarded with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) to AstraZeneca for AEs related to durvalumab and to Aravive for AE related to AVB-S6-500.

AstraZeneca's designated mailbox is AEMailboxClinicalTrialTCS@astrazeneca.com.

Aravive's designated mailbox is laura@aravive.com, and ISTAEs@aravive.com.

Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the appropriate supporting company (i.e. AstraZeneca for durvalumab-related AEs or Aravive for AVB-S6-500-related AEs) as soon as it is available; these reports can be submitted using the MD Anderson eSAE Report Form. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and Aravive. Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca and Aravive for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

8.3.3.1 OVERDOSE

An overdose is defined as a patient receiving a dose of durvalumab or AVB-S6-500 in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab and/or AVB-S6-500, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the MDACC IND Office, Aravive, and AstraZeneca Patient Safety or designee (see **Section 8.3.3** for reporting information). If the overdose results in an AE, the AE must also be recorded as an AE (see **Section 8.1.2**). 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 (see

Section 8.1.2 and **Section 8.3.3**). There is currently no specific treatment in the event of an overdose of durvalumab or AVB-S6-500.

The investigator will use clinical judgment to treat any overdose.

8.3.3.2 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 patient's inclusion in this study.

8.3.3.3 HEPATIC FUNCTION ABNORMALITY

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, 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 MDACC IND Office, Aravive, and AstraZeneca Patient Safety (see **Section 8.1.2** for SAE reporting information), unless a definitive underlying diagnosis for the abnormality (e.g., 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) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN 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 patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient 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 MDACC IND Office, Aravive, and AstraZeneca.

8.3.3.4 MATERNAL EXPOSURE

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study 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 patient 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 Aravive and AstraZeneca representatives per reporting guidelines (**Section 8.3.3**).

The designated Aravive and AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the Aravive and 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.

8.3.3.5 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 or Aravive study drug that either causes harm to the patient or has the potential to cause harm to the patient.

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 patient.

Medication error includes situations where an error:

- Occurred,
- Was identified and intercepted before the patient received the drug, and/or
- 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 e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

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

- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ or Aravive 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 Aravive and AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Aravive and 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 (see **Section 8.3.3** for reporting details) and within 30 days for all other medication errors.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

We will employ the Bayesian optimal interval (BOIN) design (Yuan et al., 2016) to find the MTD. The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 18. We will enroll and treat patients in cohorts of size 3. DLTs are defined in Section 6.2, and only those DLTs that occur within the first 6 weeks will be used for dose finding. To guide dose-escalation decisions, if the observed DLT rate at the current dose is ≤ 0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥ 0.359, the next cohort of patients will be treated at the next lower dose level. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \mid$

data) > 0.95, where p_j is the true DLT rate of dose level j, j = 1, 2, 3. When the lowest dose is eliminated, stop the trial for safety. The trial design is illustrated in **Figure 3** and described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in **Table 12**, which minimizes the probability of incorrect dose assignment. When using **Table 12**, please note the following:
    a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum of 5 evaluable patients are treated on the highest dose, or maximum sample size of 15 is reached or end enrollment when the number of patients treated at the current dose >= 9 and the decision based on **Table 12** is to stay at the current dose.

Table 12. Dose escalation/de-escalation rule for the BOIN design

Actions	The number of patients treated **at the current dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Escalate if # of DLT <=	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**
De-escalate if # of DLT >=	1	1	**1**	2	2	**2**	3	3	**3**	3	4	**4**
Eliminate if # of DLT >=	NA	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**

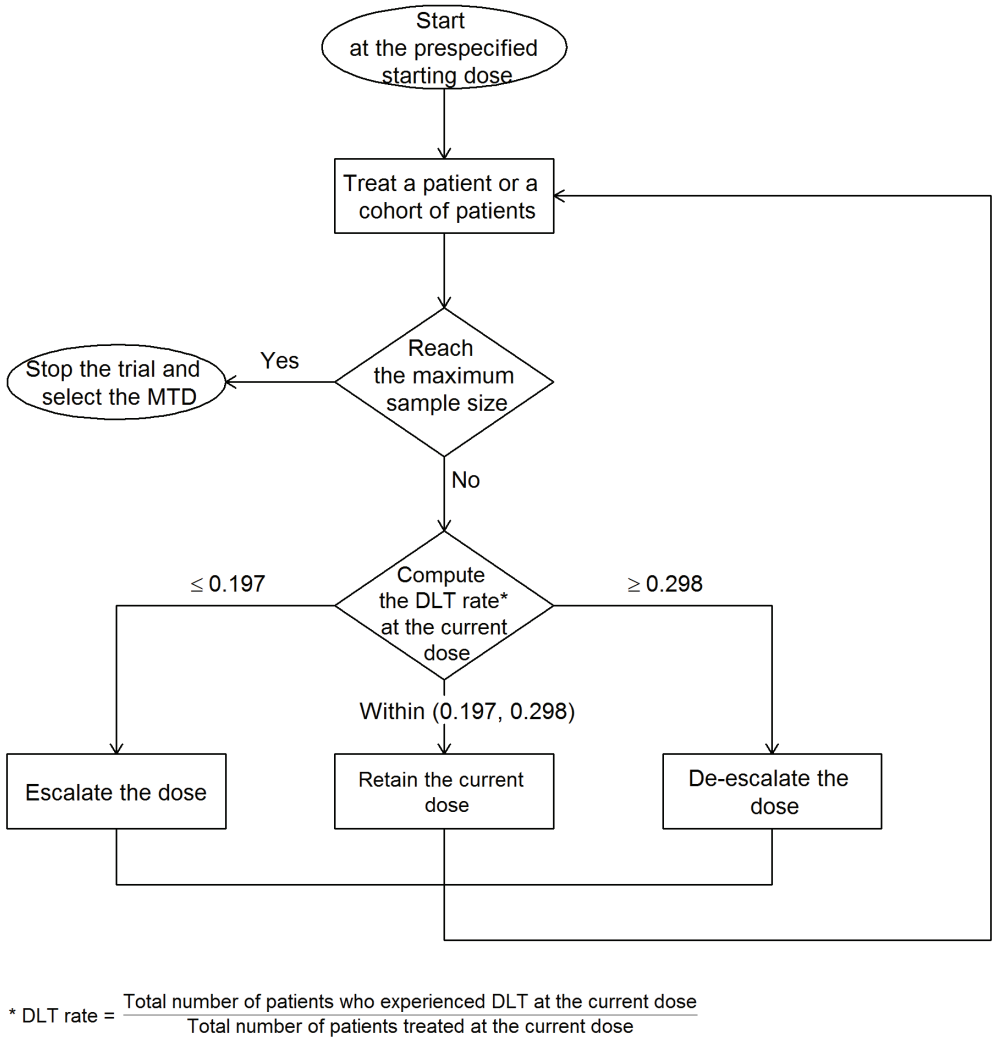

Figure 3. Flowchart for trial conduct using the BOIN design

After the trial is completed, select the MTD based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program (Venier et al., 2017). Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate. In general, the MTD will be used as the R2PD for phase II part, but might be adjusted based on the PK/PD and total evidence.

Table 13 shows the operating characteristics of the trial design based on 1000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2018). The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

Table 13. Operating Characteristics of the BOIN design

	Dose Level			Number of Patients	% Early Stopping
	1	2	3		
Scenario 1					
True DLT Rate	0.25	0.42	0.59		
Selection %	73.4	19.1	1.2		6.3
# Pts Treated	8.2	3.0	0.6	11.75	
Scenario 2					
True DLT Rate	0.10	0.25	0.40		
Selection %	28.9	56.6	14.5		0.0
# Pts Treated	6.7	5.0	2.4	14.08	
Scenario 3					
True DLT Rate	0.05	0.12	0.25		
Selection %	6.0	40.0	54.0		0.0
# Pts Treated	4.8	5.1	4.9	14.75	

The trial will be completed after the RP2D is determined as described above. The section below is maintained in the protocol in order to reference the original design and will no longer apply.

After the RP2D is determined, subsequent patients will be randomized in a 3:1 manner for enrollment into the respective AVB-S6-500 and Durvalumab monotherapy arms. We estimate accrual rate of 3 patients per month. We anticipate a dropout rate of approximately 8-10% due to possible toxicity as seen in prior literature of checkpoint inhibitor therapy [61], [62], and subsequent inability to proceed to combination treatment. All patients who complete the monotherapy treatment phase will proceed to combination treatment, at which time receipt of at least one dose of combination therapy at the final determined dosing defines evaluable patients. As mentioned above, should the safety lead-in phase in the combination treatment require dose adjustment, only those patients who received the RP2D and completed one cycle of combination treatment will be considered evaluable for the primary outcome of response rate to combination therapy and used for making go/no-go decision as described below.

In terms of outcome assessment of response rate and toxicity to combination therapy, the Bayesian optimal phase 2 (BOP2) design is utilized to jointly monitor toxicity and efficacy [63]. The first 12 patients to receive combination treatment constitutes the first stage. Of these N=12 patients, if 1 or more responses are detected and no more than 5 DLTs are observed, the trial will proceed to the second-stage and enroll an additional 15 patients. Of note, more than 3 responses and fewer than 10 DLTs in the total study cohort will indicate statistically significant improvement in response and toxicity.

Thus, the total number of evaluable patients following the second-stage will be N=27, in order to have 93% power to detect an improvement in response rate from 10% based on prior literature in this patient population to 30% with novel combination treatment and a toxicity of less than 40%. The rationale to design the study to detect this rate of improvement was that 10 to 30% is felt by the investigators to represent a clinically meaningful increase in response rate. Given the sample size of 27, a two-sided 90% confidence interval for a single proportion of ORR will extend 0.145 from the observed proportion for an expected proportion of 0.30. Similarly, the confidence interval for toxicity will extend 0.127 from the observed proportion for an expected proportion of 0.20.

We anticipate enrollment of a maximum of 39 patients: this includes the 27 total evaluable patients at RP2D; correction for an unevaluable, i.e., dropout rate of 8-10% after monotherapy (3 patients); and the dose-finding requirement of up to 9 additional patients should dose adjustment be needed due to toxicity. Further details of the statistical methods and operating characteristics of this Bayesian monitoring are found in **Section 9.2.**

9.1 DESCRIPTION OF ANALYSIS SETS

9.1.1 SAFETY ANALYSIS SET

Subjects who have received at least one dose of Durvalumab + AVB-S6-500 combination treatment will be included in the Safety Analysis Set. Safety will be monitored in the monotherapy phase and in the combination therapy phase.

9.1.2 EFFICACY ANALYSIS SET

Subjects who have received at least one dose of Durvalumab + AVB-S6-500 combination treatment will be included in the Efficacy Analysis Set. Efficacy will be monitored in the combination therapy phase.

9.2 METHODS OF STATISTICAL ANALYSES

We will use descriptive statistics to summarize the demographic and clinical characteristics of the subjects. We will estimate the objective response rate (ORR) along with a 90% confidence interval. Response is defined in **Section 7.2**. We will estimate the median immune-related progression free survival (irPFS) after treatment with combination durvalumab and AVB-S6-500 using the product-limit estimator of Kaplan and Meier. When appropriate, we will model irPFS using Cox proportional hazards regression as an exploratory analysis because of the small sample size. Immune-related PFS is defined as the time from the date of dual therapy treatment initiation to the date of initial radiologic evidence of progressive disease (**Section 7.2**) or death. Those who are immune-related progression-free and alive will have irPFS censored at their last clinic visit.

Molecular and immunological changes will be summarized with standard descriptive statistics. Changes in T cell populations and proliferation will be calculated along with 95% confidence intervals and compared between pre and posttreatment biopsies using two sample t-test. Similar summaries will be used to compare proportions of macrophage phenotypes. We will tabulate adverse events by grade, and by relationship to study drug. We will estimate the proportion of subjects that discontinue treatment due to adverse events with 90% confidence intervals. We will estimate the unacceptable toxicity rate with a 90% confidence interval.

9.2.1 SAFETY ANALYSES

We will tabulate adverse events by grade, and relationship to study drug. We will estimate the proportion of subjects that discontinue treatment due to treatment-related adverse events with 90% confidence intervals. We will estimate the unacceptable toxicity rate with a 90% confidence interval.

9.2.2 EXPLORATORY ANALYSES

Two-sample t test or chi-squared test will be used to compare continuous and binary variables for molecular and immunologic differences between pre-treatment with single agent AVB-S6-500 as compared to durvalumab.

The maximum of 6 patients who enroll directly into the safety-lead in phase of combination therapy will be separately analyzed for exploratory outcomes of response rate to combination alone. Similarly, pretreatment monotherapy arms will be compared for safety and signal of monotherapy response, as well as for impact on subsequent response rate in combination treatment.

9.2.3 INTERIM ANALYSES

We will conduct an interim analysis for efficacy and safety once 12 subjects have been evaluated for dual therapy. As stated in Section 6.2, DLTs will be evaluated from the time of first drug administration until 6 weeks. ORR will be determined at 8-week scan, but as stated in Table 10, disease progression will require a confirmatory scan. Based on Table 10, we will stop the trial if 0 responses are detected or 6 or more toxicities are observed.

We simultaneously monitor efficacy and safety endpoints using the Bayesian optimal phase 2 (BOP2) design [63]. Specifically, let n denote the interim sample size and N denote the maximum sample size. Let Y_{eff} and Y_{tox} respectively denote the efficacy and toxic endpoints, with $Y_{eff} = 1$ and $Y_{tox} = 1$ respectively indicating that patients experience efficacy and toxicity. We assume that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution with 4 elementary outcomes: (Y_{eff}, Y_{tox}) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $p_{eff} = Pr(Y_{eff} = 1)$ and $p_{tox} = Pr(Y_{tox} = 1)$. The treatment is deemed as unacceptable if $p_{eff} \leq 0.1$ or $p_{tox} > 0.4$. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.1|data) < \lambda(\frac{n}{N})^{\alpha},$$

or

$$Pr(p_{tox} \leq 0.4|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.65 and α=0.9 are design parameters optimized to maximize the probability of correctly concluding an efficacious and safe treatment as acceptable when $p_{eff} = 0.3$, $p_{tox} = 0.2$ and $p_{efftox} = 0.06$, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, with $p_{eff} = 0.1$, $p_{tox} = 0.4$ and $p_{efftox} = 0.04$, as acceptable is less than 10%. Assuming a Dirichlet prior distribution $Dir(0.04,0.06,0.36,0.54)$ for the treatment effect, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.9245 under H_1:

Table 14. Optimized stopping boundaries

# patients treated	Stop if # response <=	OR # toxicity >=
12	0	6
27	3	10

Based on Table 10, we will perform the interim analysis when the number of evaluable patients reaches 12. When the total number of evaluable patients reaches the maximum sample size of 27, we reject the null hypothesis and conclude that the treatment is acceptable if the number of responses in the efficacy

endpoint are > 3, and the number of toxicities are < 10; otherwise we conclude that the treatment is unacceptable.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 15. Operating characteristics of BOP2 design

Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early stopping (%)	Claim acceptable (%)	Sample size
0.1	0.4	0.04	51.51	7.58	19.3
0.3	0.2	0.08	3.67	92.27	26.4
0.4	0.1	0.06	0.28	99.61	27.0
0.3	0.5	0.20	61.65	5.40	17.8
0.1	0.1	0.03	28.11	26.04	22.8

The Investigator is responsible for completing safety/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review and approval. These should be submitted as follows:

Lead-In Phase: After the first 3 evaluable patients, complete 6 weeks of study treatment, and every 3 evaluable subjects thereafter, IND Office approval must be obtained prior to advancing/changing dose levels.

Phase II: After the first 12 evaluable subjects, and again after the first 27 evaluable subjects complete the first cycle of the combination treatment.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements Patient data protection.

10.2 ETHICS AND REGULATORY REVIEW

This study will be subject to subject to local IRB and federal oversight.

10.3 INFORMED CONSENT

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given 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.

10.4 CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by the IRB, Aravive, and AstraZeneca. Any changes made to the protocol must be submitted as amendments and must be approved by the IRB and Aravive and AstraZeneca prior to implementation. Any changes in study conduct must be reported to the IRB, Aravive, and AstraZeneca.

11. STUDY MANAGEMENT

11.1 MONITORING OF THE STUDY

The study will be monitored by the M.D. Anderson IND office and a protocol specific monitoring plan will be followed. We will monitor unacceptable toxicity (defined as grade 3 or greater treatment-related AEs or discontinuation of the study regimen due to side effects) independently in each monotherapy treatment arm and in subsequent combination treatment, guarding against an unacceptable toxicity rate of 40% or higher (based on published studies employing combination of other Anti-PD1/PDL1 agents), using the methods of Thall et al.[64].

11.2 DATA MANAGEMENT

Clinical study data for this trial will be collected and managed using the Prometheus database system.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number and age. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the ICF(s) (e.g., necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (e.g., HIPAA 1996, EU Data Protection Directive 95/46/EC). Study documents (including subject records, copies of data submitted to the MDACC IND Office, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the sponsor study governance and oversight.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Similarly, safety of clinical studies with Aravive are monitored on an ongoing basis by Aravive representatives. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

12. LIST OF REFERENCES

[1] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2016," *CA. Cancer J. Clin.*, 2016.

[2] R. W. Naumann and R. L. Coleman, "Management strategies for recurrent platinum-resistant ovarian cancer," *Drugs*, vol. 71, no. 11. pp. 1397–1412, 2011.

[3] A. Davis, A. V. Tinker, and M. Friedlander, "'platinum resistant' ovarian cancer: What is it, who to treat and how to measure benefit?," *Gynecologic Oncology*, vol. 133, no. 3. pp. 624–631, 2014.

[4] G. P. Dunn, L. J. Old, and R. D. Schreiber, "The Three Es of Cancer Immunoediting," *Annu. Rev. Immunol.*, vol. 22, no. 1, pp. 329–360, 2004.

[5] M. E. Keir, L. M. Francisco, and A. H. Sharpe, "PD-1 and its ligands in T-cell immunity," *Current Opinion in Immunology*, vol. 19, no. 3. pp. 309–314, 2007.

[6] T. Okazaki and T. Honjo, "PD-1 and PD-1 ligands: From discovery to clinical application," *International Immunology*, vol. 19, no. 7. pp. 813–824, 2007.

[7] D. M. Pardoll, "The blockade of immune checkpoints in cancer immunotherapy," *Nature Reviews Cancer*, vol. 12, no. 4. pp. 252–264, 2012.

[8] J. R. Brahmer *et al.*, "Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer," *N. Engl. J. Med.*, 2012.

[9] S. L. Topalian *et al.*, "Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer," *N. Engl. J. Med.*, vol. 366, no. 26, pp. 2443–2454, 2012.

[10] Y. Iwai, M. Ishida, Y. Tanaka, T. Okazaki, T. Honjo, and N. Minato, "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.*, vol. 99, no. 19, pp. 12293–12297, 2002.

[11] C. Zhang *et al.*, "Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1 - IgV," *Cytotherapy*, vol. 10, no. 7, pp. 711–719, 2008.

[12] K. Hayashi *et al.*, "Clonal expansion of T cells that are specific for autologous ovarian tumor among tumor-infiltrating T cells in humans1," *Gynecol. Oncol.*, vol. 74, no. 1, pp. 86–92, 1999.

[13] L. Zhang *et al.*, "Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer.," *N. Engl. J. Med.*, vol. 348, no. 3, pp. 203–13, 2003.

[14] G. E. Peoples, D. D. Schoof, J. V Andrews, P. S. Goedegebuure, and T. J. Eberlein, "T-cell recognition of ovarian cancer," *Surgery*, vol. 114, no. 2, pp. 227–234, 1993.

[15] C. C. Preston *et al.*, "The ratios of CD8+ T cells to CD4+CD25+ FOXP3+ and FOXP3- T cells correlate with poor clinical outcome in human serous ovarian cancer," *PLoS One*, vol. 8, no. 11, pp. 1–10, 2013.

[16] E. Sato *et al.*, "Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer," *Proc. Natl. Acad. Sci.*, 2005.

[17] J. R. Webb, K. Milne, P. Watson, R. J. DeLeeuw, and B. H. Nelson, "Tumor-infiltrating lymphocytes expressing the tissue resident memory marker cd103 are associated with increased survival in high-grade serous ovarian cancer," *Clin. Cancer Res.*, vol. 20, no. 2, pp. 434–444, 2014.

[18] C. G. Ioannides, R. S. Freedman, C. D. Platsoucas, S. Rashed, and Y. P. Kim, "Cytotoxic T cell clones isolated from ovarian tumor-infiltrating lymphocytes recognize multiple antigenic epitopes on autologous tumor cells," *J Immunol*, vol. 146, no. 5, pp. 1700–1707, 1991.

[19] J. Pappas *et al.*, "Substantial proportions of identical β-chain T-cell receptor transcripts are present in epithelial ovarian carcinoma tumors," *Cell. Immunol.*, vol. 234, no. 2, pp. 81–101, 2005.

[20] S. N. Akers *et al.*, "LINE1 and Alu repetitive element DNA methylation in tumors and white blood cells from epithelial ovarian cancer patients," *Gynecol. Oncol.*, vol. 132, no. 2, pp. 462–467, 2014.

[21] 2010 Barnett et al., "Ovarian cancer tumor infiltrating T-regulatory (T(reg)) cells are associated with a metastatic phenotype.," *Gynecol. Oncol.*, vol. 116, no. 3, pp. 556–62, 2010.

[22] B. Barnett, I. Kryczek, P. Cheng, W. Zou, and T. J. Curiel, "Regulatory T cells in ovarian cancer: Biology and therapeutic potential," *Am. J. Reprod. Immunol.*, vol. 54, no. 6, 2005.

[23] B. Melichar, M. A. Nash, R. Lenzi, C. D. Platsoucas, and R. S. Freedman, "Expression of costimulatory molecules CD80 and CD86 and their receptors CD28, CTLA-4 on malignant ascites CD3+ tumour-infiltrating lymphocytes (TIL) from patients with ovarian and other types of peritoneal carcinomatosis," *Clin. Exp. Immunol.*, vol. 119, no. 1, pp. 19–27, 2000.

[24] J. Hamanishi *et al.*, "Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 9, pp. 3360–5, 2007.

[25] J. Chatterjee *et al.*, "Clinical Use of Programmed Cell Death-1 and Its Ligand Expression as Discriminatory and Predictive Markers in Ovarian Cancer," *Clin. Cancer Res.*, vol. 23, no. 13, pp. 3453–3460, 2017.

[26] C. J. Maine *et al.*, "Programmed death ligand-1 over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer," *Cancer Immunol. Immunother.*, vol. 63, no. 3, pp. 215–224, 2014.

[27] M. L. Disis *et al.*, "Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN Solid Tumor phase Ib trial: Safety and clinical activity.," *J. Clin. Oncol.*, vol. 34, no. 15_suppl, p. 5533, 2016.

[28] L. J. Pujade-Lauraine E, Colombo N, Disis ML, Fujiwara K, "Avelumab (MSB0010718C; anti-PD-L1) +/− pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer: the phase III JAVELIN Ovarian 200 trial," *J. Clin. Oncol.*, p. TPS5600, 2016.

[29] A. Varga *et al.*, "Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study," *J. Clin. Oncol.*, vol. 33, no. 15_suppl, p. 5510, 2015.

[30] S. Koyama *et al.*, "Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints," *Nat. Commun.*, vol. 7, 2016.

[31] P. C. Tumeh *et al.*, "PD-1 blockade induces responses by inhibiting adaptive immune resistance," *Nature*, vol. 515, no. 7528, pp. 568–571, 2014.

[32] A. Ribas, "Adaptive immune resistance: How cancer protects from immune attack," *Cancer Discovery*, vol. 5, no. 9. pp. 915–919, 2015.

[33] R. S. Herbst *et al.*, "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients," *Nature*, vol. 515, no. 7528, pp. 563–567, 2014.

[34] K. M. Giles *et al.*, "Axl mediates acquired resistance of head and neck cancer cells to the epidermal growth factor receptor inhibitor erlotinib.," *Mol. Cancer Ther.*, vol. 12, no. 11, pp. 2541–58, 2013.

[35] L. A. Byers *et al.*, "An epithelial-mesenchymal transition gene signature predicts resistance to EGFR and PI3K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance," *Clin. Cancer Res.*, vol. 19, no. 1, pp. 279–290, 2013.

[36] Z. Zhang *et al.*, "Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer," *Nat. Genet.*, vol. 44, no. 8, pp. 852–860, 2012.

[37] G. Zizzo *et al.*, "AXL is a key regulator of inherent and chemotherapy-induced invasion and predicts a poor clinical outcome in early-stage colon cancer.," *Nature*, vol. 7, no. 1, pp. 1–9, 2013.

[38] M. Buehler *et al.*, "Meta-analysis of microarray data identifies gas6 expression as an independent predictor of poor survival in ovarian cancer," *Biomed Res. Int.*, vol. 2013, 2013.

[39] E. B. Rankin *et al.*, "AXL is an essential factor and therapeutic target for metastatic ovarian cancer," *Cancer Res.*, vol. 70, no. 19, pp. 7570–7579, 2010.

[40] W. Sun, J. Fujimoto, and T. Tamaya, "Coexpression of Gas6/Axl in human ovarian cancers," *Oncology*, vol. 66, no. 6, pp. 450–457, 2004.

[41] C. V. Rothlin, E. A. Carrera-Silva, L. Bosurgi, and S. Ghosh, "TAM Receptor Signaling in Immune Homeostasis," *Annu. Rev. Immunol.*, vol. 33, no. 1, pp. 355–391, 2015.

[42] R. S. Cook *et al.*, "MerTK inhibition in tumor leukocytes decreases tumor growth and metastasis," *J. Clin. Invest.*, vol. 123, no. 8, pp. 3231–3242, 2013.

[43] H. D. Skinner *et al.*, "Integrative analysis identifies a novel AXL-PI3 kinase-PD-L1 signaling axis associated with radiation resistance in head and neck cancer," *Clin. Cancer Res.*, vol. 23, no. 11, pp. 2713–2722, 2017.

[44] J. Müller *et al.*, "Low MITF/AXL ratio predicts early resistance to multiple targeted drugs in melanoma," *Nat. Commun.*, vol. 5, 2014.

[45] K. Macleod *et al.*, "Altered ErbB receptor signaling and gene expression in cisplatin-resistant ovarian cancer," *Cancer Res.*, vol. 65, no. 15, pp. 6789–6800, 2005.

[46] T. A. Aguilera *et al.*, "Reprogramming the immunological microenvironment through radiation and targeting Axl," *Nat. Commun.*, vol. 7, 2016.

[47] W. Hugo *et al.*, "Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma," *Cell*, vol. 165, no. 1, pp. 35–44, 2016.

[48] C. Wilson *et al.*, "AXL inhibition sensitizes mesenchymal cancer cells to antimitotic drugs," *Cancer Res.*, vol. 74, no. 20, pp. 5878–5890, 2014.

[49] K. Wnuk-Lipinska *et al.*, "Abstract 1747: BGB324, a selective small molecule Axl kinase inhibitor to overcome EMT-associated drug resistance in carcinomas: Therapeutic rationale and early clinical studies," *Cancer Res.*, vol. 74, no. 19 Supplement, pp. 1747–1747, 2014.

[50] Z. Guo, Y. Li, D. Zhang, and J. Ma, "Oncotarget 89761 www.impactjournals.com/oncotarget Axl inhibition induces the antitumor immune response which can be further potentiated by PD-1 blockade in the mouse cancer models," 2017.

[51] R. Stewart *et al.*, "Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody," *Cancer Immunol. Res.*, vol. 3, no. 9, pp. 1052–1062, 2015.

[52] M. S. Kariolis *et al.*, "Inhibition of the GAS6/AXL pathway augments the efficacy of chemotherapies," *J. Clin. Invest.*, vol. 127, no. 1, pp. 183–198, 2017.

[53] A. Azmi, "Unveiling the Role of Nuclear Transport in Epithelial-to-Mesenchymal Transition," *Curr. Cancer Drug Targets*, vol. 13, no. 9, pp. 906–914, 2013.

[54] K. F. Ludwig *et al.*, "Small-molecule inhibition of Axl targets tumor immune suppression and enhances chemotherapy in pancreatic cancer," *Cancer Res.*, vol. 78, no. 1, pp. 246–255, 2018.

[55] C. M. Ng, B. L. Lum, V. Gimenez, S. Kelsey, and D. Allison, "Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis," *Pharm. Res.*, vol. 23, no. 6, pp. 1275–1284, 2006.

[56] D. D. Wang, Shuzhong Zhang, Hong Zhao, A. Y. Men, and K. Parivar, "Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials," *J. Clin. Pharmacol.*, vol. 49, no. 9, pp. 1012–1024, 2009.

[57] S. Zhang, R. Shi, C. Li, K. Parivar, and D. D. Wang, "Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults," *J. Clin. Pharmacol.*, vol. 52, no. 1, pp. 18–28, 2012.

[58] R. Narwal, L. K. Roskos, and G. J. Robbie, "Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus," *Clin. Pharmacokinet.*, vol. 52, no. 11, pp. 1017–1027, 2013.

[59] J. D. Wolchok *et al.*, "Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria," *Clin. Cancer Res.*, vol. 15, no. 23, pp. 7412–7420, 2009.

[60] O. Bohnsack, K. Ludajic, and A. Hoos, "AdAptAtion of the immune-relAted response criteriA: irrecist," *Ann. Oncol.*, vol. 25, no. suppl_4, p. iv361-iv372, 2014.

[61] J. Hamanishi *et al.*, "Safety and antitumor activity of Anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer," *J. Clin. Oncol.*, vol. 33, no. 34, pp. 4015–4022, 2015.

[62] A. Varga *et al.*, "Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study," *J. Clin. Oncol.*, vol. 33, no. 15_suppl, p. 5510, 2015.

[63] H. Zhou, J. J. Lee, and Y. Yuan, "BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints," *Stat. Med.*, vol. 36, no. 21, pp. 3302–3314, 2017.

[64] P. F. Thall and R. Simon, "Practical Bayesian Guidelines for Phase IIB Clinical Trials," *Biometrics*, vol. 50, no. 2, p. 337, 1994.

Appendix A. Dosing Modifications and Toxicity Management Guidelines for Durvalumab and AVB-S6-500

Table 16. General Considerations regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. 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.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

–

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE immune-related adverse event; NCI National Cancer Institute.

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** of the start initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for IVIG and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing in children ≤ 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist.

Dose Modifications	Toxicity Management
	– With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Table 17. Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. –
	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. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			–
			– Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with study physician as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - WHEN SYMPTOMS OR EVALUATION INDICATE A PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY. - PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. Use probiotics as per treating physician's clinical judgment. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressant agents such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider.. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** • For patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 to 3 days, promptly add further immunosuppressants (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay**.
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1	• No dose modifications. • If it worsens, then treat as Grade 2.	**For Grade 1** – Continue LFT monitoring per protocol.
	Grade 2	– Hold study drug/study regimen dose until resolution to Grade≤1. – If toxicity worsens, then treat as Grade 3 or Grade 4. – If toxicity improves to Grade≤1 or baseline, resume study drug/study regimen after completion of steroid taper. – Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.b	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to ≤Grade 1 in 1 to 2 days, consider discussing with study physician as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. –
	Grade 3 or 4	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN:	**For Grade 3 or 4:**

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		• Hold study drug/study regimen dose until resolution to Grade≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 or baseline within 14 days.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressant therapy (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, perform abdominal workup, and imaging as appropriate.
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications for any patient if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAb+: Evaluate for both HBV and HCV as above

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. • If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be im AE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressants (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Consider discussing with study physician as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressive therapy (mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)** –
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consult a nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contract, medications, fluid status). Consider using steroids in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup . – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus).

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
(including Pemphigoid)	(Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)		– **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 3 or 4** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Consider, as necessary, discussing with study physician.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		• If toxicity worsens, then treat as Grade 4. **For Grade 4** Permanently discontinue study drug/study regimen.	
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	For Any Grade: – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies other than hypothyroidism and Type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper. • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen patient is clinically stable as per investigator or treating physician's clinical judgement. • If toxicity worsens, then treat based on severity.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
		1.	
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider Gastroenterology referral
	Grade 1	No dose modifications.	**For Grade 1** – IV hydration – Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not be limited to non-infectious meningitis, non-infectious encephalitis and	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations).

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	defining the CTC grade/severity)		– Perform symptomatic treatment with Neurology consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modifications.	**For Grade 1** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the study physician as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
	Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not	**For Grade 2** – Consider discussing with the study physician as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	– Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 3 or 4** – Consider discussing with study physician as needed. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		For Grade 4 Permanently discontinue study drug/study regimen.	○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the study physician as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 2, 3 or 4	• If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. • If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4** • Permanently discontinue study drug/study regimen.	– Consider discussing with the study physician as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

[c]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Table 18. Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • 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. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Table 19. Infusion-related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Table 20. Non-immune-mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the MDACC IND Office and supporting companies.).	Treat accordingly, as per institutional standard.

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

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

Appendix B. ECOG Performance Status Criteria

Table 21. ECOG Performance Status Criteria

Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix C. Durvalumab Weight-based Dose Calculations

Durvalumab Dosing

For patients weighing < 30 kg, durvalumab should be dosed at 20 mg/kg. There is no modification to the durvalumab regimen in dose de-escalation, therefore this weight based dosing applies for any patient who falls below this cut off of < 30 kg (in the combination therapy portion of the trial with durvalumab + AVB-S6-500).

Example:

1. Cohort dose: 20 mg/kg

2. Patient weight: 29 kg

3. Dose for patient: 580 mg = 20 (mg/kg) × 29 (kg)

4. Dose to be added into infusion bag: [rounded to the nearest tenth mL (0.1 mL)]:

Dose (mL) = 580 mg / 50 (mg/mL) = 11.6 mL

5. The number of vials required for dose preparation:

Number of vials = 11.6 (mL) / 10.0 (mL/vial) = 2 vials