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Protocol Title	EON: A Single-arm Phase II study of Etigilimab (OMP-313M32) in Combination with Checkpoint Inhibition (Nivolumab) in Patients with Platinum-resistant, Recurrent Epithelial Ovarian Cancer
Protocol Phase	II
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IND Sponsor	MD Anderson Cancer Center
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Principal Investigator: Shannon N. Westin, MD MPH

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Table of Contents

Table of Figures

Table of Tables

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 andhave 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 EPITHELIAL OVARIAN CANCER

It is increasingly understood that cancers are recognized by the immune system, and, under somecircumstances, 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 exploitthis 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 evadingimmune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits theinteraction 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

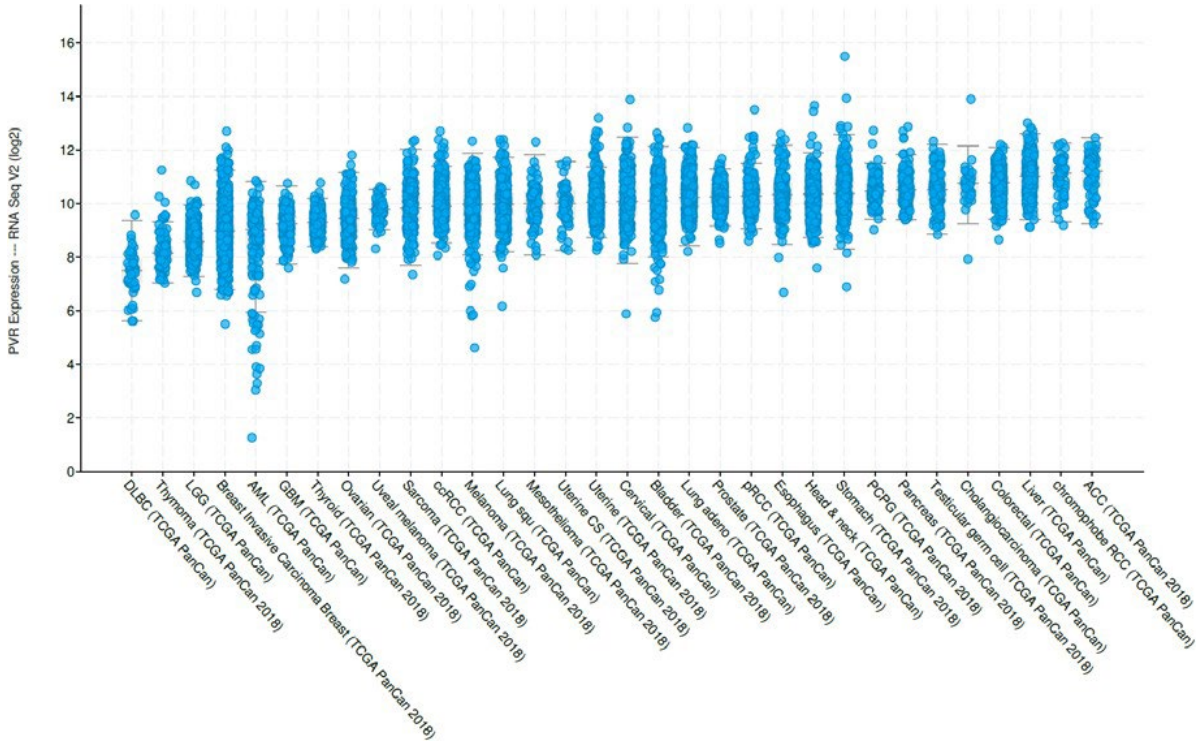
added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-L1 has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment 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, agents 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. The first tumor-type agnostic approval also occurred for pembrolizumab treatment of any tumor with microsatellite instability; these tumors have been demonstrated to have increased susceptibility to immune checkpoint inhibition. 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.

Another receptor of particular interest is TIGIT; TIGIT is found on CD4 and CD8 T-cells, on NK cells, and on a subset of Tregs (regulatory T cells) [12], [13]. Consistent with its structure and expression pattern, TIGIT was found to have an inhibitory function on both T-cells and NK cells and to increase Tregs' suppressive capacity [13]–[15]. Known ligands for TIGIT are PVR, PVRL2, and with weaker binding, PVRL3 and PVRL4 (Mereo's binding data on file). The TIGIT signaling axis also contains a co-stimulatory receptor, CD226, which binds to PVR and PVRL2 with lower affinity than TIGIT [16], [17]. Therefore, when TIGIT is expressed, the ligands preferentially engage TIGIT rather than CD226, leadingto immune suppression

Given TIGIT's immunomodulatory functions and the expression of PVR and PVRL2 in most cancers, ithas been postulated that blocking TIGIT binding to its ligands may reverse tumor-induced immune suppression and result in tumor regression in a broad range of cancer types (**Error! Reference source not found.**).

Figure 1: Broad Expression of TIGIT's Ligand PVR Across TCGA Tumor Collection

The anti-tumor activity of TIGIT blockade was verified in different murine cancer models where it was shown to



operate through multiple mechanisms to inhibit tumor growth[18], [19]. Further supporting TIGIT targeting for cancer treatment are reports of its overexpression on patient tumor-associated T-cells[18], [20], [21].

1.1.3 POTENTIAL UTILITY OF PD-1/PD-L1 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[22]–[28]. Tumor infiltrating lymphocytes (TIL) derived from patients with EOC demonstratetumor specificity by a) clonal proliferation in response to low concentrations of IL2 in the presence of autologous tumor cells [29] and b) exhibit MHC restricted killing of EOC tumor cell lines as well as cloned autologous tumor cells [28] and c) cytokine production [22], [24], [30]. 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 [31]–[36]. Indeed, expression of PDL1 and PDL2 in EOC was shown to correlate with poorer OS[34], and both ascites and peripheral blood derived monocytes from patients with EOC showed upregulated PDL1 expression [36].

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 dataon anti-PD1 / anti-PDL-1 therapies in ovarian cancer demonstrates response rates of 10-15%[8], [37]– [39]. However, there is significant interest in combinatorial approaches to checkpoint inhibition. A recent combination trial of Nivolumab and Ipilimumab (NRG-GY003) demonstrated a 30% response rate when the two drugs were used in combination [15].

In clear cell ovarian cancer specifically, a trial of pembrolizumab for recurrent ovarian cancer (KEYNOTE-100) demonstrated a respose rate of 8% in the overall population but a response rate of 15.8% in the small clear cell subset [12]. A phase I study of avelumab in recurrent ovarian cancer, JAVELIN (phase Ib), demonstrated that both included patients with clear cell histology had partial responses [13]. Similarly, a single clear cell patient was enrolled on a Phase I study of durvalumab in combination with PARP inhibitor olaparib, and also exhibited a partial response [14]. In the aforementioned randomized trial of Nivolumab versus combination Ipilimumab and Nivolumab, a total of12 patients with ovarian clear cell were included [15]. They reported that the odds of response in clear cell was five times higher than that of other histologies. Therefore, there has been significant interest in the use of immune checkpoint inhibitors for this rare pathologic subtype but the numbers of women treated remain small.

1.1.4 POTENTIAL UTILITY OF TIGIT INHIBITION IN COMBINATION WITH PD-1/PD-L1 INHIBITION IN OVARIAN CANCER

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 [40]–[43]. Factors which contribute to T-cell exclusion, and thus resistance, within the tumor microenvironment include immune cell suppression via cytokines, aberrations in antigen presentation, ormicroenvironmental factors such as hypoxia. Like other checkpoint inhibitors, such as CTLA-4 and PD- 1/PD-L1, TIGIT may disrupt CD226 costimulation and produce inhibitory signals which result in suppression of antitumor response. TIGIT has been shown to regulate immune responses through CD4+ Tregs, which is meaningful as CD4+ Tregs abundance was correlated with tumor burden in OC patients [19], [44].

In a murine model of OC, TIGIT expression was increased in immune cells, particularly CD4+ Tregs [45]. When anti-TIGIT monoclonal antibodies were used to block the function of TIGIT in OC mice, the proportion of CD4+ Tregs was decreased, while CD4+ and CD8+ T cell or natural killer cell populationsremained unaffected. A survival curve suggested that anti-TIGIT treatment can improve the survival rate of OC in mice, indicating that inhibition of TIGIT is a potential therapeutic target in OC patients.

Additionally, TIGIT expression has been negatively correlated to survival in multiple tumor types, including OC. CD155/PVR (TIGIT ligand) is more commonly expressed in TIL negative tumors, contrary to PD-L1 which is correlated with TIL in OC. Thus, while TIGIT blockade has somewhat limited efficacy as a monotherapy in preclinical models, it may significantly potentiate the efficacy ofPD-1 blockade [46].

This is supported by the fact that recent analysis demonstrated frequent TIGIT expression specifically onCD4+ and CD8+ TIL in HGOC [47]. Conversely, PD-1 has been shown to be expressed by tumor infiltrating macrophages, rather than malignant cells themselves in ovarian cancer. This suggests that thePD-1 axis may be a less significant barrier to TIL in OC than in other malignancies; this dramatically greater expression of TIGIT vs PD-1 on TIL, and of CD155/PVR vs PD-1 on tumor epithelium provides strong support for the use of TIGIT blockade in HGOC.

1.2 PD-1 INHIBITOR NIVOLUMAB: CLINICAL EXPERIENCE

Nivolumab is a human programmed death receptor-1 (PD-1) blocking antibody approved for use in several indications including advanced melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, advanced squamous cell carcinoma of the head and neck, microsatellite instability- high or mismatch repair-deficient colorectal cancer, and hepatocellular carcinoma. Randomized clinical trials are ongoing for other potential indications, including in ovarian malignancy (multiple, including butnot limited to: NCT03959761, NCT04024878, NCT02873962, NCT03245892, NCT03508570).

Substantial safety information is summarized in the Nivolumab package insert including immune-relatedadverse events occurring in subjects receiving single agent nivolumab from over 1900 subjects treated in clinical trials. Selected immune-related AEs included pneumonitis (3.1%), colitis (2.9%), hepatitis (1.8%), hypophysitis (0.6%), adrenal insufficiency (1%), hypothyroidism/hyperthyroidism (9%/2.7%), Type 1 diabetes mellitus (0.9%), nephritis (1.2%), rash (9%) and encephalitis (0.2%). Infusion-relatedreactions occurred in less than 1% of subjects.

Refer to the current Nivolumab Investigator's Brochure for a complete summary of non-clinical andclinical information including safety, efficacy and pharmacokinetics.

1.3 ETIGILMAB: CLINICAL EXPERIENCE

A Phase 1a/b open-label, dose-escalation study was conducted to evaluate the safety and pharmacokinetics of etigilimab administered as a single agent or in combination with nivolumab to subjects with locally advanced or metastatic solid tumors (study number 313M32-001). A total of 23 subjects were enrolled on the Phase 1a portion of the study for treatment with etigilimab and 10 subjectswere enrolled on the Phase 1b portion of the study for treatment with etigilimab in combination with nivolumab.

Doses investigated in the Phase 1a portion of the study were 0.3, 1, 3, and 20 mg/kg for dose escalation and 20 mg/kg for dose-expansion portion, and doses evaluated in the Phase 1b dose escalation portion ofthe study were 3, 10, and 20 mg/kg. To characterize the PK properties of etigilimab and pharmacodynamic responses to treatment, blood samples were taken at various time points before and after dosing. Subjects underwent tumor assessments at screening and every 8 weeks during the study. Subjects remained on treatment at the discretion of the investigator until disease progression, unacceptable toxicity, initiation of a new anticancer therapy, withdrawal of subject consent, physician decision, or death. Efficacy endpoints included tumor response. Time-to-event endpoints included duration of response, progression free survival, and overall survival. Safety endpoints included AEs, vital signs, 12-lead electrocardiograms, clinical laboratory testing, and immunogenicity testing. In the single agent portion of the study no RECIST response were reported. However, a number of subjects demonstrated tumor reduction or stable disease, including one patient with fallopian tube cancer (Figure 2). In the group who receive both etigilimab and nivolumab, all subjects treated received a checkpoint point inhibitor. A partial response was observed in a patient with ovarian cancer.

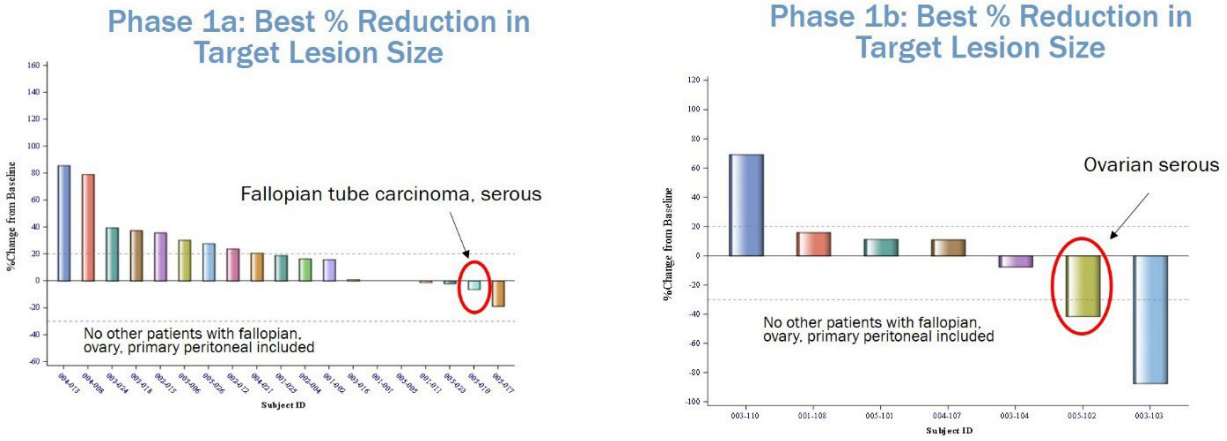


Figure 2: Best Percentage Response in Target Lesion (Phase 1A, 1B)

The median (95% CI) progression-free survival in the Phase 1a portion of the study was 56.0 (51.0, 112.0) days, and the progression-free survival estimates (95% CI) at 3, 6, and 12 months were 30.0%

(12.3, 50.1), 10.0% (1.7, 27.2), and 0%, respectively. The median (95% CI) progression-free survival in the Phase 1b portion of the study was 57.5 (14.0, 224.0) days, and the progression-free survival estimates(95% CI) at 3, 6, and 12 months were 37.5% (8.7, 67.4), 25.0% (3.7, 55.8), and 0%, respectively. The median (95% CI) overall survival in the Phase 1a portion of the study was 173.0 (88.0, 268.0) days, and the survival estimates (95% CI) at 3, 6, and 12 months were 30.0% (12.3, 50.1), 10.0% (1.7, 27.2), and 0%, respectively. The median (95% CI) overall survival in the Phase 1b portion of the study was 205.0 (19.0, N/A) days, and the survival estimates (95% CI) at 3 months were 57.9% (15.3, 85.2) and not applicable at 6 and 12 months.

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

1.4 RESEARCH HYPOTHESIS

Our overarching hypothesis is that the addition of TIGIT inhibition via the novel agent Etigilimab to Nivolumab 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 alonein patients with platinum resistant clear cell ovarian, fallopian tube and primary peritoneal cancers (that will be collectively referred to as EOC). We hypothesize that there may be unique benefit in a subset ovarian cancer population, those with clear cell histology, so these patients will be specifically studied. We hypothesize that this combination will be associated with an acceptable toxicity profile in both groups. Additionally, dual targeting of programmed cell death protein ligand 1 (PD1) and TIGIT 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 thecombination of TIGIT and Nivolumab.

1.5 RATIONALE FOR CONDUCTING THIS STUDY

1.5.1 NIVOLUMAB DOSE

Nivolumab is supplied as an injection in 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), or 240mg (24 mL) solutions in a single-use vial and should be diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP prior to use. It is administered over 30 minutes through an intravenous line containing as sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2micrometer to 1.2 micrometer). Please refer to package insert (Ref 33) for nivolumab for further administration instructions.

Nivolumab will be dosed at standard 240 mg IV Q2W for all indications in this study. This flat dose of240 mg is supported by pharmacokinetic analyses showing that 240 mg flat dose had similar overall exposure when compared to 3 mg/kg Q2W dosing which led to dose modification of nivolumab in September 2016, in the U.S., in metastatic melanoma, NSCLC and renal cell carcinoma (Ref 33).

Tolerability of this dose with Etigilimab dose has been demonstrated in prior Phase I study (refer to Etigilimab section). Given completion of Phase 1a/1b study, dosing is determined by these results. Basedon data from 10 subjects in the Phase 1b portion of the study, the presence of nivolumab did not have an identifiable impact on the pharmacokinetics of etigilimab.

1.5.2 ETIGILIMAB DOSE

The flat dose of etigilimab of 1000 mg for subjects ≥ 50 kg was selected based on data from study 313M32-001. In this study, a trough exposure of approximately 20-30 ug/mL was associated with maximum reduction in Treg and maximal increase in Ki67 biomarkers. This exposure was also associatedwith subjects who appeared to achieve clinical benefit from etigilimab. The trough exposure is this range can be obtained with a dose of 1000 mg every 2 weeks. See the Investigator Brochure for more detailed information.

Doses investigated in the Phase 1a portion of the study were 0.3, 1.0, 3.0, 10.0 mg/kg and 20.0 mg/kg fordose escalation and 20.0 mg/kg for dose-expansion portion, and doses evaluated in the Phase 1b dose- escalation portion of the study were 3, 10, and 20 mg/kg. Therefore, for subjects < 50 kg, a weight-baseddose of 20 mg/kg will be utilized to not exceed the highest dose examined in the 313M32-001 study.

Treatment with etigilimab was well-tolerated; no DLTs were reported in either the Phase 1a or Phase 1bportions of the study. Thus, the MTD was not reached.

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 largenumber 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 TIGIT inhibition represents a valuable and important avenue ofinvestigation 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 tumorcells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoringand/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 hepatitisand liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism. Specific management strategies have been laid out in this protocol to ensureappropriate care of adverse events, refer to Section 6.3

1.6.2.1 Etiligimab

Treatment with etigilimab was well-tolerated in study 313M32-001; no DLTs were reported in either the Phase 1a or Phase 1b portions of the study. Thus, the MTD was not reached. All subjects in the study reported 1 or more treatment-emergent AEs (TEAEs). The most commonly reported TEAEs in the Phase 1a portion of the study were nausea (8 subjects, 34.8%) and fatigue (7 subjects, 30.4%), and the most commonly reported TEAEs in the Phase 1b portion of the study were decreased appetite and nausea (eachreported by 5 subjects, 50.0%). Immune-related TEAEs were reported by 10 subjects (43.5%) in the Phase 1a and 5 subjects (50.0%) in the Phase 1b portions of the study. The most commonly reported immune-related TEAEs in the Phase 1a portion of the study were pruritus, rash, and maculopapular rash (each reported by 3 subjects, 15.0%). In the Phase 1b portion of the study, the most commonly reported immune-related TEAEs were pruritus, rash, and pruritic rash (each reported by 2 subjects, 20.0%). The most commonly reported National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or higher abnormal laboratory test results in the Phase 1a portion of the study were lymphocytes (8 subjects 34.8%), alkaline phosphatase (3 subjects 13.0%), and alanine aminotransferase and sodium (each reported by 2 subjects, 8.7%). In the Phase 1b portion of the study, the most commonly reported

CTCAE Grade 3 or higher laboratory results were alkaline phosphatase (3 subjects, 30.0%) and aspartate aminotransferase (2 subjects, 20.0%). Treatment-emergent AEs with a fatal outcome were reported for 3 subjects (13.0%) in the Phase 1a portion of the study and 2 subjects (20.0%) in the Phase 1b portion of the study. There were no related TEAEs with a fatal outcome in the Phase 1a and the Phase 1b portions of the study.

However, the combination of TIGIT inhibition with Nivolumab 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 6.3.1.

1.6.2.2 Nivolumab

Risks with Nivolumab 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 Nivolumab please always refer to the current version of the Nivolumab IB.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and inthe case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated adverse events Section 6.3.

1.6.3 OVERALL BENEFIT-RISK

Ovarian cancer is the deadliest gynecologic malignancy, with a short progression free interval and limitedtreatment 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 isexpected, such as with TIGIT inhibition, represents an essential approach to advancing the care of these women. Additionally, rapid expansion of the use of immunotherapies have demonstrated that the majorityof 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 PD-1 checkpoint and TIGIT inhibitor therapy combinations and their associated toxicities in this population.

2 STUDY OBJECTIVES

2.1 PRIMARY

1. To estimate the objective response rate of the combination of etigilimab and nivolumab inpatients with platinum resistant clear cell ovarian cancer.
2. To evaluate the toxicity of the combination of etigilimab and nivolumab in patients with platinumresistant clear cell ovarian cancer.

2.2 SECONDARY

1. To determine PFS of the combination of etigilimab and nivolumab in patients with platinumresistant clear

cell ovarian cancer.

2. To estimate the disease control rate of the combination of etigilimab and nivolumab in patientswith platinum resistant clear cell ovarian cancer.
3. To investigate molecular and immunological changes associated with the combination of TIGITand PD-1 inhibition; 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)
4. To determine feasibility of interrogating the gut microbial signatures and dietary patterns in an ovarian cancer cohort.
5. Identify components and determinants of the gut microbiome that could modulate toxicity or provide a signature of excellent or poor response to cancer immunotherapy.

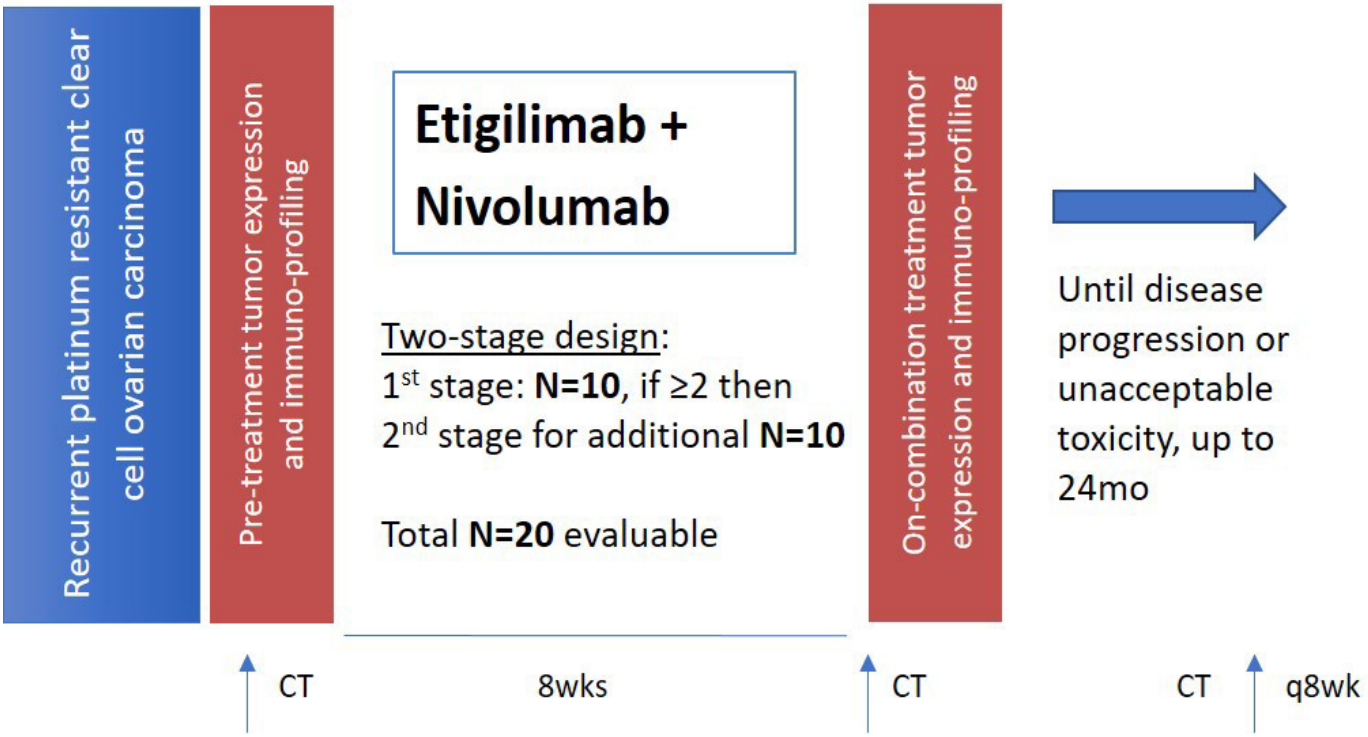
3 STUDY DESCRIPTION

3.1 STUDY DESIGN

This is a phase II trial of the combination of PD-1 checkpoint inhibitor therapy and TIGIT inhibition in patients with recurrent platinum resistant clear cell ovarian carcinoma (Figure 3).

Figure 3. Study Schema

Clear cell histology isspecifically enrolled due to signal from other trials that these women may represent a cohort of ovarian cancer with potentially increased likelihood of response to checkpoint inhibition.



The design is based on the clinical rationale that the combination of inhibition of TIGIT and PD-1 may have increased efficacy but at the risk of potentially greater toxicity. The appropriate combination dosingof these agents has already been established, thus this trial will provide further safety assessment and initial efficacy signal, to

allow for development of a superior suitable regimen for a follow-up phase IIIinvestigation based on these efficacy and toxicity tradeoffs. It will also be informative regarding responserates associated with this combination regimen, and will generate key preliminary data to determine impact on irPFS to the combination of both therapies. Furthermore, translational correlative studies will investigate biological correlates for response, possible sensitization of immune microenvironment, and any indication of adverse event. Progression during investigational agent treatment cycles will be definedbased on immune-related response criteria (irRC; including computed tomography (CT) confirmation at least 5 weeks apart to determine progression).

Eligible subjects will receive the combination therapy at the RP2D, as defined by prior phase I study. 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. Patients will receive treatment up to 24 months or until disease progression or unacceptable toxicity with combination therapy. Per the investigator's assessment, subjectsmay continue to receive study treatment beyond RECISTv1.1 defined progression at the discretion of the investigator and be assessed at a subsequent timepoint to confirm disease progression. Subjects may onlycontinue therapy in this situation in the absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and no significant, unacceptable or irreversible toxicities related to study treatment. 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 4 for complete details (Section 6.5).

3.2 TRANSITION FROM PROTOCOL 2021-0511

Protocol 2021-0511 opened in October 2021 at the University of Texas MD Anderson Cancer Center and through December 2022, 14 subjects were enrolled, 10 subjects received treatment, one subject in follow up, and 4 subjects were actively receiving treatment.

In October 2022, the Human Subjects Protections Office instructed the PI to transition protocol 2021-0511 to an external IRB due to an institutional conflict of interest. A new protocol submission was required to initiate the transition; thus, protocol 2022-0896 version 1.0 is exactly the same as protocol 2021-0511 with the exception of additional language listed below.

1. Protocol 2022-0896 version 1.0 allows the 4 subjects actively receiving treatment and the one subject in follow up on protocol 2021-0511 to be eligible to enroll onto protocol 2022-0896 version 1.0 as Cohort 1. See Section 4.1.
2. Protocol 2022-0896 version 1.0 requires all subject data to be analyzed in aggregate with protocol 2021-0511 and protocol 2022-0896 Version 1.0 including all future amendments. See Section 9.
3. The allowance of the subjects actively receiving treatment on protocol 2021-0511 to resume treatment uninterrupted upon consenting onto protocol 2022-0896 Version 1.0.
4. Addition of new cohort language. See Section 4 and Section 9
5. Addition of remote consent language. See Section 10.3.

Protocol 2022-0896 Version 1.0 will have two cohorts. Cohort 1 will consist of the subjects that were enrolled and receiving active treatment and/or in follow up on protocol 2021-0511. Upon signing informed consent onto protocol 2022-0896 Version 1.0, the subjects in Cohort 1 will resume treatment on protocol 2022-0896 on the

cycle that they stopped on protocol 2021-0511. The subjects in Cohort 1 will resume treatment per the Schedule of Assessments, detailed on Table 4. Schedule of Assessments and Procedures, respective to their enrollment date onto protocol 2021-0511.

Subjects may choose not to participate, enroll, or withdraw consent at any time on either protocol 2021-0511 or protocol 2022-0896. When all subjects that are receiving active treatment or in follow up on protocol 2021-0511 have signed consent for protocol 2022-0896 will be taken off-study on protocol 2021-0511. Please see Section 9. regarding data management and reconciliation between the two protocols.

4 PATIENT SELECTION

4.1 ELIGIBILITY FOR COHORT 1

Current subjects, including those in follow up, on protocol 2021-0511 are eligible to enroll on protocol 2022-0896.

4.2 ELIGIBILITY FOR COHORT 20

4.2.1 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. Willingness and ability to comply with the protocol for the duration of the study includingundergoing treatment, biopsy, and scheduled visits and examinations including follow up.
4. Histology showing recurrent clear cell 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 whenmeasured 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. 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 inthe 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 itmust be ≤5x ULN.
   f. Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min bythe

Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

9. Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausalpatients. Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatmentsand 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 amenorrhoeic for 12 months or more following cessation of all exogenous hormonaltreatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgicalsterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
10. Has primary central nervous system (CNS) malignancy or known unrelated/active CNSmetastases and/or carcinomatous meningitis.
   a. Subjects with previously treated, asymptomatic brain metastases may participate provided they meet the following criteria: clinically stable for at least 4 weeks and haveno evidence of new or enlarging brain metastases and are off steroids 14 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study drug.
   b. Subjects with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will requireregular imaging of the brain as a site of disease.
   c. Subjects with CNS symptoms should undergo a computed tomography (CT) scan ormagnetic resonance imaging (MRI) of the brain to exclude new or progressive brainmetastases. Spinal cord metastasis is acceptable. However, subjects with spinal cordcompression must be excluded.

4.2.2 EXCLUSION CRITERIA

Exclusion criteria will be assessed within 28 days of starting study treatment and is listed below.

1. Participation in another clinical study with an investigational product during the last 28 days.
2. Prior treatment with CD137 agonists, anti-TIGIT antibody, anti-CTLA-4 or anti-PDL1/PD1antibodies.
3. 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.
4. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy,targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤28 days or 5 half-lives, whichever is shorter, 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 study sponsors and the investigator.
5. 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 afterconsultation with the primary investigator.
b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatmentwith investigational therapy may be included only after consultation with the primary investigator.

6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
7. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose ofIP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
8. History of allogenic organ transplantation.
9. 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 criteria.
    a. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormonereplacement.
    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 consultationwith the primary investigator.
    e. Patients with celiac disease controlled by diet alone.
10. 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 associatedwith 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.
11. Any medical, social, or psychological condition that would interfere with evaluation of studytreatment or interpretation of patient safety or study results.
12. 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 thepresence 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.
13. 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 ofdisease.
    c. Adequately treated carcinoma in situ without evidence of disease.
14. History of leptomeningeal carcinomatosis.
15. 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 ofthe brain prior to study entry.
16. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms.
17. Current or prior use of immunosuppressive medication within 14 days before the first dose of trial therapies. Listed below are the 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 itsequivalent.
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

18. 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 doseof IP.
19. Female patients who are pregnant or breastfeeding or of reproductive potential who are notwilling to employ effective birth control from screening to 180 days after the last dose of Nivolumab/Etigilimab combination therapy.
20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
21. Unresolved partial or complete small or large bowel obstruction.
22. Judgment by the investigator that the patient is unsuitable to participate in the study and thepatient 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 ETIGILIMAB + NIVOLUMAB

Patients will complete study treatment once receiving 24 months of study drug or until disease progression or unacceptable toxicity with combination therapy. There may be circumstances when a subject may need to discontinue treatment and/or the study early. An individual subject will not receiveany 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 atstudy 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. See Section 6.2 for definition of DLT and Section 6.3 for individual drug dose holds. Following DLTresolution investigational drugs may be restarted, but only as per included guidelines.).
7. Grade ≥3 infusion reaction.
8. Patient noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusalto 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 longerbenefiting from treatment with etiligilimab and nivolumab. See Section 7.2.
11. Per direction of regulatory bodies such as the IRB or FDA.
12. Per PI, IND, or supporting pharmaceutical company discretion.
13. 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 investigationalproduct 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 tofurther 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 endof the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that thepatient 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 thepresence 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:

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

4.3.3 REPLACEMENTS 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 NIVOLUMAB

5.1.1 FORMULATION/PACKAGING/STORAGE

Nivolumab will be ordered and accounted for according to institutional standard of care.

Nivolumab is stored under refrigeration at 2°C to 8°C (36°F to 46°F). It will be protected from light bystoring in the original package until time of use. Do not freeze or shake

5.1.2 PRODUCT PREPARATION AND DOSE ADMINISTRATION

Nivolumab will be dosed at standard 240 mg IV Q2W for all indications in this study. The product doesnot contain a preservative. It should be diluted in 0.9% sodium chloride injection, USP or 5% dextrose injection, USP prior to use. After preparation, store the nivolumab infusion either:

1. At room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
2. Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
3. Do not freeze.

4. Administer the infusion over approximately 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion. Please refer to package insert for nivolumab for further administration instructions (Ref 33).
5. For the first cycle, etigilimab and nivolumab should be given on separate days (day 1 etigilimab and day2 nivolumab). . If the 60- minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes followed by a 30-minute observation period per investigator's discretion.

5.1.3 MONITORING OF DOSE ADMINISTRATION

Patients will be monitored before, during and after the infusion with assessment of vital signs at the timesspecified in the Schedule of Assessment. 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 (halfwaythrough 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.

As with any antibody, allergic reactions to dose administration are possible as described in 8.1.4. 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 admitpatients to an intensive care unit if necessary.

5.2 ETIGILIMAB

5.2.1 FORMULATION/PACKAGING/STORAGE

Dosing and formulation include:

	Etigilimab
Dosage formulation:	10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to delivera total of 200 mg per vial
Unit dose strength(s)/Dosage level(s):	1000 mg if subject is ≥ 50 kg 20 mg/kg if subject is < 50 kg
Route of Administration	IV

Dosing instructions:	The initial dose of etigilimab will be delivered on Day 1 over 90 ± 10 minutes followed by a 90-minute observation period. If the 90-minuteinfusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 ± 10 minutes followed by a 60-minute observation period. If the 60- minute infusion is well tolerated, allsubsequent infusions may be delivered over 30 ± 10 minutes followed by a 30-minute observation period per investigator's discretion. For Cycle 1 only, the two drugs will be given separately with Etigilimab delivered on Day 1 (Nivolumab on Day 2). If the subject is < 50 kg,the dose will be based on the subject's weight at each treatmentvisit.
Packaging and Labeling	Study Treatment will be providedas 10 vials in a carton. Each vial and carton will be labeled as required per country requirement.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before useof the study treatment.

Refer to Investigator's brochure and pharmacy manual for additional details.

5.2.2 PRODUCT PREPARATION AND DOSE ADMINISTRATION

1. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. Any unused portion left in a vial may not be used for another subject, as the product contains no preservative (i.e., they are single-use vials).
3. The diluted etigilimab solution may be stored at room temperature for up to 4 hours or 48 hours at 2°C-8°C.
4. The dose of etigilimab will be based on the subject's weight at baseline (Day 1). If the subject's weight changes by >10% during the course of the study, the etigilimab dose should be recalculated.
5. The initial dose of etigilimab will be delivered over 90 ± 10 minutes (although the infusion may be slowed or interrupted for subjects who experience infusion-associated symptoms), followed by a 90- minute observation period. If the 90-minute infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 ± 10 minutes, followed by a 60-minute observation period. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10minutes per investigator discretion, followed by a 30-minute observation period.
6. Dosing of etigilimab should be within +/- 2 days of the Study Day listed in the schedule of assessments.If etigilimab cannot be administered in this 2 day window, then that dose is considered missed.

7. If a Grade ≥2 infusion-related reaction occurs, the infusion should be stopped and any appropriate medical care administered. Once the infusion reaction has resolved, and at the discretion of the Investigator, the infusion may be resumed at one-half of the initial rate of infusion. Subsequent infusions for that subject should then be administered at the reduced rate of infusion. If no reactions occur with subsequent infusions, the infusion rate may be increased. If a semi-permanent peripheral or central line isused to administer the drug, the catheter should be flushed per institutional standard procedures prior to and at the end of each infusion.

5.2.3 DOSE HOLDS, MODIFICATIONS, DISCONTINUATION

5.2.3.1 Dose Hold Criteria

Dosing with etigilimab should be held for the following toxicities; the maximum duration of a dose holdis 28-days, unless a longer hold is approved by the Medical monitor or designee; thereafter, the subject should be discontinued from etigilimab treatment. Tumor assessments should continue as per protocol even if dosing is delayed.

5.2.3.2 Dose Discontinuation Criteria

Hematology labs

- ≥Grade 4 neutropenia persisting for ≥7 days and/or complicated by infection (Febrileneutropenia)
- ≥Grade 4 thrombocytopenia.
- Grade 3 drug-related thrombocytopenia >7 days or associated with clinically significant bleedingrequires discontinuation

Non-hematology labs

Any ≥Grade 3 non-hematologic toxicity, except:

- Grade ≥3 AST, ALT, total bilirubin requires dose discontinuation; concurrent AST or ALT >3 xULN and total bilirubin >2 x ULN requires permanent dose discontinuation. However, while, in most cases of Grade 3 AST or ALT elevation study treatment will be permanently discontinued, liver function test elevations should be reviewed with the investigator. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, adiscussion between the investigator and the Medical Monitor or designee must occur.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours oftheir onset do not require dose discontinuation
- Grade 3 events specifically mentioned in dose-delay section below do not require dosediscontinuation

5.2.3.3 Dose Delay Criteria

- Grade 3 fatigue lasting >7 days
- Grade 3 nausea, emesis, or diarrhea not responding to supportive treatment within 5 days
- Grade 2 drug-related AST, ALT and/or total bilirubin
- Grade 3 drug-related AE of the skin

- Grade 3 drug-related laboratory abnormality with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay.

5.3 ACCOUNTABILITY AND DISPENSATION

The investigator, or a responsible party designated by the investigator, must maintain a careful record ofthe 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 ENROLLMENT

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 clear cell 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 20 evaluable subjects at an expected rate of 2 subjects per month. Subjects will be evaluable for the primary objective once they have completed one cycle of combination therapy. To replace patients that are registered but do not proceed to treatment (e.g. screen failures), an additional 6 patients may be registered; however, a maximum of 20 evaluable patients will be treated as per the protocol. Subjects will be treated for up to 24 months or until disease progression or until unacceptabletoxicity. We will follow all patients for at least 12 months, and we will employ safety and efficacy monitoring rules as described in Section 9.1.1 and Section 9.1.2.

Subjects who are incorrectly enrolled but have not been initiated on treatment will be withdrawn from thestudy. Such subjects will be replaced. Any subjects who are incorrectly enrolled 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 from the time of first administration of study drug until 8 weeks. Given that DLTshave been previously established and investigated and MTD was not reached in prior studies, DLT will not result in any change of the RP2D. 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. 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 regimenand 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.

6.2.1 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 notimprove by at least 1 grade within 7 days
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

6.2.2 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 notresolve 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 concurrentincrease 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 andmyasthenia 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 3days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30days of

initiating optimal medical management including systemic corticosteroids or that exhibitssigns of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baselinecreatinine elevated above ULN
- Any death not clearly due to the underlying disease of extraneous causes.

The DLT definition excludes the conditions listed below.

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed withor 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., inflammatoryreaction 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) thatresolves 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 symptomsand are reversed with appropriate maximal medical intervention within 14 days

In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted toconfirm 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 treatinginvestigator may elect to hold the study drug they deem attributable to the experienced AE.

6.3.1 NIVOLUMAB

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for Nivolumab are provided in the Nivolumab 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. All toxicities will be gradedaccording to NCI CTCAE, Version 5.0.

In addition, there are certain circumstances in which Nivolumab should be permanently discontinued(Appendix A).

6.3.2 ETIGILIMAB

The safety, pharmacokinetic and pharmacodynamic profile of etigilimab has been previously evaluated ina Phase

1a/1b study. Dosing was well tolerated at all doses evaluated, as described in dosing selection section. Guidelines for monitoring, management of immune-mediated and infusion-related reactions are provided in the Investigator's Brochure. Immune-mediated AE management is the same for both etigilimab and nivolumab (Appendix A), while infusion related reactions are specific to etigilimab.

Please refer to management guidelines below.

The maximum duration of a dose hold is 28-days, unless a longer hold is approved by the MedicalMonitor or designee; thereafter, the subject should be discontinued from etigilimab treatment.

Etigilimab infusions may be delayed to allow subjects to recover from study treatment related AEs or intercurrent illness. Subjects who require delay of etigilimab should be re-evaluated weekly or more frequently if clinically indicated and resume etigilimab dosing when re-treatment criteria are met (see below) following discussion with the Investigator and IND office. Individual subject cases should be discussed with the Investigator and IND office or designee for individual treatment decisions. Benefit/riskdecision making may also include Mereo medical monitor as needed.

If the decision is to resume etigilimab dosing, the subject should restart treatment on the next regularlyscheduled dosing visit. Skipped doses are not to be replaced.

6.3.3 COMBINATION TREATMENT REGIMEN

Etigilimab and Nivolumab have potential overlapping toxicities which should be managed as per guidelines. For AEs that are considered at least partly due to administration of Etigilimab and Nivolumab,treat each of the toxicities with maximum supportive care (including holding agents suspected of causing the toxicity where required). If the symptoms promptly resolve with supportive care, consideration shouldbe given to continuing the same dose of Etigilimab and Nivolumab 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, Etigilimab and Nivolumab 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 28 days for the subject to be considered for continued treatment. If the AE does not resolve toGrade 1 or baseline within 28 days, the investigator should consult the MDACC IND Office to determinefeasibility of continued treatment with Etigilimab and Nivolumab.

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 nonsterilized male partner -must use at least 1 highly effective method of contraception (Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 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 afterthis point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, andthe 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., bilateralsalpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

1. Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic 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 theinstitution.
2. Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic 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 1. Note that some contraceptionmethods 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 1. 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 etigilimab and Nivolumab.

6.4.3 CONCOMITANT TREATMENT(S)

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary, as briefly listed in Table 2. Permitted Supportive Medications, to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Table 3. Prohibited Concomitant Medications. The Principal

Investigator must be informed as soon as possible about any medication taken from the time of screeninguntil 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 2. 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 identifiedas "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 allpatients
Inactivated viruses, such as those in the influenzavaccine	Permitted

Table 3. Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy otherthan those under investigation in this study	Should not be given concomitantly whilst the patientis 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 patientis 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 fornon-cancer-related conditions [e.g., insulin fordiabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent isacceptable [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, andtumor 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 forthe management of IP-related AEs,* *Use in patients with contrast allergies.* *In addition, use of inhaled, topical, andintranasal 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 Etigilimab, Nivolumab during thestudy
Live attenuated vaccines	Should not be given through 90 days after the last doseof IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by Mereo, study sponsor and Investigators

6.5 SCHEDULES OF STUDY ASSESSMENTS AND PROCEDURES

Table 4. Schedule of Assessments and Procedures

				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 2	Day 15	Day 22	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
Vital Signs[f]	X		X[g]	X[h]	X[i]		X	X	X	X	X	X	X
ECOG PS	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
Concomitant medications	X		X	X	X		X	X	X	X	X	X	X
CBC w/Diff[j]	X		X		X		X	X	X	X	X	X	X
Chemistry Panel[k]	X		X		X		X	X	X	X	X	X	X
Beta hCG[l]	X		X				X		X		X		
Thyroid Function[m]	X		X				X		X		X		
Urinalysis[n]	X		X				X		X		X	X	X
Coagulation[o]	X												
Hepatitis/HIV Screening[p]	X												
ECG[q]	X												
Tumor Imaging[r]	X[s]							X[t]					
RECIST[u]	X							X					
Archival Tissue[v]	X												
Biopsy[w]	X[x]	X[y]						X[z]					
CA125			X				X		X		X		
Research Blood[aa]			X[bb]		X	X	X		X				X
Buccal Collection[ee]	X									X	X		

Fecal Collection[ff]	X									X	X		
Dietary Intake[gg]	X									X	X		
Etigilimab dosing[cc]			X		X		X	X	X	X			
Nivolumab dosing[dd]				X	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 EOTvisit.
[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 alternativetrial. 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 6weeks 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 tumorbiopsy sample acquisition and analysis prior to study treatment. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these canbe used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of study treatment.
[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 atscreening 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 30minutes during the infusion (halfway through infusion), and at the end of the infusion (see below)..
[g] A 90min observation period is recommended after the first dose of investigational therapy administered over 90±10min .
[h] A 60min observation period is recommended after the first dose of investigational therapy administered over 60±10min.
[i] A 30min observation period is recommended after the first dose (and subsequent doses) of investigational therapy administered over 30±10min. Following determination of infusion time for a given subject, any delay beyond the regular infusion time for said subject e.g. slowing of infusion rate during an infusion, BPand pulse measurements should follow the principles described above or be taken more frequently if needed.
[j] 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 cellcount, and total white cell count.

[k] 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, cortisol, 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, lipase, and cortisol 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 testingare 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.

[l] 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).

[m] TSH and free T4, additional studies will be ordered only if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

[n] Urinalysis includes: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color, and appearance. Microscopy should be used as appropriate to investigate whiteblood cells and use the high-power field for red blood cells
May be performed more frequently than noted in the schedule if clinically indicated. Coagulation testing includes: PT, aPTT, and INR.

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

[q] 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 abrief period (e.g., 30 minutes) to confirm the finding. ECGs may be performed more frequently than noted in the schedule if clinically indicated.

[r] 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 4 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.[s] Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with intravenous (IV) contrast of the brain.

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

[u] RECIST measurements will be performed in line with imaging. Refer to Section 7.

[v] Refer to Section 6.6.2 for details regarding archival tissue collection.

[w] Refer to Section 6.6.3 for details regarding Tumor sample.

[x] Biopsy can be newly acquired or archival ≤3 years old. It is preferred that both archival tissue and newly acquired tissue be obtained. Refer to Section

6.6.3 for detailsregarding tumor sample.

[y] 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 aresearch-only biopsy procedure. Refer to Section 6.6.3 for details regarding tumor sample.

[z] To occur immediately prior to Cycle 3 where possible. Refer to Section 6.6.3 for details regarding tumor sample.

[aa] Sample will be collected before dosing on dosing days for cycles 1-4. Additional research blood timepoint will be obtained on C1D15 and C1D22 for cycle 1 only. .Refer to Section 6.6.1.

[bb] Samples will be taken before dosing begins, two samples will be obtained to allow for control predose sample. Refer to Section 6.6.1.

[cc] Refer to Section 5.2.

[dd] Refer to Section 5.1.

[ee] Directly following consent, participants will provide a buccal sample. The second buccal sample will be collected after 3 cycles of treatment. A third and final buccal sample will be collected either during a toxic event or 6 months post cycle whichever occurs first.

[ff] Directly following consent, participants will be handed or mailed a fecal collection kit, complete with instructions (Appendix B), together with a stamped, return envelope addressed to the Program for Innovative Microbiome and Translational Research (PRIME-TR) laboratory, located on the 5th floor of the South Campus Research Building 4. The PRIME-TR team will conduct all follow-up to obtain return of stool samples (Appendix C & D). Follow-up will be once per week for a maximum of 3 times. The second fecal sample will be collected after 3 cycles of treatment. A third and final fecal sample will be collected either during a toxic event or 6 months post cycle whichever occurs first.

[gg] Participants will complete online dietary and health screening questionnaire via REDCap (Appendices E & F). Dietary intake will be assessed in collaboration with Dr. Carrie Daniel-MacDougal

6.6 BIOLOGICAL SAMPLING PROCEDURES

6.6.1 RESEARCH BLOOD

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

Table 5. Detailed Research Blood Collection Schedule

Time point	PK/ADA Serum	Plasma PBMC/WBC	PBMC	Blood TMB	Paxgene
Cycle 1 Day 1: Pre-treatment	X	X	X	X	X
Cycle 1 Day 15	X				
Cycle 1 Day 22	X	X	X		X
Cycle 2 Day 1: Pre-treatment	X	X	X		X
Cycle 3 Day 1: Pre-treatment	X	X	X		X
Cycle 4 Day 1: Pre-treatment	X	X	X		X
90-day Follow-Up	X[a]	X[a]	X		X

[a] Only for patients who have received at least one dose of IP.

A predose sample will be drawn on Study Days 1, 15 and 22 for Cycle 1, and subsequently predose on Day 1 for all subsequent cycles through cycle 4. A sample will also be collected at the time of treatmenttermination, unless one has been obtained during the prior 14 days.

Serum fractions will be isolated from blood samples collected in Serum Separating tubes for PK/ADA anaylsis. Plasma, PBMCs, WBCs will be collected in K2EDTA-containing tubes and whole blood collected in Paxgene tubes. The Paxgene tubes will be batch shipped to Almac. Tumor TMB will be collected in Guardant provided RUO kits and will be shipped to Guardant Health on the same day of collection. PBMCs will be collected in Na Heparin tubes and will be shipped to Primity on the same dayof collection. These samples 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 thetime of specimen analysis.

6.6.2 ARCHIVAL TUMOR COLLECTION

Archival tumor will be collected either from primary surgery or recurrence. IF available, FFPE block will be obtained. If block is not available 10 to 20 USSs (unstained slides - standard sections) will be obtained.If available, archival tissue will be collected either from primary surgery or recurrence.

6.6.3 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 will be obtained after combination treatment with Etigilimab and Nivolumab when there is a lesion amenable tobiopsy 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-treatmentbiopsy.

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 amountsof tumor can be obtained, the priority will be as follows: 1) FFPE, 2) fresh, 3) fresh, 4) fresh, 5) frozen, 6)FFPE, 7) frozen, 8) FFPE, 9) frozen, and 10) FFPE. 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 TIGIT and PVR IHC (CLIA assays in central lab) and tumor immune and gene expression profiling will be performed with collaborators at MD Anderson group. 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 withthe 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.

6.6.4 MICROBIOME COLLECTION

Directly following consent, participants will provide a buccal sample. The second buccal sample will be collected after 3 cycles of treatment. A third and final buccal sample will be collected either during a toxic event or end-of-treatment visit whichever occurs first.

Directly following consent, participants will be handed or mailed a fecal collection kit, complete with instructions, together with a stamped, return envelope addressed to the Program for Innovative Microbiome and Translational Research (PRIME-TR) laboratory, located on the 5th floor of the South Campus Research Building 4. The PRIME-TR team will conduct all follow-up to obtain return of stool samples (Appendix C & D). Follow-up will be once per week for a maximum of 3 times. The second fecal sample will be collected after 3 cycles of treatment. A third and final fecal sample will be collected either during a toxic event or end-of-treatment visit whichever occurs first.

6.6.5 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 immediatelyidentified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consentimmediately 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 cytotoxicchemotherapy. These differences include the following [48], [49]:

- 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 Etigilimab and Nivolumab would continue between theinitial assessment of progression and confirmation for progression.

In addition, patients may continue to receive Etigilimab and Nivolumab beyond confirmed PD inthe 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 Etigilimab and Nivolumab 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 programmaticallyderiving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitatestreatment with anticancer therapy other than Etigilimab and Nivolumab or with symptomatic progressionthat 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 recommendedfor 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 shouldbe 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 forserial 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 planeof 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 thicknessand 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 Nonmeasureable 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/pericardialeffusion, 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 ofall involved organs should be identified as target lesions. It may be the case that, on occasion, the largestlesion 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 fromEtigilimab and Nivolumab treatment for reasons other than confirmed PD will continue to have objectivetumor 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, takingas reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking asreference 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 qualifyfor 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 markerlevel. 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 asthe overall level of substantial worsening in non-target disease such that, even in presence of SDor 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,’ anincrease 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 maynot 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 itsantitumor activity than would be seen with conventional response criteria.

Table 6 provides overall responses for all possible combinations of tumor responses in target and non- target lesions with or without the appearance of new lesions. Disease control rate is defined as the rate ofcombination of overall responses including complete response, partial response, and stable disease.

Table 6. 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 anassessment
[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 scansafter 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 scenarioabove. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlierthan 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 aremet 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 tonadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existingnew 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 meetingthe PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progressioncriteria (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 immediatesubsequent 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 declaredas the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient shouldcontinue 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 radiologicprogression, 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 inthe follow-up schedules of assessments.

8 ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff members involved in the study arefamiliar 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

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site INDProtocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either theinvestigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- 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 maybe 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 ofthe 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 donot result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Anyimportant medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE mustbe 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 on Reporting Adverse Events for Drugs and Devices".
- Serious adverse events will be captured from the time of the first protocol-specific intervention,until 90 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 testshave returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution.
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 90 day time period that are related tothe study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office andMD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

8.1.3 REPORTING TO FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR312.32.

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 sponsor's guidelines, and Institutional Review Board policy.

8.1.4 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 seriousor non-serious.

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

AESIs for this study include, but are not limited to, those listed below:

1. Diarrhea / Colitis and intestinal perforation
2. Pneumonitis / ILD

3. hepatitis / transaminase increases
4. Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
5. Rash / Dermatitis
6. Nephritis / Blood creatinine increases
7. Pancreatitis / serum lipase and amylase increases
8. Myocarditis
9. Myositis / Polymyositis
10. Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
11. Other inflammatory responses that are rare / less frequent with a potential immune-mediatedaetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current versions of the Etigilimab investigator brochure and Nivolumab Product Label. These guidelines have been prepared andagreed upon to assist the Investigator in the exercise of his/her clinical judgment in treating these types oftoxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

8.1.4.1 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 includehypotension, 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.

8.1.4.2 Pneumonitis

AEs of pneumonitis are also of interest, as pneumonitis has been observed with use of anti-PD-1 mAbs(but not with anti-PDL1 mAbs). Initial work-up should include a highresolution 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.

8.1.4.3 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 derivefrom 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 theIP. Guidelines on management can be found in Appendix A.

8.1.4.4 Gastrointestinal Disorders

Diarrhea/colitis is a commonly observed treatment emergent SAE when PD-1 is used as monotherapy. Inrare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome ifnot properly managed. Guidelines on management can be found in Appendix A.

8.1.4.5 Endocrine Disorders

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

8.1.4.6 Neurotoxicity

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

8.1.4.7 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. Guidelinesfor the management of patients with immune-mediated renal events are provided in Appendix A.

8.1.4.8 Infusion Related Reactions

The management of infusion-related reactions will be according to severity as follows:

In the event that a subject experiences a mild (NCI CTCAE Grade 1) infusion-related event, theinfusion rate should be reduced to half the rate being given at the time of event onset.

Approximately 30 minutes after the event has resolved, the infusion may be resumed at theoriginal rate.

In the event that a subject experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the subject should receive aggressive symptomatic treatment. The infusion should be restarted only after thesymptoms have adequately resolved to baseline grade. The infusion rate at restart should be at most half of the infusion rate that was in progress at the time of the onset of the infusion-related event.

For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusionshould be stopped immediately, aggressive resuscitation and supportive measures should be initiated, and no further etigilimab or nivolumab for that cycle will be administered. Subjects who experience Grade 3 events can receive subsequent cycles with premedication following approval of the Medical Monitor, provided that the next dose is infused over 90 minutes.

Subjects experiencing Grade 4 events will permanently discontinue etigilimab and nivolumab.

If 1 Grade 5 or 2 Grade 4 events of infusion or hypersensitivity reactions occur, enrollment willbe halted pending a safety review by the sponsor and subsequent review with the agency.

No premedication will be allowed for the first dose of etigilimab. Subjects who experience an infusion–associated adverse event may be premedicated for Cycles ≥2 as per institutional guidelines and at the discretion of the treating physician after consultation with the IND Office, but the infusion time may notbe decreased for that infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes as long as the subject continues to be premedicated.

If a subject experiences an infusion-associated adverse event with the 60-minute infusion despite premedication, all subsequent doses should be delivered over 90 ± 10 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion despite premedication, allsubsequent doses should be delivered over 60 ± 10 minutes

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 allother events not listed in the CTCAE should be made by the investigator based upon medical judgmentand 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 ortherapeutic 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 butposes no significant or permanent risk of harm to the patient.
- Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interruptsusual 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 thepatient 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 maynot 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 tothe investigational product as “related” or “not related”.

An event will be considered “not related” to use of the investigational product if any of the following testsare met.

- An unreasonable temporal relationship between administration of the investigational product andthe 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 biologicallyimplausible (e.g., death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (e.g., typical adversereaction 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 “notrelated” 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 7. 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

8.4 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 (90 days after the last dose of Etigilimab and Nivolumab). 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 reportto 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.

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

8.4.1 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 foras long as medically indicated, but without further recording in the eCRF. Mereo 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.

8.4.2 INVESTIGATOR COMMUNICATIONS WITH MEREO

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 Mereo (MPH313SafetyAlerts@mereobiopharma.comsafetyreporting@syneoshealth.com) and MDA IND Office.

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 bereported to the appropriate supporting company 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 relevantfollow-up information must also be provided to Mereo.

8.4.2.1 Overdose

An overdose is defined as a patient receiving a dose of Etigilimab and Nivolumab in excess of thatspecified in the protocol and Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with Etigilimab and/or Nivolumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the MDACC IND Office, and Mereo.

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 notautomatically make an AE serious, but if the consequences of the overdose are serious, for example deathor 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 Etigilimab or Nivolumab.

The investigator will use clinical judgment to treat any overdose.

8.4.2.2 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that arenot the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

8.4.2.3 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, and Mereo 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 increasein 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 initiatedby the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated bythe MDACC IND Office, and Mereo.

8.4.2.4 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 defectsand 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 shouldinform the appropriate Mereo representatives per reporting guidelines (Section 8.3).

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

The same timelines apply when outcome information is available.

8.4.2.5 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a 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 whilethe drug is in control of the study site staff or patient.

Important Medical Events" including pregnancy, the submission is to be done via eSAE application as"Other Important Medical Event".

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 thepatient
- 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

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 Mereo representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Mereo 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 Section8.3 for reporting details) and within 30 days for all other medication errors.

9 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Patients will be enrolled and receive combination Etigilimab and Nivolumab, at which time receipt of atleast one dose of combination therapy at the final determined dosing defines evaluable patients. We estimate accrual rate of 2 patients per month.

In terms of outcome assessment of response rate and toxicity to combination therapy, the Bayesian optimal phase 2 (BOP2) design is utilized to monitor toxicity and efficacy [50]. The first 10 patients to receive combination treatment constitutes the first stage. Of these N=10 patients, if 2 or more responses are detected, the trial will proceed to the second-stage and enroll an additional 10 patients. Of note, more than 3 responses in the total study cohort will indicate statistically significant improvement in response.

Further details of the statistical methods and operating characteristics of this Bayesian monitoring arefound in Section 9.

Please refer to section 3.2 for the detailed explanation of the transition from protocol 2021-0511 to the current

protocol 2022-0896.

A total of 20 evaluable subjects will be included in the analysis of 2022-0896. These 20 subjects will include the 3 evaluable subjects who have completed participation on 2021-0511, the 5 subjects who are currently participating on 2021-0511, and 12-14 additional evaluable subjects. Please see Table 8 for a detailed review of participants who enrolled on 2021-0511.

Table 8 Participants consented onto Protocol 2021-0511

Status	Total	Evaluable
Enrolled	14	8
Screen Fail	4	N/A
Received Treatment	10	8
Actively Receiving Treatment on 2021-0511 as of February 3, 2023	4	4
Follow Up as on 2021-0511 as of February 3, 2023	1	1
Off Study	5	3

Description of Analysis Sets

9.1.1 SAFETY ANALYSIS SET

Subjects who have received at least one dose of Etigilimab and Nivolumab combination treatment will beincluded in the Safety Analysis Set.

9.1.2 EFFICACY ANALYSIS SET

Subjects who have received at least one dose of Etigilimab and Nivolumab combination treatment and have had at least one follow up response assessment will beincluded in the Efficacy Analysis Set.

9.1.3 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) and disease control rate (DCR) along with a 90% confidence interval. Best overall response will be used for estimating ORR (CR/PR) and DCR (CR/PR/SD >4 cycles). Response is defined in Section 7.2. We will estimate the median immune- related progression free survival (irPFS) after treatment with combination Etigilimab and Nivolumab using the product-limit estimator of Kaplan and Meier. When appropriate, we will model irPFS using Coxproportional 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. Changesin T cell populations and proliferation will be calculated along with 95% confidence intervals and compared between pre

and posttreatment biopsies using paired t-test. Similar summaries will be used to compare proportions of macrophage phenotypes. Logistic regression and Cox proportional hazards modelwill be used to assess the relationship between clinical responses and the molecular and immunological changes.

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.

Logistic regression with variable selection (e.g., LASSO method) will be used to identify components and determinants of the gut microbiome that could modulate toxicity, ORR and DCR. Proportional hazard model will be used to identify signature of the gut microbiome that predicts irPFS and other time-to-event endpoints. When appropriate, false discovery rate will be controlled using Benjamini-Hochberg method.

9.1.4 SAFETY ANALYSES

We will tabulate adverse events by grade, and relationship to study drug. We will estimate the proportionof 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.

9.1.5 INTERIM ANALYSES

We monitor the ORR using the Bayesian optimal phase 2 (BOP2) design [50]. The go/no-go rule is provided in Table 9. At the first stage, 10 evaluable patients are enrolled. If the number of responses ≤ 1, stop the trial; otherwise, enroll additional 10 more patients. When the total number of evaluable patients reaches the maximum sample size of 20, we reject the null hypothesis and conclude that the treatment is acceptable if the number of responses are greater than 3; otherwise we conclude that the treatment is unacceptable.

Table 9. Optimized Stopping Boundaries

Number of evaluable patients treated	Stop the accrual if the number of responses <=
10	1
20	3

The above decision rule is obtained based on the following statistical consideration. Let $\boldsymbol{n}$ denote the interim sample size and $\boldsymbol{N}$ denote the maximum sample size. Let $\boldsymbol{p_{eff}}$ denote the objective response rate and define the null hypothesis $\boldsymbol{H_0}: \boldsymbol{p_{eff}} \leq \boldsymbol{0.1}$, under which the treatment is deemed as unacceptable. We will stop enrolling patients and claim that the treatment is unacceptable if

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

where $\boldsymbol{\lambda}$=0.72 and $\boldsymbol{\alpha}$=0 are design parameters optimized to maximize power under the alternative hypothesis $\boldsymbol{H_1}: \boldsymbol{p_{eff}} = \boldsymbol{0.3}$, (i.e., the probability of correctly claiming that the treatment is acceptable under $\boldsymbol{H_1}$), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under $\boldsymbol{H_0}$) at 0.101. This optimization is performed assuming a vague prior Beta(0.1,0.9) for $\boldsymbol{p_{eff}}$. The design yields a statistical power of 0.808 under $\boldsymbol{H_1}$.

Below are the operating characteristics of the design using the BOP2 web application (BOP2 V1.4.6.0),which is available at http://www.trialdesign.org.

Table 10. Operating Characteristics of BOP2 Design

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.1	73.61	10.13	12.6
2	0.2	37.58	48.91	16.2
3	0.3	14.93	80.83	18.5
4	0.4	4.64	94.67	19.5

In addition, we will monitor safety using the following decision table obtained form BOP2 design.

Table 11. Toxicity Stopping Boundaries

# patients treated	Stop if # of DLT >=
3	2
6	3
10	4
15	6
20	8

When the safety boundary is crossed, the accrual will be halted and investigators will assess the totality of safety data for possible termination of the trial. As mentioned in prior sections, DLTs will not result in any change of the RP2D for etigilimab.

Let $\boldsymbol{p_{tox}}$ denote the true toxicity rate, the above stopping rule is obtained by maximizing Pr(claim that the treatment is safe | $\boldsymbol{p_{tox} = 0.2}$), while controlling Pr(claim that the treatment is safe | $\boldsymbol{p_{tox} = 0.4}$) = 0.2, based on the following Bayesian stopping rule: the treatment is deemed unacceptably toxic if

$$\boldsymbol{Pr(p_{tox} \leq 0.4 | data) < \lambda \left(\frac{n}{N}\right)^{\alpha/3}},$$

where, $\boldsymbol{n}$ is the interim sample size, $\boldsymbol{N}$ is the maximum sample size, and $\boldsymbol{\lambda}$=0.52 and $\boldsymbol{\alpha}$=0 are design parameters optimized, assuming a vague prior Beta(0.4,0.6) for $\boldsymbol{p_{tox}}$ to make "go/no-go" decision. Note that the original publication of the design used the probability cutoff $\boldsymbol{\lambda(n/N)^{\alpha}}$, here the attenuation factor 3 is added (i.e., $\boldsymbol{\alpha}$/3) to obtain stricter interim stopping boundaries to enhance safety.

Below in Table 12 are the operating characteristics of the design for safety monitoring using the BOP2 web application (BOP2 V1.4.7.0), which is available at http://www.trialdesign.org.

Table 12. Operating Characteristics of the Design for Safety Monitoring

Scenario	Toxicity Rate	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.1	4.15	95.85	19.4
2	0.2	20.52	79.11	17.1

3	0.3	47.60	50.37	13.5
4	0.4	74.34	22.17	9.7
5	0.5	91.33	6.02	6.8

The Investigator is responsible for completing efficacy/safety summary reports and submitting them tothe IND Office Medical Affairs and Safety Group, for review and approval. These Toxicity reports should be submitted after the first 3, 6, 10, 15 and 20 evaluable patients complete 8 weeks of study treatment, respectively.

An efficacy summary will be submitted with the best overall response obtained at any time during the study after 10 and 20 evaluable patients enrolled. A copy of this summary report should be placed in the Investigator's Regulatory Binder.

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 Declarationof 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 external 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 and will be obtained via in person or remote processes according to institutional standard operating procedures. 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 copyof 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 and Mereo. Any changes made to the protocol must be submitted as amendments and must be approved by the IRB and Mereo prior to implementation. Any changes in study conduct must be reported to the IRB and Mereo.

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 using the rule as previously described in Section 9.1.5.

The study will also be monitored by the MD Anderson External DSMB annually.

11.2 DATA MANAGEMENT

Consented study subjects will be registered in the institutional database, OnCore. 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 maintainedelectronically 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 Mereo clinical studies is closely monitored on an ongoing basis by Mereo representativesin consultation with Patient Safety as per above AE recording and reporting section. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

11.3 ANALYSES AND PROCESSES FOR OVARIAN CANCER MOONSHOT

DNA/RNA next generation sequencing may be performed for genotype-protein expression. Internal/External Sequencing may be done at MDACC, in one of the Core labs such as the Cancer Genomics Lab. We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally, in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under Institutional Review Board (IRB)-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

11.3.1 SAMPLE SHARING

In some cases samples may be sent to or received from outside collaborators such as Broad Institute for next-generation sequencing and/or analysis. All samples will be sent under a specific contract or Material Transfer Agreement (MTA). We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

11.3.2 INTERNAL/EXTERNAL SEQUENCING

Internal/External sequencing may be done here at MD Anderson, in one of the Core labs such as Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as Broad Institute. Sequencing performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA).

11.3.3 DATA SHARING

Researchers can do more powerful studies when they share with each other the information they get from studying human samples. NGS data may be placed in a local M.D. Anderson Institutional Data Repository, commonly referred to as BigData; where both deposition of and access to data require governance and approval. **Any sequencing data shared or deposited in Ovarian Cancer Moonshot/MD Anderson Institutional Data Repositary or any similar respositary used for this purpose may only be linked with the drug class anti-TIGIT, and must not be associated or linked with or be capable of being associated or linked with the drug name etigilimab, Mereo, OMP 313M32 or any similar identifier**. In some cases, grant requirements may require deposition of large-scale data into the public Genotypes and Phenotypes database (dbGaP) an access controlled database overseen by the National Center for Biotechnology Information (NCBI). In other cases peer reviewed Journals may require data to be shared through a resource such as dbGaP. Data submitted to those repositories will only be shared in a de- identified fashion and without associated clinical data or identifiers. This data will be used only for research purposes, and the data elements collected and analyzed will only be those that are necessary to conduct this research.

11.3.4 DATABASE ACCESS ADDITIONAL PROTECTIONS

The precedent to publicly broadcast sequence data has been set by large consortial projects, such as The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE), in order to maximize data utility. However, we know there is the potential for privacy risks associated with the release of sequence data to databases and while the risk may be small it could grow in the future as technology advances. To minimize this potential, we will implement good faith efforts to ensure patient confidentiality and reduce patient exposure. The database of Genotypes and Phenotypes and others like it are extremely access restricted. Only authorized researchers may deposit or access the data and either or both efforts require MD Anderson institutional approval.

Sequence data will only be broadcast through secure transmission processes. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees. Only non-identifiable data will be deposited to dbGaP i.e., no linking table or access to a linking table will be available. Research records will be kept separate from medical records and patients will not have access to any of the research data.

11.3.5 PROTECTED HEALTH INFORMATION

Protected health information (PHI) may be collected from medical records that are related to health and/or disease history including test results, medical procedures, and images (such as X- rays) in addition demographic and environmental factors may be requested. Researchers will use this information to better understand how genes affect health and response to treatment. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees.

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APPENDIX A: DOSING MODIFICATIONS AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION-RELATED, AND NON-IMMUNE-MEDIATED REACTIONS (ETIGILIMAB AND NIVOLUMAB) (CTCAE V5.0)

Table 13. General Considerations

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1:** No dose modification **Grade 2:** • Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed onceevent stabilizes to Grade ≤1 after completion ofsteroid taper. • Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: a. The event stabilizes and is controlled. b. The patient is clinically stable as per Investigator or treating physician's clinical judgement. c. Doses of prednisone are at ≤10 mg/day or equivalent.	It is recommended that management of immune-mediated adverse events(imAEs) follows the guidelines presented in this table: • It is possible that events with an inflammatory or immune mediatedmechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. • Whether specific immune-mediated events (and/or laboratoryindicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of aclear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. • Symptomatic and topical therapy should be considered for low-grade(Grade 1 or 2, unless otherwise specified) events. • For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IVequivalent. • Some events with high likelihood for morbidity and/or mortality –e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/orthere has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. • If symptoms recur or worsen during corticosteroid tapering (28 daysof taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at slower rate (>28 days of taper).

Dose Modifications	**Toxicity Management**
Grade 3: • Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. • Please refer to guidelines below. **Grade 4**: • Permanently discontinue study drug/study regimen. **Note**: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up showsno evidence of pancreatitis, study drug/study regimen may be continued or resumed. **Note:** Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similarevents even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihoodfor morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upontreatment with systemic steroids and following full taper. **Note:** There are some exceptions to permanent discontinuationof study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	• More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEsfor specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. • With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinalprotection, and glucose monitoring. • Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Table 14. Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** • Monitor patients for signs and symptoms of pneumonitisor ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention; not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinicallyappropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** • Monitor and closely follow up in 2 to 4 days for clinicalsymptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. • Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1, then the decision to reinitiate study drug /study regimen will be based upon treating physician's clinical judgement and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** • Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids (e.g., prednisone 1 to2 mg/kg/day PO or IV equivalent). • Reimage as clinically indicated. • If no improvement within 3 to 5 days, additional workupshould be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			• If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCNguidelines for treatment of cancer-related infections)[a] • Consider Pulmonary and Infectious Disease consults. • Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-careADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy of intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. • Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. • Hospitalize the patient. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days, additional workupshould be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks'dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer tocurrent NCCN guidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Diarrhea/Colitis **Large intestine perforation/** **Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** • Monitor for symptoms that may be related diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus).\ • When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. • Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. • Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** • Monitor closely for worsening symptoms. • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 2 (Diarrhea: stool frequency of 4 to6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., AmericanDietetic Association colitis diet), and loperamide and/or budesonide. • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsensdespite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/orcolonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4mg/kg/day started. • If still no improvement within 3 to 5 days despite 2 to 4mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg onceevery 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections) [a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: invasive intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. • Monitor stool frequency and volume and maintain hydration. • Urgent GI consult and imaging and/or colonoscopy as appropriate. • If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and referto infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeonexperienced in abdominal surgery immediately without any delay. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**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 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baselineif baseline abnormal; and/orTB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	No dose modifications. If it worsens, then treat as Grade 2.	Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/orTB >1.5×ULN and ≤3.0×ULN if baseline normal,	Hold study drug/study regimen dose until resolution to Grade≤1. If toxicity worsens, then treat as Grade 3. If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** • Regular and frequent checking of LFTs (e.g., every 1 to 2days) until elevations of these are improving or resolved. • If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. • If event is persistent (>3 to 5 days) or worsens, promptlystart prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IVmethylprednisolone 2 to 4

	>1.5- 3.0×baseline if baseline abnormal)		mg/kg/day. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] • Discuss with study physician if mycophenolate mofetil isnot available. **Infliximab should NOT be used.** • Once the patient is improving, gradually taper steroidsover ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/orTB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal)	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimendose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgradeto Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days.	**For Grade 3 or 4:** • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. • If still no improvement within 3 to 5 days despite 1 to4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with studyphysician if mycophenolate is not available. **Infliximab should NOT be used.** • Request Hepatology consult, and perform abdominalworkup and imaging as appropriate. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections) [a]
	Grade 4 (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinuestudy drug/study regimen. 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]	

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** • Consult with nephrologist. • Monitor for signs and symptoms that may be related tochanges in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinineclearance, electrolyte imbalance, decrease in urine output, or proteinuria). • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). • Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (serum creatinine >ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** • Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume itsregular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. • Consider symptomatic treatment, including hydration,electrolyte replacement, and diuretics. • If baseline serum creatinine is elevated above normal,and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline,	**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

		then resume study drug/study regimen after completion of steroid taper.	clinically indicated. • If event is persistent (>3 to 5 days) or worsens, promptlystart prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsensdespite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered andprompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroidsover ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-relatedinfections).[a] • When event returns to baseline, resume study drug/studyregimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Carefully monitor serum creatinine on daily basis. • Consult nephrologist and consider renal biopsy if clinically indicated. • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsensdespite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered andprompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroidsover ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Dermatitis (including Pemphigoid)	(refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)		• Monitor for signs and symptoms of dermatitis (rash and pruritus). • IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXICEPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1or 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 (e.g., urea cream). • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3 to5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. • Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 3 or 4 (or life-threatening):** • Consult Dermatology. • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
		If temporarily holding the study drug/study regimen does not provideimprovement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. For Grade 4 (or life-threatening): Permanently discontinue study drug/study regimen.	• Consider hospitalization. • Monitor extent of rash [Rule of Nines]. • Consider skin biopsy (preferably more than 1) as clinically feasible. • Once the patient is improving, gradually taper steroidsover ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-relatedinfections).[a] • Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** • Consider consulting an endocrinologist for endocrine events. • Consider, as necessary, discussing with study physician. • Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits,polydipsia, polyuria, hypotension, and weakness. • Patients should be thoroughly evaluated to rule out anyalternative etiology (e.g., disease progression including brain metastases, or infections). • Depending on the suspected endocrinopathy, monitor andevaluate thyroid function tests: TSH, free T3 and free T4and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
			• For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptomsof pancreatic inflammation. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriateautoimmune antibody testing.
	Grade 1	**No dose modifications.**	**For Grade 1 (including those with asymptomatic TSH elevation):** • Monitor patient with appropriate endocrine function tests. • For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). • If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistentlyout of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable.	**For Grade 2 (including those with symptomatic endocrinopathy):** • Consult endocrinologist to guide evaluation of endocrinefunction and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
		• If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable asper investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	• For all patients with abnormal endocrine work up, exceptthose with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-termcorticosteroids (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 replacementtherapy, without study drug/study regimen interruption, and without corticosteroids. • Isolated Type 1 diabetes mellitus (DM) may be treatedwith appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. • Once patients on steroids are improving, gradually taperimmunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and considerprophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] • For patients with normal endocrine workup (laboratoryassessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** • Consult endocrinologist to guide evaluation of endocrinefunction and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. • For all patients with abnormal endocrine work up, exceptthose with isolated hypothyroidism or Type 1 DM, and asguided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones).

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
		Patients with endocrinopathies whomay require prolonged or continuedsteroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable asper investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	• For adrenal crisis, severe dehydration, hypotension, orshock, immediately initiate IV corticosteroids with mineralocorticoid activity. • Isolated hypothyroidism may be treated with replacementtherapy, without study drug/study regimen interruption, and without corticosteroids. • Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. • Once patients on steroids are improving, gradually taperimmunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and considerprophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** • Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). • Monitor patient for general symptoms (headache, nausea,vertigo, behavior change, or weakness). • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). • Perform symptomatic treatment with Neurology consult as appropriate.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
	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. If toxicity worsens, then treat asGrade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of <u>steroid taper.</u>	**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 to2 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:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Consider, as necessary, discussing with study physician. • Obtain Neurology consult. • Consider hospitalization. • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. • If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptlytreat with additional immunosuppressants (e.g., IV IG). • Once stable, gradually taper steroids over ≥28 days.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
Peripheral neuromotor syndromes **(such as Guillain-Barre and myasthenia gravis)**	**Any Grade**	**General Guidance**	**For Any Grade:** • The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidityor in the worst case, death. Special care should be takenfor 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 myastheniais suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of aNeurology 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.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
	Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** • Consider, as necessary, discussing with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. • Obtain a Neurology consult.
	Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	For Grade 2: • Consider, as necessary, discussing with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. • Obtain a Neurology consult • Sensory neuropathy/neuropathic pain may be managedby appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* • Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. • Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking intoaccount the unique needs of each patient.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
			• 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 thediagnosis. *GUILLAIN-BARRE:* • It is important to consider here that the use ofsteroids as the primary treatment of Guillain-Barre is not typically considered effective. • Patients requiring treatment should be startedwith IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4 (Grade 3 GB: severe symptoms;limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL; Grade 4 MG: life threatening consequences; urgent intervention indicated.	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAEdoes not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen/	**For Grade 3 or 4 (severe or life-threatening events):** • Consider, as necessary, discussing with study physician. • Recommend hospitalization. • Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* • Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. • Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. • If myasthenia gravis-like neurotoxicity present,consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful,can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* • It is important to consider here that the use ofsteroids as the primary treatment of Guillain-Barre is not typically considered effective. • Patients requiring treatment should be startedwith IV IG and followed by plasmapheresis if not responsive to IV IG.

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediatedmyocarditis.	**For Any Grade:** • The prompt diagnosis of immune-mediated myocarditisis important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. • Consider, as necessary, discussing with the study physician. • Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrythmia, 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 pericardialeffusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnosticprocedures. • Initial work-up should include clinical evaluation, BNP,cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications or infections)
	Grade 1 (asymptomatic ormild symptoms*;clinical or diagnostic observations only; interventionnot indicated) *Treat myocarditis withmild symptoms <u>as Grade 2.</u>	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 studydrug/study regimen is held, resume after complete resolution to Grade 0	**For Grade 1 (no definitive findings):** • Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-upas 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 (Grade 2: Symptoms with moderate activityor exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated;new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) *Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	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 clinicaljudgment and after completion ofsteroid 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 diagnosticprocedures including a cardiac biopsy. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It isimportant to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCNguidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
Myositis/ **Polymyositis (“Poly/myositis”)**	**Any Grade**	**General Guidance**	**For Any Grade:** • Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. • If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown)autoimmune disorder, consider Rheumatology consultation. • Consider, as necessary, discussing with the study physician. Initial work-up should include clinical evaluation,creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work- up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti- smooth muscle, antisynthetase [such as anti-Jo-1], and/orsignal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conductionstudies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia ordysphonia. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications,or infections).

Adverse Events	Severity Gradeof the Event	Dose Modifications	Toxicity Management
	Grade 1 (mild pain)	No dose modifications.	**For Grade 1:** • Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. • Consider Neurology consult. • Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** • Monitor symptoms daily and consider hospitalization. • Obtain Neurology consult, and initiate evaluation. • Consider, as necessary, discussing with the study physician. • If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptlystart IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurologyconsultant • If clinical course is *not* rapidly progressive, start systemicsteroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAEdoes 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.	**For Grade 3 or 4 (severe or life-threatening events):** • Monitor symptoms closely; recommend hospitalization. • Obtain Neurology consult, and complete full evaluation. • Consider, as necessary, discussing with the study physician. • Promptly start IV methylprednisolone 2 to 4 mg/kg/daysystemic steroids along with receiving input from Neurology consultant. • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days,consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Consider whether patient may require IV IG, plasmapheresis. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCNguidelines for treatment of cancer-related infections).[a]

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

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

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for AdverseEvents; 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 Upperlimit of normal.

Table 15. Infuse-Related Reactions

Severity Grade of the Event	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 administeredper 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 institutionalstandards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

Table 16. Non-Immune-Mediated Reactions

Severity Grade of the Event	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 laboratoryabnormalities not deemed to be clinically significant.	Treat accordingly, as per institutionalstandard.
Grade 1	No dose modifications.	Treat accordingly, as per institutionalstandard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutionalstandard.
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 21 days, resume study drug/study regimen administration.Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutionalstandard.
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 institutionalstandard.

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 17. 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.