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| **Protocol Title** | A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (MPH313) Administered in Combination with Nivolumab to Subjects with Locally Advanced or Metastatic Solid Tumors (ACTIVATE) |
| **Protocol Number** | MPH313-1-02 |
| **Product Number** | MPH313 (previously OMP-313M32) |
| **Sponsor Name and Registered Address** | Mereo BioPharma 5, Inc.<br>800 Chesapeake Drive<br>Redwood City, California 94063<br>United States |
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# 1. INTRODUCTION AND BACKGROUND

## 1.1. Introduction

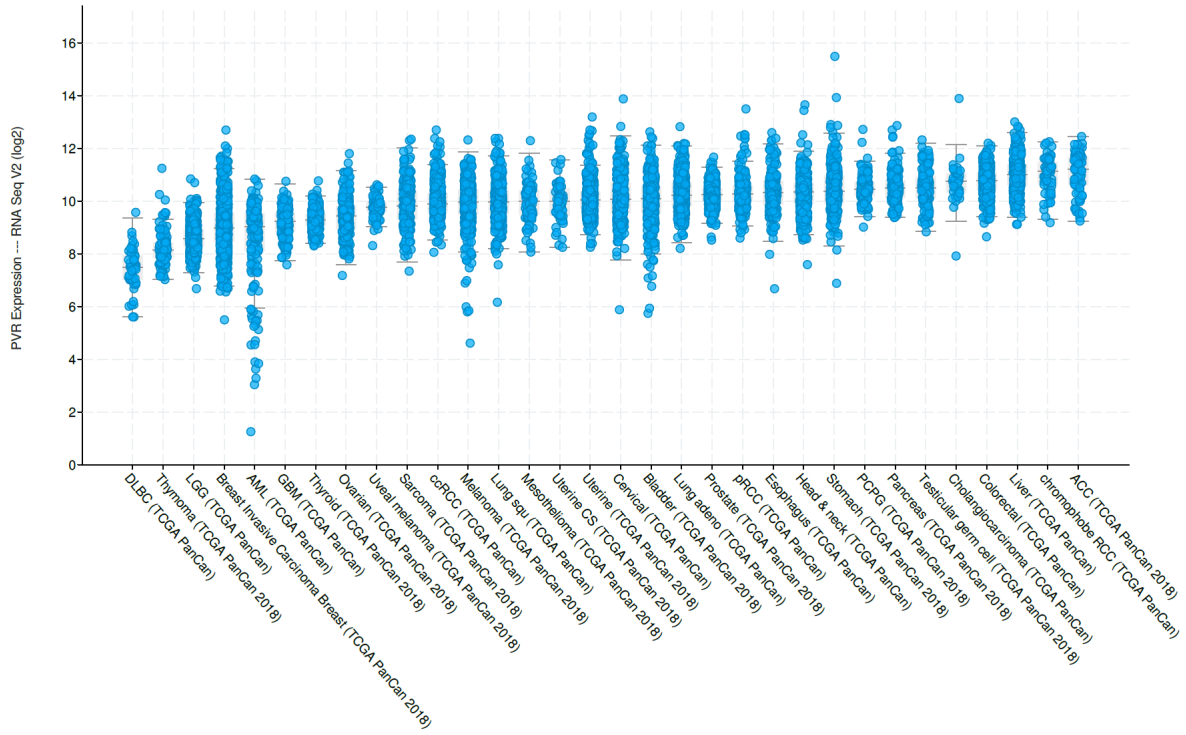
Etigilimab, a humanized immunoglobulin G (IgG1) monoclonal antibody that specifically binds to human TIGIT (T-cell immunoreceptor with Ig and ITIM domains), blocks TIGIT interaction with its ligand PVR (poliovirus receptor), inhibits downstream signaling, and mediates target cell killing. Anti-TIGIT was shown preclinically to inhibit tumor growth in mouse models. Etigilimab is being developed for the treatment of solid cancer tumors in humans.

## 1.2. Background

TIGIT is an important co-inhibitory receptor; it contains 2 immunoreceptor tyrosine-based inhibition motifs (ITIMs) and its expression at the surface of immune cells is markedly increased upon activation. TIGIT is found on CD4 and CD8 T-cells, on natural killer (NK) cells, and on a subset of Tregs (regulatory T cells) (Chan et al 2012, Yu et al 2009, Joller et al 2014). 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 (Joller et al 2014, Joller et al 2011, Levin et al 2011, Stanietsky et al 2009). Known ligands for TIGIT are PVR, PVRL2, and with weaker binding, PVRL3 and PVRL4 (Yu et al 2009) (data on file at Mereo). The TIGIT signaling axis also contains a co-stimulatory receptor, CD226, which binds to PVR and PVRL2 with lower affinity than TIGIT (Bottino et al 2003, Martinet & Smyth 2015). Therefore, when TIGIT is expressed, the ligands preferentially engage TIGIT rather than CD226, leading to immune suppression.

Given TIGIT's immunomodulatory functions and the expression of PVR and PVRL2 in most cancers (Stanietsky et al 2009, Gromeier et al 2000), it has 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 (Figure 1).

**Figure 1 Broad Expression of TIGIT's Ligand PVR across TCGA Tumor Collection**




**Abbreviations:** PVR = poliovirus receptor; TCGA = The Cancer Genome Atlas; RPKM = reads per kilobase per million; TIGIT = T-cell immunoreceptor with Ig and ITIM domains

**Legend:** PVR gene expression levels are plotted for 32 different tumor types as available from The Cancer Genome Atlas (TCGA). Each symbol represents one patient. Levels are expressed in reads per kilobase per million (RPKM).

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 (Johnston et al 2014, Kurtulus et al 2015). Further supporting TIGIT targeting for cancer treatment are reports of its overexpression on patient tumor-associated T-cells (Johnston et al 2014, Chauvin et al 2015).

TIGIT targeting is likely to be most efficient when combined with other immunotherapies. In preclinical and clinical studies, targeting TIGIT together with the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pathway demonstrated superior tumor suppression compared to either monotherapy.

A Phase 1a/b open-label, dose-escalation study was conducted to evaluate the safety and pharmacokinetics (PK) 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 subjects were 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 [redacted] mg/kg (for dose-escalation) and [redacted] mg/kg (for dose-expansion) , and doses evaluated in the Phase 1b dose-escalation portion of the study were [redacted] mg/kg. To characterize the PK properties of etigilimab and pharmacodynamic responses to treatment, blood samples were taken at various timepoints 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 (DoR), progression-free survival (PFS), and overall survival. Safety endpoints included adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity testing.

Treatment with etigilimab was well-tolerated in study 313M32-001; no dose-limiting toxicities (DLTs) were reported in either the Phase 1a or Phase 1b portions of the study. Thus, the maximum tolerated dose 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 (each reported 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 (ALT) 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 (AST) (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.

In the single agent portion of the study no Response Evaluation Criteria in Solid Tumors (RECIST) responses were reported. However, a number of subjects demonstrated tumor reduction or stable disease (SD). The tumor types where clinical benefit was observed included endometrial, fallopian tube, parotid adenocarcinoma, salivary duct adenocarcinoma, and colorectal cancer. In the group who received both etigilimab and nivolumab, all subjects treated received a prior checkpoint point inhibitor. A partial response was observed in a patient with ovarian cancer, and other patients with microsatellite instability (MSI), colorectal (CRC), head and neck, gastric and renal cancer appeared to benefit with evidence of tumor reduction or stabilization.

The median (95% confidence interval [CI]) PFS in the Phase 1a portion of the study was 56.0 (51.0, 112.0) days, and the PFS 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) PFS in the Phase 1b portion of the study was 57.5 (14.0, 224.0) days, and the PFS 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.

### 1.3. Study Design

This is an open-label, multicenter, Phase 1b/2 basket study designed to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etigilimab in combination with nivolumab in subjects with recurrent, locally advanced and/or metastatic solid tumors who are not candidates for available, curative standard of care therapies. In cohorts enrolling tumor types for whom anti-PD-1 antibody therapy is approved treatment for recurrent, locally advanced or metastatic disease, subjects may be enrolled prior to treatment with anti-PD-1 antibody therapy.

Subjects will be assigned to receive etigilimab ([redacted] mg every 2 weeks for subjects ≥50 kg, [redacted] mg/kg dose every 2 weeks for subjects <50 kg) in combination with nivolumab (240 mg every 2 weeks) and will continue until protocol-defined discontinuation criteria are met (refer to Section 7). Additional doses and schedules may also be evaluated. This study will evaluate both subjects who have not previously been treated with immune checkpoint inhibitors (CPI) as well as those who have received prior CPI therapy and will include tumor types chosen for higher prevalence of TIGIT, and in select cohorts, subjects with high PD-L1 expressing tumors as measured by immunohistochemistry (IHC). Tumor types selected for this study include recurrent, locally advanced and/or metastatic endometrial carcinoma (EC), cervical cancer (CC), gastric cancer and gastro-esophageal junction carcinoma (GC), squamous cell carcinoma of the head and neck (HNSCC), ovarian cancer (OC), rare cancers (metastatic testicular germ cell tumor, uveal melanoma and sarcoma) and any subject with concomitant tumor mutation burden high (TMB-high) and microsatellite stable (MSS) tumors. As TIGIT has been implicated in PD-L1 resistance, subjects who have received or progressed following a CPI (post-CPI subjects) will also be enrolled in select tumors including EC, HNSCC and TMB-high/MSS tumors. Parallel cohorts of up to 20 subjects per cohort will be evaluated.

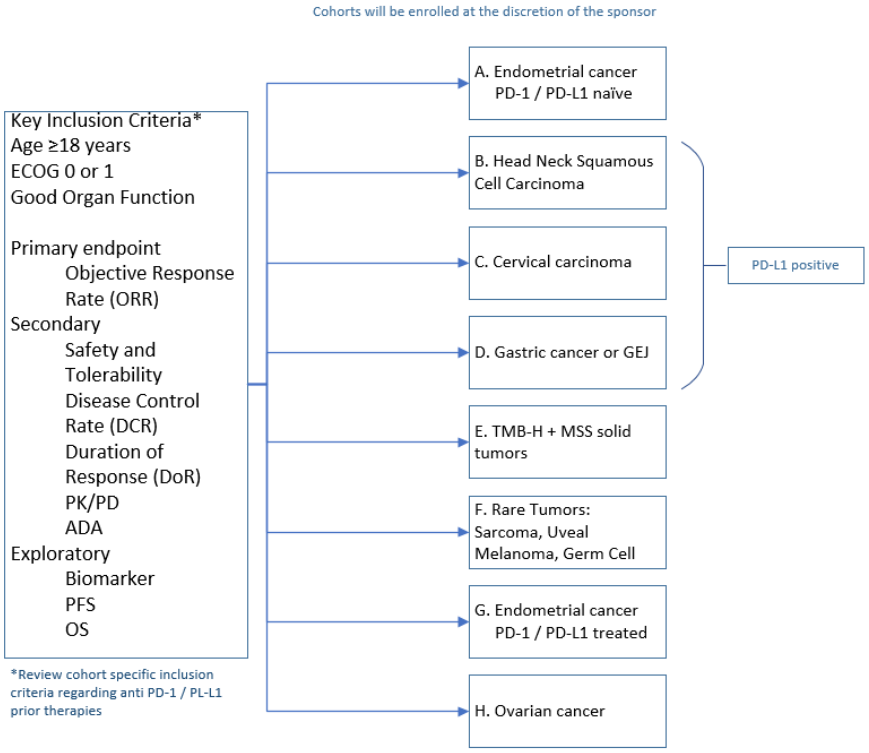
Cohorts will be enrolled at the discretion of the sponsor. Selected cohorts will be open for the first 20 subjects enrolled without increasing the total number of subjects proposed for the trial. During the conduct of this open-label study an Independent Data Monitoring Committee (IDMC) will be established and will review study data on an ongoing basis. The IDMC will consist of at least 3 members with expertise in their field of practice as well as in the conduct of clinical studies. The committee members will be free of significant conflicts of interest. The IDMC will hold regularly scheduled data review meetings at pre-specified intervals as defined in the IDMC charter. The IDMC will also be available on an ad hoc basis e.g., to provide guidance related to any emerging safety signals or if requested by the sponsor.

The IDMC will have periodic safety reviews of the study that will start after the first 20 subjects are enrolled. A safety review of the study will be conducted by the IDMC approximately every 3 months. The IDMC and sponsor may decide to meet less frequently, based upon rate of accrual and the amount of new data generated (refer to the IDMC charter). .

Futility monitoring will be evaluated in each cohort of the study using a Simon's two-stage design as described in Section 9.1 of the protocol. For each cohort, the second stage may be opened for enrollment only after discussion with the IDMC and the sponsor. The sponsor may have an independent assessment of responses to verify investigator-reported responses. The responses based on independent assessments, if available, will be used for sensitivity analysis with sponsor and will make recommendations regarding study conduct, including whether to continue, modify, or stop the study.

An analysis will be conducted when the first 30 TIGIT IHC biopsy results have been complete. This is to confirm the expected TIGIT positive rate based on data on file and reported in the literature. The efficacy of the combination will be evaluated by cohort and efficacy of the combination will be evaluated based on TIGIT IHC positive subjects.

**Figure 2 Study Schema**




**Abbreviations:** ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction adenocarcinoma; Tumor mutation burden – high (TMB-H) + microsatellite stable (MSS); OS = overall survival; PD = pharmacodynamic; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PFS = progression-free survival; PK = pharmacokinetic; ADA=anti-drug antibody

## 1.4. Study Rationale

### 1.4.1. Rationale for Study Design

A number of checkpoint inhibitors such as PD-L1 and PD-1 can act by blocking interactions between ligands and receptors on tumor cells and T cells and lead to enhanced anti-tumor immunity. A number of anti-PD-1 inhibitors, including nivolumab and anti-PD-L1 antibodies have been approved for numerous indications. However, a large proportion of patients who receive CPI do not derive a clinical benefit, progress or become resistant. Strategies improving the effectiveness or reversing resistance to these agents in high unmet need indications are being studied.

One such strategy explored is inhibiting TIGIT. It has 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. Etigilimab is a novel immunotherapy that binds to TIGIT, an immune checkpoint protein found on immune cells. Both TIGIT and PD-1 are involved in immune suppression and blocking both pathways have the potential for improving anti-tumor activity.

A Phase 1 study of single agent etigilimab (n = 23) and in combination with nivolumab (n = 10) in heavily pretreated advanced cancer subjects was completed. Clinical benefit was noted in subjects with endometrial, ovarian, head and neck, and some MSI high and TMB-H tumors (data on file at Mereo). Finally, other anti-TIGIT anti-bodies in development have reported preliminary evidence of potential clinical benefit by stabilization of disease activity in both CPI naïve and post-CPI subjects in a number of tumor types including non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), ovarian, cervical and gastroesophageal junction adenocarcinoma.

The tumor types selected for evaluation in this study have been identified based on the likelihood of high TIGIT/PVR expression and co-expression of both TIGIT and PD-1 (Figure 3 and Figure 4).

## Figure 3 Prevalence of TIGIT in TCGA Tumors

| Code | Tumor | >3rd Quartile (100.3) | Total Samples | Freq | Rank |
|---|---|---|---|---|---|
| DLBC | Lymphoid Neoplasm Diffuse Large B-cell Lymphoma | 46 | 48 | 95.83% | 1 |
| TGCT | Testicular Germ Cell Tumors | 88 | 150 | 58.67% | 2 |
| LUAD | Lung adenocarcinoma | 267 | 515 | 51.84% | 3 |
| HNSC | Head and Neck squamous cell carcinoma | 235 | 520 | 45.19% | 4 |
| SKCM | Skin Cutaneous Melanoma | 206 | 470 | 43.83% | 5 |
| LUSC | Lung squamous cell carcinoma | 214 | 502 | 42.63% | 6 |
| CESC | Cervical squamous cell carcinoma and endocervical adenocarcinoma | 127 | 305 | 41.64% | 7 |
| KIRC | Kidney renal clear cell carcinoma | 181 | 533 | 33.96% | 8 |
| STAD | Stomach adenocarcinoma | 132 | 415 | 31.81% | 9 |
| BRCA | Breast invasive carcinoma | 344 | 1097 | 31.36% | 10 |
| PAAD | Pancreatic adenocarcinoma | 51 | 178 | 28.65% | 11 |
| BLCA | Bladder Urothelial Carcinoma | 109 | 408 | 26.72% | 12 |
| MESO | Mesothelioma | 20 | 87 | 22.99% | 13 |
| SARC | Sarcoma | 56 | 259 | 21.62% | 14 |
| UCEC | Uterine Corpus Endometrial Carcinoma | 114 | 545 | 20.92% | 15 |
| THYM | Thymoma | 24 | 120 | 20.00% | 16 |
| CHOL | Cholangiocarcinoma | 7 | 36 | 19.44% | 17 |
| ESCA | Esophageal carcinoma | 33 | 184 | 17.93% | 18 |
| THCA | Thyroid carcinoma | 86 | 505 | 17.03% | 19 |
| LIHC | Liver hepatocellular carcinoma | 57 | 371 | 15.36% | 20 |
| COAD | Colon adenocarcinoma | 65 | 460 | 14.13% | 21 |
| READ | Rectum adenocarcinoma | 16 | 166 | 9.64% | 22 |
| LAML | Acute Myeloid Leukemia | 16 | 173 | 9.25% | 23 |
| UVM | Uveal Melanoma | 6 | 80 | 7.50% | 24 |
| OV | Ovarian serous cystadenocarcinoma | 20 | 305 | 6.56% | 25 |
| UCS | Uterine Carcinosarcoma | 3 | 57 | 5.26% | 26 |
| PRAD | Prostate adenocarcinoma | 26 | 497 | 5.23% | 27 |
| KIRP | Kidney renal papillary cell carcinoma | 13 | 290 | 4.48% | 28 |
| ACC | Adrenocortical carcinoma | 2 | 79 | 2.53% | 29 |
| LGG | Brain Lower Grade Glioma | 4 | 516 | 0.78% | 30 |
| GBM | Glioblastoma multiforme | 1 | 161 | 0.62% | 31 |
| KICH | Kidney Chromophobe | 0 | 66 | 0.00% | 32 |
| PCPG | Pheochromocytoma and Paraganglioma | 0 | 179 | 0.00% | 32 |

**Abbreviations:** RSEM = RNA-Seq by Expectation-Maximization; TCGA = The Cancer Genome Atlas; TIGIT = T-cell immunoreceptor with Ig and ITIM domains

**Legend:** Prevalence of TIGIT gene expression in tumor types as available from TCGA. The quartile RSEM value of TIGIT gene expression is 100.

## Figure 4 TIGIT and PD1 Co-expression on TCGA

| TCGA | Detail | TIGIT:PD1 (CD279) R (correlation) |
|---|---|---|
| UVM | Uveal Melanoma | 0.95 |
| SARC | Sarcoma | 0.92 |
| SKCM | Skin Cutaneous Melanoma | 0.91 |
| TGCT | Testicular Germ Cell Tumors | 0.9 |
| KIRP | Kidney renal papillary cell carcinoma | 0.88 |
| HNSC | Head and Neck squamous cell carcinoma | 0.87 |
| BLCA | Bladder Urothelial Carcinoma | 0.86 |
| COAD | Colon adenocarcinoma | 0.86 |
| ESCA | Esophageal carcinoma | 0.84 |
| LUSC | Lung squamous cell carcinoma | 0.83 |
| MESO | Mesothelioma | 0.83 |
| BRCA | Breast invasive carcinoma | 0.82 |
| PRAD | Prostate adenocarcinoma | 0.82 |
| PAAD | Pancreatic adenocarcinoma | 0.81 |
| THCA | Thyroid carcinoma | 0.81 |
| UCEC | Uterine Corpus Endometrial Carcinoma | 0.8 |
| KICH | Kidney Chromophobe | 0.78 |
| CESC | Cervical squamous cell carcinoma and endocervical adenocarcinoma | 0.76 |
| OV | Ovarian serous cystadenocarcinoma | 0.76 |
| READ | Rectum adenocarcinoma | 0.74 |
| KIRC | Kidney renal clear cell carcinoma | 0.73 |
| LUAD | Lung adenocarcinoma | 0.73 |
| ACC | Adrenocortical carcinoma | 0.72 |
| STAD | Stomach adenocarcinoma | 0.72 |
| UCS | Uterine Carcinosarcoma | 0.72 |
| PCPG | Pheochromocytoma and Paraganglioma | 0.52 |
| DLBC | Lymphoid Neoplasm Diffuse Large B-cell Lymphoma | 0.49 |
| GBM | Glioblastoma multiforme | 0.46 |
| LIHC | Liver hepatocellular carcinoma | 0.46 |
| CHOL | Cholangio carcinoma | 0.34 |
| LGG | Brain Lower Grade Glioma | 0.3 |
| LAML | Acute Myeloid Leukemia | 0.076 |
| THYM | Thymoma | 0.047 |

**Abbreviations:** PD-1 = programmed death-1; TCGA = The Cancer Genome Atlas; TIGIT = T-cell immunoreceptor with Ig and ITIM domains

**Legend:** TIGIT and PD1 expression in TCGA. Tumor ranked by R value; tumors with correlation greater than R=.7 are shaded.

The purpose of the study is to determine preliminary clinical activity of this combination in several selected tumor groups and identify which subject characteristics, based on histology, biomarker or prior therapy are most like to benefit from this combination.

This open-label basket study trial design is the most effective to evaluate pan tumor safety and clinical activity by histology, TIGIT, and PD-L1 status.

Subject selected for evaluation in this study all have advanced or metastatic disease, who are not candidates for available, curative standard of care therapies, with cancer types considered as high unmet therapeutic need indications for which limited therapeutic options exist. Table 1 illustrates

the historic objective response rate (ORR) for monotherapy with anti-PD-1/anti-PD-L1 antibodies in the tumor types included in this study.

**Table 1 Historical ORR with CPI monotherapy for Treatment Cohorts**

| Tumor Type | ORR for Single Agent CPI |
|---|---|
| **PD-L1 Positive tumors** | |
| Advanced and/or recurrent or metastatic squamous cell carcinoma of the head and neck or for the first-line treatment of subjects with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) | 14%-18% |
| Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 | 14% (Chung et al 2019) |
| Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. | 16%-22% |
| **TMB-H** | |
| Advanced or metastatic TMB-H and MSS solid tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options. | 28% |
| **Independent of PD-L1 Status** | |
| Advanced and/or metastatic endometrial carcinoma, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation | 23% ~ 40% |
| Histologically confirmed high grade serous and endometrioid recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer following platinum-based front-line regimen per standard of care after primary or interval debulking surgery with documented radiological recurrence. | ~10% (Matulonis et al 2020) |
| Rare disease with high prevalence of TIGIT expression | |
| • germ cell tumors | 0%-15% |
| • sarcoma | 0%-15% |
| • uveal melanoma | 0%-15% |

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**Abbreviations**: CPI = checkpoint inhibitor; MSS = microsatellite stable; ORR = overall response rate; PD-L1 = programmed death ligand-1; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; TMB-H = tumor mutational burden-high

This ORR together with the DoR is expected to inform future studies of this combination depending on tumor type.

### 1.4.2. Scientific Rationale for Selected Endpoints

In oncology clinical trials, many different endpoints can be used as primary or secondary endpoints including OS, ORR, DoR, disease control rate (DCR), disease-free survival (DFS), and PFS.

The ORR, as per RECIST v1.1, is an increasingly important endpoint for accelerated development of highly active anticancer therapies and will be the primary endpoint for this study. This surrogate marker, used in single arm studies, is able to evaluate early if there is a direct effect on tumor size seen on radiology. The ORR has correlated with endpoints such as PFS and OS.

As per Food and Drug Administration (FDA) guidance document on oncology endpoints, ORR was chosen because:

- ORR is generally assessed earlier and with smaller sample size compared with survival studies.
- ORR measures the effect on tumor attributable to drug(s), not natural history.
- ORR is generally based on objective and quantitative assessment.

Additional secondary and exploratory endpoints that will also be evaluated include the following:

The DoR is defined as the time from first documented objective response (RECIST v1.1) by Independent Central Review until the date of documented disease progression. Cancer drugs that demonstrate improved DoR can produce a durable, meaningful delay in disease progression, as opposed to a temporary response without any lasting benefit. The DCR, as per RECIST v1.1 is a modification of ORR that includes subjects with SD exceeding a minimum duration as responders. This may be a suitable preliminary or exploratory measure of antitumor activity for indications where complete response (CR) or partial responses (PR) may be more difficult to attain, stable disease does not reflect the natural history of the disease, and SD is a clinically meaningful outcome. Duration of stable disease is measured from the start of the treatment (the first treatment date for non-randomized studies, the randomization date for randomized studies) until the date when the criteria for overall disease progression are first met also provides supportive data for assessment of clinical activity of experimental anti-cancer regimens.

### 1.4.3. Justification for Dose and Schedule

The flat dose of etigilimab of [redacted] mg for subjects ≥50 kg was selected for MPH313-1-02 based on data from study 313M32-001. In this study, a trough exposure of approximately 20 to 30 µg/mL was associated with maximum reduction in Treg and maximal increase in Ki67 biomarkers. This exposure was also associated with subjects who appeared to achieve clinical benefit from etigilimab. The trough exposure is this range can be obtained with a dose of

[redacted] mg every 2 weeks. See the Investigator Brochure Section 5.3.4 (data on file at Mereo) for more detailed information. For subjects <50 kg, a weight-based dose of [redacted] mg/kg will be utilized to not exceed the highest dose examined in the 313M32-001 study.

Nivolumab is an FDA-approved human IgG4 kappa immunoglobulin that blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2 indicated for the treatment of advanced melanoma, NSCLC, renal cell carcinoma, Hodgkin lymphoma, advanced HNSCC, MSI-high or mismatch repair-deficient CRC, and hepatocellular carcinoma (OPDIVO 2018). The mechanism of action of nivolumab involves blocking inhibiting signals mediated by the PD-L1/L2-PD-1 interaction on effector T-cell function leading to enhanced T-cell activity/immunosurveillance within the tumor microenvironment.

Nivolumab is given at either 3 mg/kg or flat 240 mg intravenous (IV) every 2 weeks (Q2W) with similar safety, PK and efficacy seen between the 2 dosing strategies in several FDA-approved tumor types (OPDIVO 2018). For this study, nivolumab will be dosed at the flat rate of 240 mg IV Q2W. Clinical trial data on over 1900 patients treated with nivolumab as a single agent and 400 melanoma patients treated with nivolumab in combination with ipilimumab provide a substantial database of safety information. Immune-related toxicities are common and well-described and include pneumonitis, colitis, hepatitis endocrinopathies, nephritis, skin reactions, encephalitis, infusion reactions and others. Many of these adverse effects are managed with corticosteroid immunosuppression with interruption/stopping rules guided by the nivolumab package insert (OPDIVO 2018).

### 1.5. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of etigilimab may be found in the Investigator's Brochure (data on file at Mereo). There are risks from some of the study-specific procedures. If a fresh tumor biopsy is required, the risks include pain and discomfort, bleeding, tenderness, scaring, and rarely infection. Uncommonly, complications from biopsies can be life threatening. Potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention. Collection of blood samples may cause fainting, redness, pain, bruising, bleeding, and infection. The ECG sticky pads may cause redness or itching and if the hair under the patches needs to be shaved, this may cause irritation of the skin.

# 2. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **PRIMARY** | |
| To make a preliminary assessment of the antitumor activity of etigilimab in combination with nivolumab in subjects with pre-specified recurrent solid tumors. Each cohort will be evaluated independently. | • Objective response rate (ORR) |
| **SECONDARY** | |
| Evaluate the safety and tolerability of etigilimab administered in combination with nivolumab. | • Count and % of subjects who experience at least 1 adverse event (AE) and abnormal safety laboratory parameters<br>• Adverse events of special interest [(AESIs) infusion reactions, immune-related adverse events)]<br>• Relationship of PK and safety |
| To evaluate preliminary anti-tumor activity of etigilimab in combination with nivolumab in subjects with pre-specified recurrent solid tumors. Each cohort will be evaluated independently. | • Disease control rate (DCR; is the proportion of subjects whose BOR is CR, PR, or SD)<br>• Duration of response (DoR)<br>• Duration of stable disease |
| To characterize the PK of etigilimab in a subset of subjects who have advanced, relapsed, or refractory solid tumors in combination with nivolumab. | • PK levels of etigilimab in combination with nivolumab |
| To characterize the immunogenicity of etigilimab in a subset of subjects who have advanced, relapsed, or refractory solid tumors in combination with nivolumab. | • Anti-drug antibodies (ADA) to etigilimab; Impact of developed etigilimab ADAs on PK levels of etigilimab |
| **EXPLORATORY** | |
| To assess exploratory pharmacodynamic biomarkers following etigilimab treatment in combination with nivolumab. | Pharmacodynamic biomarkers will be assessed to determine their correlation with response to etigilimab treatment as follows:<br>• Changes in peripheral blood mononuclear cell populations and activation<br>• TIGIT and immune-related gene expression by messenger RNA (mRNA) detection (eg, CD226, TIGIT, T-cell genes)<br>• Plasma proteins (eg, interleukin 17 [IL17], interleukin 2 [IL2], interferon gamma [IFNγ] |

| Objectives | Endpoints |
|---|---|
| To assess potential predictive biomarkers for correlation with response to etigilimab treatment and exploratory biomarkers with treatment response. | • To correlate levels of TIGIT, PVR, TMB, PD-L1, and other immune markers with anti-tumor activity endpoints<br>• BAP1 (BRCA1 associated protein-1) tumor mutations with etigilimab treatment response |
| To evaluate preliminary anti-tumor activity of etigilimab in combination with nivolumab according to iRECIST.<br>Each cohort will be evaluated independently. | • ORR (proportion of iCR plus iPR subjects)<br>• DoR (iRECIST)<br>• Progression-free survival (PFS) using RECIST v1.1 and iRECIST<br>• OS |

**Abbreviations:** BOR = best overall response; CR = complete response; DoR = duration of response; ORR = overall response rate; OS = overall survival; PD-L1 = programmed death ligand-1; PK = pharmacokinetic; PR = partial response; PVR = poliovirus receptor; SD = stable disease; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; RECIST = Response Evaluation Criteria in Solid Tumors; TMB = tumor mutational burden

### 2.1. Number of Subjects

Approximately 135 subjects may be screened to achieve 125 enrolled such that 115 evaluable subjects complete the study. Cohorts will be enrolled at the discretion of the sponsor. Selected cohorts may be open for the first 10 subjects enrolled without increasing the total number of subjects proposed for the trial.

### 2.2. Study Start and End Definition

#### 2.2.1. Start of Study Definition

The start of the study is defined as the date of the first visit involving a trial procedure, excluding consent, of the first subject in the study.

#### 2.2.2. End of Study Definition

The trial is considered completed when the last subject dies or withdraws from the trial. However, the maximum trial duration is 3 years after the last subject's first treatment in the trial.

#### 2.2.3. Post Study Access to Therapy

At the end of the protocol-specified maximum trial duration, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

In the event of approval of study drug by the responsible health authority, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug up to 12 months after or

until the study drug becomes commercially available within the country, whichever occurs sooner. Sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

### 2.2.4. Trial Termination

The sponsor reserves the right to close a given trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Reasons for the early closure of a trial site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the independent ethics committee (IEC) and institutional review board (IRB) or local health authorities, the sponsor's procedures, or International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further trial drug development.

# 3. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 3.1. Inclusion Criteria

### 1) Type of Subject and Disease Characteristics by Cohort

**Cohort A**

- Histologically confirmed diagnosis of **endometrial carcinoma (EC);** Note: carcinosarcoma (malignant mixed Mullerian tumor), endometrial leiomysarcoma and endometrial stromal sarcomas are excluded.
- Recurrent, advanced, and/or metastatic disease without potential for local curative surgery or radiation.
- Radiographic evidence of progression after 1 prior systemic platinum-based chemotherapy regimen for EC with at least 1 measurable target lesion according to RECIST 1.1 that is suitable for repeat measurement including:
    - non-nodal lesion that measures ≥10 mm in the longest diameter
    - radiographic evidence of subsequent growth after locoregional therapy or external beam radiotherapy (EBRT).

- Up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting. There is no restriction regarding prior hormonal therapy.
- Treatment with prior anti-PD-1/anti-PD-L1/2 antibodies is not allowed.

**Cohort B**

- Histological or cytological evidence of advanced and/or recurrent or metastatic **HNSCC** or for the first-line treatment of subjects with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (combined positive score [CPS] >1%). Diagnosis of squamous cell carcinoma of the oral cavity, nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx. or larynx are permitted. Primary or recurrent disease for which no curative or established palliative treatments are amenable.
- Subjects without prior anti-PD-1/anti-PD-L1/2 antibody treatment are eligible.
- Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are eligible provided they have had (i) documented best observed response (BOR) of SD or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥6 weeks interval since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment

**Cohort C**

- Histologically confirmed **cervical cancer**
- Recurrent, advanced and/or metastatic disease with disease progression on or after one or more lines of chemotherapy, without potential for local curative treatment options including systemic chemotherapy, surgery or radiation and PD-L1-expressing tumors (CPS >1%).
  Note: Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a systemic therapy regimen.
- Treatment with prior anti-PD-1/anti-PD-L1/2 antibodies is not allowed.

**Cohort D**

- Histological or cytological evidence of recurrent advanced and/or metastatic **gastric or gastroesophageal junction adenocarcinoma** whose tumors express PD-L1 (CPS >1%), with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.
- Subjects without prior anti-PD-1/anti-PD-L1/2 antibody treatment are eligible.
- Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are eligible provided (i) they have had documented best observed response (BOR) of SD or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥6 weeks interval since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment

**Cohort E**

- Histological or cytological evidence of unresectable or metastatic **TMB-H** and **MSS** solid tumors (TMB as defined by an FDA-approved test, e.g., Foundation Medicine >10 mutations/megabase or a Laboratory Developed Test approved by the sponsor (e.g., Guardant Health), that have progressed following prior treatment and who have no satisfactory alternative treatment options. Subjects without prior treatment with anti-PD-1/anti-PD-L1/2 antibody treatment are eligible. Subjects who have received prior anti-PD-1/PD-L1/2 treatment are eligible with at least 6 weeks since their last dose of these prior treatments. Subjects must have had a previous SD or better in response to an anti-PD1/PDL-1/2 therapy. Subjects with the following TMB-H and MSS solid tumors will enroll into the tumor specific cohorts noted below after discussion with the sponsor:

  Cohort A: Endometrial cancer PD-1/PD-L1/2 naïve
  Cohort C: Cervical carcinoma
  Cohort F: Rare tumors (sarcoma, uveal melanoma, germ cell carcinoma)
  Cohort H: Ovarian cancer

**Cohort F**

**Rare Tumors**

**1. Germ Cell Tumors**

- Histologically or cytologically confirmed seminoma or non-seminoma testicular **germ cell tumors**.

- Recurrent, advanced and/or metastatic disease, including new lesions, persistently elevated β- human chorionic gonadotropin (HCG) or alpha 1-fetoprotein (AFP) or increase in consecutive elevated serum tumor markers (β-HCG or AFP) done at least one week apart after prior high-dose chemotherapy (HDCT).

  Subjects **deemed not to be candidates for benefit from potentially curative HDCT may also be eligible** including those with:

  (i) inadequate renal function for HDCT
  (ii) relapse >2 years after last therapy
  (iii) inadequate stem cell collection to move forward with HDCT
  (iv) significant medical or psychosocial comorbidities that are felt to be a contraindication to HDCT by the treating investigator.

- Subjects with serum tumor marker ≥S2 HCG and AFP (levels ≥1000 for AFP and ≥5000 for HCG are excluded).

- Subjects who have received prior anti-PD1/anti-PD-L1/2 antibodies are excluded.

**2. Sarcoma**

- Histological diagnosis (with archival or new biopsy sample available for pathology review) of locally advanced/unresectable and/or metastatic soft tissue **sarcoma histopathological subtypes** as noted below, who have radiological evidence of measurable disease and are not candidates for any curative surgery of multimodality therapy:
    - De-differentiated liposarcoma (n=10)
    - Undifferentiated pleomorphic sarcoma (UPS) (n=10)
    - Alveolar soft part sarcoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma (grade 2 or higher), OR pleomorphic dermal sarcoma (total n=5)
- Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies as standard of care are excluded.

**3. Uveal Melanoma**

- Histologically confirmed recurrent **uveal melanoma** with disease progression beyond prior approved standard of care therapy administered in the advanced setting (prior surgical resection of liver metastases, local radiation therapy and adjuvant systemic therapy are acceptable) are eligible.

- Subjects who have received prior anti-PD1/anti-PD-L1/2 antibodies are excluded.

**Cohort G**

- Histologically confirmed diagnosis of **EC;**
  Note: carcinosarcoma (malignant mixed Mullerian tumor), endometrial leiomyosarcoma, and endometrial stromal sarcomas are excluded.

- Subjects must have recurrent, advanced, and/or metastatic disease and must not be candidates for local curative surgery and radiation or intolerant to known standard of care systemic chemotherapy.

- Radiographic evidence of progression after >1 and no more than 3 prior systemic anti-cancer therapy regimens for EC (neoadjuvant, adjuvant, and maintenance treatment are considered part of one treatment line).

- At least 1 measurable target lesion according to RECIST 1.1 that is suitable for repeat measurement including (i) non-nodal lesion that measures ≥10 mm in the longest diameter, and (ii) radiographic evidence of subsequent growth after locoregional therapy or EBRT.

- Prior treatment with any treatment targeting vascular endothelial growth factor (VEGF)-directed angiogenesis, any anti-PD-1, anti-PD-L1/2 agent is allowed.
    - Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are also eligible provided (i) they have had documented BOR of SD or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥3 months interval prior to first study drug administration (C1D1) since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment

**Cohort H**

- Histologically confirmed **high grade serous and endometrioid ovarian cancer**, **fallopian tube cancer or primary peritoneal cancer**
- Must have received a front-line platinum-based regimen per standard of care after primary or interval debulking surgery and have documented radiological disease recurrence
- Must have measurable disease by RECIST 1.1 as determined by the local investigator/radiology assessment including 2 sites of disease/biopsy accessible disease. Subjects with less than 2 sites will need approval of sponsor prior to enrollment. Note: Maintenance treatment following front-line treatment is permitted and counted together as part of the front-line treatment.
- Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies as treatment are excluded.

Subjects are eligible to be included in the study only if the following criteria apply:

**2) Prior Therapy**

- Radiation therapy must be completed >3 weeks prior to first study drug administration (C1D1). Participants must have recovered from all radiation-related toxicities and/or complications prior to enrollment. Palliative radiotherapy is allowed if completed at least 2 weeks prior to first study drug administration. Subjects must have recovered from all radiation-related toxicities and/or complications prior to enrollment. Subjects must have measurable disease outside the radiation field to be eligible; subjects with progression in a previously radiated field will also be eligible.
- All toxicities attributed to prior anticancer therapy, with the exception of peripheral neuropathy, alopecia, vitiligo, active thyroiditis, and fatigue, must have resolved to Grade 1 (per NCI CTCAE version 5 or higher) or baseline of prior treatment prior to enrollment. Peripheral neuropathy must have resolved to Grade 2 (per NCI CTCAE version 5 or higher).

### 3) Tumor Specimen

- Confirmed availability of representative tumor specimens in paraffin blocks is required for enrollment with an associated pathology report including PD-L1status for PD-L1 positive cohorts.

- Latest available archival tumor sample eg, ideally within 6 months or up to 1 year prior to screening is strongly preferred. In instances where archival tissue is not available, a pre-dose biopsy will be required for submission with 3 core samples from an 18-gauge needle or larger. Only tissue from a surgical resection or a core needle, punch, or excisional/incisional biopsy sample collection will be accepted. Fine needle aspirate samples are not acceptable. Sponsor medical review is required if a fresh tumor biopsy cannot be provided during screening due to potential risk to subject from procedure.

    - For endometrial cancer (Cohorts A and G) archival or fresh biopsy specimen for determination of mismatched repair (MMR) status is required if historical MMR result is unavailable.

    - For study participants with sarcoma, archival tumor sample must be available for pathology review. If no archival material is available, a fresh biopsy should be performed to obtain tissue.

### 4) Hematologic and End Organ Function

- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

    a. Absolute neutrophil count ≥1500 cells/μL.
    b. Platelet count ≥100,000/μL (without transfusion within 14 days prior to Cycle 1, Day 1).
    c. Hemoglobin ≥9.0 g/dL (without transfusion of packed red blood cells (RBCs) or erythropoietic treatment within 14 days prior to Cycle 1, Day 1).
    d. Total bilirubin ≤1.5 × upper limit of normal (ULN) unless elevated due to Gilbert's syndrome.
    e. AST (SGOT) and ALT (SGPT) ≤3.0 × ULN with the following exception:
        – Subjects with documented liver metastases:
        AST and/or ALT ≤5.0 × ULN.
        – Total bilirubin <1.5 × ULN (subjects with Gilbert's syndrome may be enrolled with sponsor approval).
    f. Prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT) ≤1.5 × ULN and INR ≤1.5 × ULN in subjects not on anticoagulant therapy; subjects receiving therapeutic anticoagulation should be on a stable dose with PT, INR, and aPTT within the intended therapeutic range.

g. Creatinine ≤1.5 × ULN or measured or calculated creatinine clearance **≥45 mL/min** on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

(140-age) × (weight in kg) × (0.85 if female) 72 × (serum creatinine in mg/dL).

**5) Contraception**

NOTE: The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- **Male Subject:**
  A male subject must agree to use a highly effective contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 6 months after the last dose of study treatment and refrain from donating sperm during this period.
- **Female Subject:**
  A female subject is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:
  a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

  OR

  b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 6 months after the last dose of study treatment.

**6) Age**

- Age ≥18 years.

**7) ECOG Performance Status**

- ECOG performance status of 0 or 1.

**8) Life Expectancy**

- Life expectancy ≥12 weeks.

**9) Informed Consent**

- Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

**10) Compliance with Study Procedure and Visits**

- Ability to adhere to the study and follow-up procedures.

**11) Measurable Disease**

- Have measurable disease based on RECIST 1.1 as determined by the local investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

## 3.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

**1) Medical Conditions**

a) Severe allergic or anaphylactic reaction to any monoclonal antibody therapy, murine protein, or known hypersensitivity to any excipient in the study drugs.
b) Major surgery within 4 weeks prior to screening.
c) Subjects who have received radiotherapy within <1 week of starting study treatment, or who have unresolved associated AEs.
d) Following known active viral infections:
    - Known HIV infection.
    - Active hepatitis B or hepatitis C infection at the time of screening for the study. Active hepatitis B is defined as a known positive hepatitis B surface antigen (HBsAg) result. Active hepatitis C is defined as a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limit of detection of the assay.
    - Subjects with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. HBV DNA must be obtained in these subjects prior to randomization. Subjects with positive hepatitis B serology who are immune due to vaccination, resolved wild-type infection or passive immunization due to immunoglobulin therapy will be eligible.
    - Subjects with past hepatitis C (HCV) infection and positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
    - History of active non-infectious pneumonitis or history of pneumonitis that required steroids or current pneumonitis.
e) Ongoing systemic bacterial, fungal, or viral infections at screening.
    - NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met.
f) Female subjects who are pregnant or breastfeeding. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1 Day 1.

g) Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia.

h) Subjects with active, known, or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with minor autoimmune disease after discussion with the Medical Monitor.

i) History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to screening.

j) Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the subject associated with his or her participation in the study.

k) History of any Grade 3 or 4 immune-related AE toxicity from prior immunotherapy that resulted in treatment discontinuation.

l) Has primary central nervous system (CNS) malignancy or known untreated/active CNS metastases and/or carcinomatous meningitis.

- Subjects with previously treated, asymptomatic brain metastases may participate provided they meet the following criteria: clinically stable for at least 4 weeks and have no 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.
- Subjects with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease.
- Subjects with CNS symptoms should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, subjects with spinal cord compression must be excluded.

m) Medical psychological or social conditions that may interfere with the subject's participation in the trial ore evaluation of trial results

**2) Prior Therapy**

a) Prior treatment with CD137 agonists, anti-CTLA-4 and anti-TIGIT antibodies for all cohorts. Any prior anti-PD-1 and anti-PD-L1/2 therapeutic antibodies is excluded for Cohorts A, C, F and H only.

b) Immune-related AEs that lead to discontinuation of prior immune therapies including anti-PD-1 or anti-PDL-1/2 or anti-CTLA-4 therapies.

c) Treatment with systemic immunostimulatory agents (including but not limited to IFNα, IL2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1.

d) Systemic anti-cancer chemotherapy, biologic therapy, or other investigational agent within <5 times the half-life of the agent or <28 days (whichever is shorter) of starting study drug with the following exceptions:

- Hormone-replacement therapy or oral contraceptives.
- Herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week before Cycle 1, Day 1.
- Subjects with castrate resistant prostate cancer should be allowed to remain on luteinizing hormone-releasing hormone analogues for medical castration.
- Previously initiated chronic bisphosphonate or denosumab therapy for bone metastases may be continued during study participation.

e) Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

f) Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1:
Subjects receiving prophylactic antibiotics (eg, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

g) Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study. Inactivated influenza vaccination is permitted during influenza season only.

h) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

**3) Prior Procedures**

a) Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.

b) Subjects who received investigational (not authorized or approved by relevant Health Authorities) COVID-19 vaccine or therapies prior to screening are not eligible without discussion with sponsor.

c) History of additional prior malignancy with the exception of cured skin, bladder, prostate, cervical, or other carcinoma in situ with no evidence of active disease for at least 1 year.

### 3.3. Prohibited Concomitant Medications and Treatments

Use of the following therapies is prohibited during the study:

- Any concomitant therapy intended for the treatment of subject's current cancer, whether health authority-approved or experimental, including (but not limited to) the following: chemotherapy, hormonal therapy for cancer treatment, immunotherapy, radiotherapy, investigational agents, or herbal therapy.
- Immunostimulatory agents or immunotherapy not specified in the protocol.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and immunosuppressive doses of corticosteroids (i.e. >10 mg daily prednisone equivalent). (These agents may be administered at the discretion of the treating physician in an emergency or after consultation with the Medical Monitor).
- Surgical resection except for palliative surgical resection.

### 3.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE) related to protocol required procedures. Retesting of individual laboratory parameters to determine eligibility is permitted if the values are:

- Not consistent with life or the subject's current medical status.
- Aberrant due to a spoiled sample. e.g., hemolyzed hematology sample.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, if their medical status changes and they subsequently qualify for the study or there is an amendment to the protocol which allows participation. Rescreened subjects should not be assigned the same subject number as for the initial screening.

Screen failures may be rescreened only once, after approval from the sponsor. If rescreening is less than 28 days prior to first study drug administration (Cycle 1, Day 1), the following assessments may be used for rescreening:

- Previously submitted CT and MRI scans with acquisition date ≤28 days prior to Cycle 1 Day 1. Scans that exceed the 28-day window may be used for enrollment with sponsor approval.
- Previously submitted tumor biopsy sample
- Screening laboratory assessments that meet protocol-defined timelines as indicated in Table 3

If rescreening is more than 28 days after the initial screen failure, the subject must be re-consented, and all eligibility criteria must be re-assessed with repeat screening assessments as per protocol specified guidelines with the following exceptions:

- Scans that exceed the 28-day window may be used for enrollment with sponsor approval.
- Previously submitted tumor biopsy sample

# 4. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

## 4.1. Treatments Administered

| **Study Treatment Name:** | **Etigilimab** | **Nivolumab** |
|---|---|---|
| **Dosage formulation:** | [redacted] mg/mL in a [redacted]-mL single-use glass vial filled to [redacted] mL to deliver a total of [redacted] mg per vial | 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), or 240 mg (24 mL) solution in a single-use vial |
| **Unit dose strength(s) /Dosage level(s):** | [redacted] mg if subject is ≥50 kg<br>[redacted] mg/kg if subject is <50 kg | 240 mg |
| **Route of Administration:** | IV | 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-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 ± 10 minutes followed by a 30-minute observation period per investigator's discretion. Etigilimab will be delivered prior to nivolumab. The etigilimab observation period will need to be completed before dosing nivolumab. If the subject is <50 kg, the dose will be based on the subject's weight at each treatment visit. | Vials will be diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP prior to use. It is administered over 30 + 10 minutes (never <30 minutes) through an intravenous line containing as sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). The initial dose of nivolumab will be delivered on Day 3. |
| **Packaging and Labeling:** | Study Treatment will be provided as 10 vials in a carton. Each vial and carton will be labeled as required per country requirement. | Commercial stock will be utilized. |

### 4.2. Treatment Discontinuation

Treatment discontinuation occurs when a subject is no longer receiving study drug(s).

Note that treatment discontinuation is not the same as study withdrawal. A subject should be discontinued from study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. All subjects who discontinue study treatment should enter safety follow-up followed by survival follow-up; if a subject discontinues study treatment prior to confirmed progression of disease, the subject will continue to be followed for disease progression as per the planned study visits and procedures.

Subjects will be discontinued from study treatment for any the following reasons:

- An AE that requires permanent discontinuation of study drug(s).
- Confirmed progression of disease (Note: subjects may continue treatment beyond RECIST v1.1 determined PD).
- Noncompliance with protocol.
- Investigator decision.
- Subject becomes pregnant.
- Subject death.
- Subject lost to follow-up.
- Termination of the study by the sponsor.
- Voluntary withdrawal from the study treatment by the subject.

### 4.3. Method of Treatment Assignment

Upon enrollment, subjects will be assigned a unique number in ascending numerical.

### 4.4. Preparation/Handling/Storage/Accountability

1. 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 use of the study treatment.
2. Store etigilimab and nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake.
3. The diluted etigilimab solution may be stored for no more than 8 hours at room temperature or at 2°C- 8°C for up to 48 hours.
4. Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
5. Any unused portion left in a vial may not be used for another subject, as the product contains no preservative (ie, they are single-use vials).

6. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
7. Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

## 4.5. Treatment Compliance

Etigilimab and nivolumab are administered IV by study site personnel. Thus, compliance with each infusion will be documented in the subject's medical records and then recorded on the appropriate electronic case report form (eCRF) screen. In addition, drug accountability and PK monitoring will be done.

## 4.6. Permitted Concomitant Therapy or Standard of Care Treatment

Investigators may prescribe concomitant medications deemed necessary to provide adequate supportive care except those identified as prohibited (refer to Section 3.3). Standard supportive medications may be used in accordance with institutional guidelines and investigator discretion. These may include hematopoietic growth factors to treat neutropenia or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines (but not for prophylaxis in Cycle 1), packed RBC and platelet transfusions, and anti-emetics and antidiarrheals.

Palliative surgical resection and palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician provided that:

- Subjects are otherwise deriving benefit (i.e., subject does not have progressive disease).
- Target lesions being used to measure response are not irradiated without discussion with the Medical Monitor. Irradiated lesions will be considered not evaluable for response but still can be used to assess disease progression. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRF.

Because COVID-19 vaccine response and safety may have the potential to be affected by administration of a particular investigational product (IP), a decision to vaccinate individuals with approved COVID-19 vaccines while on treatment with study drug is up to the individual and the treating physician. When feasible, the full vaccination series should be completed prior to enrollment when a delay in enrollment would not put the study participant at risk. Because potential AEs related to vaccine administration may confound study treatment infusion reactions, overlap of administration should be avoided (with study drug and vaccine dosing at least 7 days apart)

The administration of all other vaccines (with the exception of live, attenuated vaccines) is allowed on study as per institutional or standard of care guidelines. Note: vaccines should be administered within 2 days before or after study drug administration.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment through 90 days after treatment termination must be recorded on the Concomitant Medications eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.
- Appropriate information to assess any potential vaccine- related AEs.

Subjects who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the U.S., equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists). Premedication may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (single dose up to less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Systemic corticosteroids >10 mg daily, TNFα antagonists, and other immunosuppressive agents may attenuate potential beneficial immunologic effects of treatment with etigilimab and nivolumab but may be administered at the discretion of the treating physician in an emergency or after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone for subjects with orthostatic hypotension or adrenocortical insufficiency) is allowed. Physiologic doses of corticosteroids for adrenal insufficiency are allowed. Megestrol administered as an appetite stimulant is also permitted.

Subjects who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other maintenance therapy for non-malignant indications should continue their use.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

# 5. DISCONTINUATION, DOSE HOLD, AND RESUMPTION

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the NCI CTCAE version 5.0 or higher.

If a subject has an AE related to etigilimab and/or nivolumab then dose interruptions/holds may occur as described below.

## 5.1. Etigilimab Dose Holds and Discontinuation

Permanent Discontinuation Criteria for Etigilimab

Dosing with etigilimab should be permanently discontinued for the following toxicities:

- ≥Grade 4 neutropenia persisting for ≥7 days and/or complicated by infection febrile neutropenia.
- ≥Grade 4 thrombocytopenia.
- Grade 3 drug-related thrombocytopenia >7 days or associated with clinically significant bleeding requires discontinuation.
- Any ≥Grade 3 non-hematologic toxicity, except:
  - Grade 3 fatigue lasting <7 days.
  - Grade 3 nausea, emesis, or diarrhea responding to supportive treatment within 5 days.
- Grade 3 drug-related AE of the skin requires dose discontinuation.
- ≥ Grade 3 non-hematological laboratory abnormalities do not require treatment discontinuation except:
  - Grade ≥3 AST, ALT, total bilirubin requires dose discontinuation
  - Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN requires permanent dose discontinuation.

  Note: In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion 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 of their onset.

Etigilimab may be held/delayed due to toxicity. The dose level of etigilimab will not be modified for individual subjects in this study.

Dose Delay Criteria for Etigilimab

- Grade 2 non-skin, drug-related AE, except for fatigue.
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities.
- Grade 3 skin drug-related AE.
- Grade 3 drug-related laboratory abnormality with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

The maximum duration of a dose hold is 28-days, unless a longer hold is approved by the Medical Monitor 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 Medical Monitor. Individual subject cases should be discussed with the Sponsor Medical Monitor or designee for individual treatment decisions.

Dosing visits are not skipped, only delayed. Tumor assessments should continue as per protocol even if dosing is delayed.

Criteria to Resume Etigilimab Dosing

- Subjects will be permitted to resume etigilimab therapy following resolution of the AE to ≤Grade 1 or to baseline value, with the following exceptions.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete (See Appendix 8).
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor or designee.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor or designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Subjects who meet criteria for permanent discontinuation must not receive further study therapy.

### 5.2. Nivolumab Dose Hold, Resumption and Discontinuation

Nivolumab may be held/interrupted due to toxicity. The dose level of nivolumab will not be modified in this study. Repeat nivolumab infusions may be delayed to allow subjects to recover from study treatment related AEs or intercurrent illness. Dosing visits are not skipped, only delayed. Tumor assessments should continue as per protocol even if dosing is delayed.

A pattern of immune-related AEs has been defined for nivolumab treatment for which management algorithms have been developed (OPDIVO 2018). Most high- grade events were manageable with dose delays and the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Details on dose delays, re-initiation of treatment and discontinuation of nivolumab are provided below.

Dose Delay Criteria for Nivolumab

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, except for fatigue.
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities.
- Grade 3 skin drug-related AE.
- Grade 3 drug-related laboratory abnormality with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay.
    - Grade ≥3 AST, ALT, total bilirubin required dose discontinuation (see below).
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (see below).

If the decision is to resume nivolumab dosing, the subject should restart treatment on the next regularly scheduled dosing visit. Skipped doses are not to be replaced. If treatment is delayed >8 weeks, the subject may potentially be permanently discontinued from all study therapy, except as specified in the treatment discontinuation criteria below. Individual subject cases should be discussed with the Medical Monitor or designee for individual treatment decisions.

Criteria to Resume Nivolumab Dosing

Subjects will be permitted to resume nivolumab therapy following resolution of the AE to ≤Grade 1 or to baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- For subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor or designee.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor or designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Subjects who meet criteria for permanent discontinuation must not receive further study therapy.

Permanent Treatment Discontinuation Criteria for Nivolumab

Subjects meeting any of the following criteria will be required to permanently discontinue nivolumab:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 8 weeks OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting >7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction **of any duration** requires discontinuation.
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with clinically significant bleeding requires discontinuation.
    - Grade ≥3 drug-related AST, ALT, or total bilirubin requires discontinuation.
    - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN.
    - In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor or designee must occur.

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤7 days.
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy AEs such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor or designee.
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment.

Criteria for Further Discussion with Medical Monitor or Designee Before Deciding to Continue or Discontinue Nivolumab Treatment

For subjects meeting any of the following criteria, discussion with the Medical Monitor or designee is to occur to determine whether treatment should continue. Any dosing interruption of nivolumab lasting >8 weeks after the last dose. Dosing interruptions to allow for prolonged steroid tapers to manage drug- related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting >8 weeks after the last dose and with no more than 2 missed doses, the Medical Monitor or designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

### 5.3. Dosing Interruptions

Dose interruptions >8 weeks after the last dose, which occur for non-drug related reasons, may be allowed if approved by the Medical Monitor or designee. Prior to re-initiating treatment in a subject with a dosing interruption lasting >8 weeks after the last dose and with no more than 2 missed doses, the Medical Monitor or designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted, and subjects must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

### 5.4. Toxicity Management Guidelines for Specific Adverse Events

Because of the potential for clinically meaningful immune-related AEs requiring early recognition and prompt intervention, established management algorithms are recommended for suspected pulmonary toxicity, gastrointestinal (GI) toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity.

These AE management algorithms are included in Appendix 8.

# 6. RESPONSE ASSESSMENTS

## 6.1. Radiographic Evaluations and Confirmation of Disease Progression

Response and progression will be determined by investigator assessment of on-trial radiographic evaluations, that will be conducted every 8 (±1) weeks through Week 48 and then at least every 12 (±1) weeks until confirmed progression of disease (as defined below), alternate anticancer therapy, withdrawal of consent, or death, whichever occurs first. The radiographic assessments are to be conducted as noted, independent of dose delays and/or dose interruptions. RECIST 1.1 criteria will be used for primary endpoint evaluation (Eisenhauer et al., 2009), iRECIST will be used for exploratory endpoint response evaluation (Seymour et al., 2017).

Radiographic evaluation may be done using either CT or MRI, but the modality chosen to evaluate each individual subject should be the same as the screening evaluation throughout the duration of the study.

Under specific circumstances subjects who develop PD per RECIST v1.1 may continue treatment and be followed for improved response or confirmed progression of disease [treatment beyond progression (Section 6.2)]. Regardless of whether or not a subject continues treatment in the event of RECIST-determined PD, follow-up radiographic assessments to confirm progression or show improvement in response are to be conducted at least 4 weeks after the assessment of PD per RECIST v1.1 (unless there is prior clinical deterioration, initiation of other cancer therapy, or withdrawal of consent).

For subjects who continue treatment beyond progression (Section 6.2), iRECIST PD should be confirmed at least 4 to 8 weeks after the first radiologic evidence of PD in clinically stable participants.

Subjects who have unconfirmed PD (iUPD) may continue study treatment until progression is confirmed as long as the subject is clinically stable and has provided written informed consent prior to receiving additional treatment (Section 6.2). Clinically unstable subjects should be discontinued from study treatment at the first occurrence of radiographic PD (iUPD) and are not required to have repeat imaging to confirm PD by iRECIST (though a confirmation of progression scan may be obtained at the investigator's discretion after consultation with the sponsor).

If repeat imaging shows iRECIST confirmed disease progression (iCPD), subjects will discontinue treatment. However, if the subject is deriving benefit after iCPD is observed, an exception to continue study treatment must be approved by the sponsor's Medical Monitor. Subjects who have repeat imaging to confirm progression are not required to undergo the next scheduled tumor imaging if it is less than 4 weeks later.

If repeat imaging shows iRECIST stable disease (iSD), iRECIST partial response (iPR), or iRECIST complete response (iCR), imaging should be continued every 8 (±1) weeks and the subject should continue on trial treatment.

Note that the date of progression to be used for all relevant efficacy endpoints will be based on first documentation of PD (ie, RECIST v1.1 date of PD), regardless of date of confirmation of PD for subjects who continue on treatment.

All radiographic evaluations performed on the study will be collected and held for a potential independent review. Details regarding initiating an independent review will be outlined in the statistical analysis plan (SAP).

**Confirmed progression of disease** is defined as one of the following:

Clinical deterioration with or without radiographic PD per RECIST v1.1 (See Appendix 7) will confirm progression of disease. Note, however, that radiographic evaluation should be conducted at the time of clinical signs and/or symptoms of PD whenever possible.

- In subjects without clinical deterioration at the time of a radiographic scan showing PD per RECIST v1.1, a second scan conducted at least 4 weeks later showing progression of disease as outlined below will confirm progression:
- An additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD.
- New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

Subjects should discontinue study therapy upon evidence of confirmed progression. Subjects who discontinue study treatment prior to confirmed progression of disease will continue to undergo radiographic and response assessments per protocol.

Note that all radiographic scans will be collected and archived for potential independent central review of response.

### 6.2. Treatment Beyond Progression

Accumulating evidence indicates that a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of radiographic PD. Following approval of the medical monitor or designee and consent of the subject for continued treatment beyond initial RECIST v1.1-defined PD, subjects who meet the following criteria will be permitted to continue on their treatment:

- Investigator-assessed clinical benefit and without rapid disease progression; Subject continues to meet all other study protocol eligibility criteria.
- Subject tolerates study drug.

- Subject has stable ECOG performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial RECIST v1.1 PD must be discussed with the Medical Monitor or designee, and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records.

Subjects should continue to attend study visits and undergo monitoring according to the protocol-defined on-treatment assessments. Radiographic assessment is required when subjects continue treatment after RECIST v1.1 determined PD.

### 6.3. Response Evaluation Criteria in Solid Tumors

Assessment of response and progression status in all subjects will be evaluated using the definitions from RECIST v1.1 for clinical decision-making and assessment of endpoints. Evaluation for target, non-target, and new lesions based on RECIST v1.1 are to be considered.

For a best overall response of CR or PR, confirmation of the response is required at a subsequent timepoint at least 4 weeks after the initial observation. Confirmed CR or PR will be claimed only if the criteria for each are met at that subsequent timepoint as outlined in Appendix 7.

**Table 2 Evaluation of Best Overall Response When Confirmation of CR and PR Required**

| Overall Response | | Best Overall Response at that Time Point |
|---|---|---|
| First Time Point | Second Time Point | |
| CR | CR | CR |
| CR | PR | SD, PD, or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met[b], otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met[b], otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met[b], otherwise, PD |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met[b], otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met[b], otherwise, PD |

**Abbreviations**: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum required duration of SD is 6 weeks.

# 7. PERMANENT AND TEMPORARY DISCONTINUATION CRITERIA

In the absence of unacceptable toxicities or disease progression, subjects will be offered continued study treatment up until disease progression. Regardless of discontinuation of study drug, subjects should continue on study with regular follow-up. All subjects who have discontinued etigilimab and nivolumab will return to the clinic for a treatment termination visit within 30 days after the last dose of etigilimab study treatment or nivolumab, whichever occurs last).

Subjects may withdraw or be withdrawn from the study at any time.

Subjects will be withdrawn from the study treatment for the following reasons:

- Clinically significant disease progression, as assessed by the investigator.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable AEs.
- Dose delay due to drug-related toxicity >28 days.
- Non-protocol anti-cancer therapy.
- Subject decides to withdraw from the study.
- General or specific changes in the subject's condition render further treatment unacceptable for the subject in the judgment of the investigator.
- Protocol non-compliance.

In the absence of progressive disease and additional anti-cancer therapy, all attempts should be made to continue tumor assessments per RECIST criteria until disease progression or initiation of subsequent anti-cancer therapy for up to 2 years.

All subjects will undergo the treatment termination evaluations.

## 7.1. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- In cases in which the subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Once the screening process has been completed, the investigator must submit a completed enrollment form to the sponsor for approval. Once the investigator has received the signed and dated form back from the sponsor, the subject is considered to be enrolled in the study.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA

## 8.1. Schedule of Assessments

| Cycle Day | Screening | Cycle 1 | | | Cycle 2 | | Cycle 3 | | Cycle 4 | | Cycle 5 | | Cycle 6[w] | | Treatment Termination[x] | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D3 | D8 | D1 | D8 | D1 | D8 | D1 | D8 | D1 | D8 | D1 | D8 | | |
| **Study Day** | **-28 to 1** | **1** | **3** | **8** | **15** | **22** | **29** | **36** | **43** | **50** | **57** | **64** | **71** | **78** | | |
| Informed consent[a] | X | | | | | | | | | | | | | | | |
| Review of eligibility criteria | X | | | | | | | | | | | | | | | |
| Medical, surgical, and cancer histories, and demographic data[b] | X | | | | | | | | | | | | | | | |
| Tumor assessment[c] | X | | | | | | | | | | X | | | | X | |
| Concomitant medications[d] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Complete physical examination[f] | X | | | | | | | | | | | | | | | |
| Symptom-directed physical examination | | X | | X | X | X | X | | X | | X | | X | | X | |
| Height | X | | | | | | | | | | | | | | | |
| Weight[g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| ECOG performance status | X | X | | X | X | X | X | | X | | X | | X | | X | |
| 12-Lead ECG[h] | X | X | | | | | | | X | | | | | | X | |

| **Cycle Day** | **Screening** | **Cycle 1** | | | **Cycle 2** | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6[w]** | | **Treatment Termination[x]** | **Follow up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **D1** | **D3** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | | |
| **Study Day** | **-28 to -1** | **1** | **3** | **8** | **15** | **22** | **29** | **36** | **43** | **50** | **57** | **64** | **71** | **78** | | |
| Hematology[i] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Serum or plasma chemistry[j] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Etigilimab infusion[k] | | X | | | X | | X | | X | | X | | X | | | |
| Nivolumab infusion[l] | | | X | | X | | X | | X | | X | | X | | | |
| Adverse event evaluation[m] | | ----------→ | | | | | | | | | | | | | | |
| TSH, free T3, free T4[n] | X | | | | | | | | | | X | | | | X | |
| Coagulation (INR/PT/aPTT) | X | | | | | | | | | | | | | | X | |
| Urinalysis[o] | X | | | | | X | | | | | | X | | | X | |
| Serum pregnancy test[p] | X | | | | | | | | | | | | | | X | |
| Tumor marker assessment[q] (if applicable) | X | | | | | | X | | | | X | | | | | |
| Pharmacokinetics[r] | See Table 3 below for PK Schedule for Ph Ib Subjects | | | | | | | | | | | | | | | |
| Anti-drug antibody[r] | See Table 3 below for ADA Schedule for Ph Ib Subjects | | | | | | | | | | | | | | | |
| Blood for PD biomarkers[s] | X | X | | X | | X | | X | | | | | | X | X | |
| Blood for pharmacogenomics[t] | | X | | | | | | | | | | | | | | |
| Blood for cell free DNA[u] | X | X | | | | | | X | | | | | | X | X | |

| **Cycle Day** | **Screening** | **Cycle 1** | | | **Cycle 2** | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6[w]** | | **Treatment Termination[x]** | **Follow up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **D1** | **D3** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | | |
| **Study Day** | **-28 to -1** | **1** | **3** | **8** | **15** | **22** | **29** | **36** | **43** | **50** | **57** | **64** | **71** | **78** | | |
| Tumor biopsy[v] | X | | | | | | | | | | X | | | | | |
| Archival FFPE tumor tissue[v] | X | | | | | | | | | | | | | | | |
| Survival and anti-cancer therapy follow up | | | | | | | | | | | | | | | | X |
| Contrast Enhanced Head CT or MRI scan | X | | | | | | | | | | | | | | | |

**Abbreviations**: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed, paraffin-embedded; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; mRNA = messenger RNA; MSS = microsatellite stable; PBMC = peripheral blood mononuclear cells; PT = prothrombin time; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors; TIGIT = T-cell immunoreceptor with Ig and ITIM domains; TMB-H = tumor mutational burden-high; TSH = thyroid-stimulating hormone; WBC = white blood cell

**Notes to Schedule of Assessments**

a. Written informed consent is required before performing any study-specific tests or procedures and may be obtained at any time prior to such tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used for screening assessments rather than repeating such tests. Results for the following laboratory tests must be obtained within 14 days prior to Cycle 1 Day 1: hematology, serum or plasma chemistry and coagulation panel.

b. Medical and surgical histories are required. Cancer history includes stage, date of diagnosis, and prior anti-cancer therapy. Demographic information includes sex, age, and self-reported race/ethnicity.

c. Screening and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest, abdomen, and pelvis. If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan. Brain imaging (either MRI or contrast-enhanced CT) is required at screening for all subjects. Further investigations such as bone scans and CT scans of the neck should also be performed if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of assessments listed above. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

   The same radiographic procedures used to assess disease sites at screening should be used throughout the study (eg, the same contrast protocol for CT scans). Response will be assessed by the investigator on the basis of physical examinations and the imaging modalities detailed above, using RECIST criteria. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

Tumor assessments will be performed every 8 weeks (±1) from Cycle 1 Day 1 or as clinically indicated through to week 48 and then at least every 12 (±1) weeks. Response assessment data (i.e., progressive disease or no progression of disease) will continue to be collected (based on standard-of-care radiographs) for subjects who have not progressed at the time of the termination visit. until the subject starts alternative anti-cancer treatment or develops progressive disease, whichever occurs first. Response assessment and assessment of tumor markers will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 14 days or at a prior response assessment that documented progressive disease. At the investigator's discretion, scans may be performed at any time if progressive disease is suspected.

d. Concomitant medications include any prescription medications or over-the-counter medications. At subsequent visits, changes to current medications, or medications used since the last documentation of medications will be recorded.
e. Vital signs include heart rate, respiratory rate, blood pressure and temperature. For the first etigilimab infusion, measure vital signs within 60 minutes before infusion, every 15 (±5 minutes) during the infusion and 30 (±10 minutes) and 90 (±15) minutes after the end of the infusion. For subsequent etigilimab infusions, measure vital signs within 60 minutes before infusion, during infusion if clinically indicated and 30 (±10) minutes after the end of the etigilimab infusion. Vital signs during and after nivolumab infusion are per institutional guidelines.
f. A complete physical examination will be done at baseline. At all other study visits a symptom-directed physical examination must be performed focusing on the subject's signs and symptoms. A more complete physical examination should be conducted when clinically indicated.
g. The etigilimab dose should be based on the Cycle 1 Day 1 weight throughout the study, unless the weight changes by >10%.
h. A 12-lead ECG will be obtained during screening, 30 (+30 minutes) after infusion of etigilimab on Cycle 1 Day 1, and 30 (+30 minutes) after infusion of etigilimab on Cycle 4 Day 1 and at treatment termination. Subjects should be resting and in a supine or semi-recumbent position for at least 10 minutes prior to each ECG collection.
i. Hematology can be performed within a -2-day window of the visit and consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils,), and platelet count. A manual differential can be done if clinically indicated. During screening, hematology results must be obtained within 14 days prior to Cycle 1, Day 1. If screening laboratory results available within 72 hours C1D1 laboratory tests do not need to be repeated.
j. Serum or plasma chemistry can be performed within a -2 day window of the visit and includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. During screening, serum or plasma chemistry results must be obtained within 14 days prior to Cycle 1, Day 1. If screening laboratory results available within 72 hours C1D1 laboratory tests do not need to be repeated.
k. Etigilimab must be dosed as described in the Protocol. 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. If treatment with etigilimab is delayed for >4 weeks, etigilimab will be permanently discontinued.
l. Nivolumab must be dosed as described in the Protocol within ± 2 days of the Study Day listed in the schedule of assessments. If the etigilimab dose is delayed ± 2 days then the nivolumab dose would be delayed and administered on the same day as the etigilimab (except for C1D1 where etigilimab is administered without nivolumab).
m. After initiation of study drug, report all adverse events until 90 days after the treatment termination visit.
n. Thyroid function tests (TSH, free T3, and free T4) must be performed every 8 weeks or as clinically indicated and at treatment termination.
o. Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) will be obtained during screening, at Study Days 22, 64, and at the time of treatment termination. Microanalysis is required if protein or blood is detected.
p. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1, Day 1 and at treatment termination.
q. Perform tests for pertinent tumor markers (e.g., CEA for subjects with colorectal cancer or others) every 4 weeks or as needed starting at Cycle1 Day1.
r. PK and ADA samples will be drawn according to Table 3 listed below.

s. A pre-dose sample of 33 mL will be drawn during screening and on Study Days, 1, 8, 22, and 36 and every 6 weeks after day 36 for subjects continuing on study drug to evaluate changes in plasma proteins (8 mL) by immunochemistry, TIGIT and immune-related gene expression by mRNA (5 mL) and changes in peripheral blood mononuclear cell (PBMC, 20 mL) populations and activation. A sample will also be collected at the time of treatment termination, unless one has been obtained during the prior 14 days. Instructions for the collection, handling, storage, and shipment are provided in the Laboratory Manual.
t. A 6 mL of blood will be collected for pharmacogenetic testing if the subject has consented to have this optional sample collected.
u. For TMB-H/MSS cohort, a 20 mL blood collection will occur during screening using the Guardant provided IUO kit. If collected in screening for TMB-H/MSS cohort, Study Day 1 collection does not need to occur. For all other cohorts, a 10 mL of plasma for cell-free tumor DNA assessment will be collected pre-dose on Study Days 1, 36, 78, and at treatment termination. As outlined in Section 3.1 TMB-H/MSS (Cohort E) subjects with the following solid tumors will enroll into respective tumor specific cohorts after discussion with the sponsor: Cohorts A, C, F and H. For these subjects, a 20 mL blood collection will still be required using the Guardent Health provided IUO kit.
v. Archival FFPE is required for enrolment and must have been collected preferably within 6 months but no longer than 1 year from screening. If **archival tumor tissue is not available** either fresh core or punch needle biopsy at study entry (3 fresh cores/punches preferred whenever possible) is required. Fine needle aspirate samples are not acceptable. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Laboratory Manual.
. Pre-treatment Biopsy: Baseline fresh tumor tissue samples consisting of 3 core needle biopsies of deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies of cutaneous, subcutaneous, or mucosal lesions will be obtained for all subjects. Subjects undergoing core needle biopsy should have accessible lesion(s) that permit a total of at least two biopsies (pretreatment and on-treatment) without unacceptable risk of major procedural complication (one pretreatment and at least one on-treatment biopsy will be performed; minimum diameter, 18 gauge). If possible, at least 3 cores should be collected from each lesion.
Optional On-treatment Biopsy may be considered only in patients who provided fresh baseline biopsy. This subsequent fresh biopsy may be performed approximately 8 weeks (within ± 5 days of Day 57) following the first administration of etigilimab.
An additional optional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. Requirements and procedures for pre-treatment and on-treatment biopsy collection are identical.
For pre and on-treatment, 1-2 cores will be fixed and shipped to central lab in ethanol and an additional 1 core will be fresh frozen as specified in the Laboratory Manual.
w. At Cycle 7 and beyond. safety laboratory testing is completed every two weeks at each treatment visit only.
x. The termination visit should be done as soon as possible, but no later than 30 days, after one of the discontinuation criteria for the study are met (See Protocol). The termination visit may occur later after discussion with the Sponsor Medical Monitor for specific circumstances, such as prolonged hospitalization. The visit at which a tumor assessment shows progressive disease may be used as the treatment termination visit provided that all required assessments were performed as outlined in the Schedule of Assessments. Tumor assessments do not have to be repeated if they were performed within 14 days of the termination visit or at a prior response evaluation that documented progressive disease. ECG does not have to be repeated if they were performed within 14 days of the termination visit.

## Table 3 Phase 1b Subjects: PK and ADA Sample Collection Schedule

| Cycle | | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Cycle 8 | Cycle 9 | Cycle 10 | Cycle 11 | Treatment Termination | 4 Week Post Termination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day | | Day 1 | Day 15 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 99 | Day 113 | Day 127 | Day 141 | | |
| MPH313 Infusion | | X | X | X | X | X | X | X | X | X | X | X | | |
| PK | On Day | | | | | | | | | | | | X | X |
| | Pre-Infusion | X | X | X | X | X | X | X | X | X | X | X | | |
| | 15 Minutes Post Infusion | X | | | X | | | X | | | | | | |
| ADA | Pre-Infusion | X | | X | | X | | X | | X | | X | X | X |

**Abbreviations:** ADA = anti-drug antibody; AE = adverse event; PK = pharmacokinetics

PK will be drawn pre-infusion every cycle of etigilimab until treatment termination. ADA will be drawn pre-infusion every other cycle of etigilimab through the first 6 months of treatment. After 6 months, ADA will be collected pre-infusion every 3 months and then once every 6 months after the first year until treatment termination. Should any immune-related AE continue beyond the 4-week post treatment termination visit, a blood sample for PK and ADA may be requested by the Medical Monitor.

## 8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

Screening and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the head and neck, chest, abdomen, pelvis and other site of disease for sarcoma as needed. If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan. Brain imaging (either MRI or contrast-enhanced CT) is required at screening for all subjects. Further investigations such as bone scans and CT scans of the neck should also be performed if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of assessments listed above. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

The same radiographic procedures used to assess disease sites at screening should be used throughout the study (eg, the same contrast protocol for CT scans). Response will be assessed by the investigator on the basis of physical examinations and the imaging modalities detailed above, using RECIST criteria. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Tumor assessments will be performed every 8 (±1) weeks from Cycle 1 Day 1 through Week 48 and then at least every 12 (±1) weeks or as clinically indicated until confirmed progression of disease (as defined below), alternate anticancer therapy, withdrawal of consent, or death, whichever occurs first. The radiographic assessments are to be conducted as noted, independent of dose delays and/or dose interruptions. RECIST 1.1 criteria will be used for primary endpoint evaluation (Eisenhauer et al., 2009), iRECIST will be used for exploratory endpoint response evaluation (Seymour et al., 2017).

Response assessment data (ie, progressive disease or no progression of disease) will continue to be collected (based on standard-of-care radiographs) for subjects who have not progressed at the time of the termination visit. until the subject starts alternative anti-cancer treatment or develops progressive disease, whichever occurs first. Response assessment and assessment of tumor markers will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 14 days or at a prior response assessment that documented progressive disease. At the investigator's discretion, scans may be performed at any time if progressive disease is suspected.

## 8.3. Safety

Planned timepoints for all safety assessments are provided in the SoA.

### 8.3.1. Adverse Events

Measures will be taken to ensure the safety of subjects participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 3.1 and Section 3.2) and close monitoring. All subjects will be monitored closely for toxicity. Administration of etigilimab and nivolumab will be performed in a setting with available emergency medical facilities with access to a critical care unit and staff who are trained to monitor for and respond to medical emergencies.

The definitions of an AE or SAE can be found in Appendix 4. Management guidelines for specific AEs can be found in Appendix 8.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AE that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study treatment.

#### 8.3.1.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the start of treatment with etigilimab until 90 days after the treatment termination visit and at the timepoints specified in the SoA. SAEs will be collected starting after signature of the informed consent until 90 days after the treatment termination visit.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

#### 8.3.1.2 Method of Detecting AE and SAE

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

#### 8.3.1.3 Follow-up of AE and SAE

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and immune-related AEs will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.1). Further information on follow-up procedures is given in Appendix 4.

#### 8.3.1.4 Regulatory Reporting Requirements for SAE

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.2. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until the pregnancy outcome is known.
- If a pregnancy is reported, the investigator should inform sponsor within 24 hours of learning of the pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.3. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A symptom-driven physical examination will focus on the evaluation of the subject's reported signs and symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.3.4. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.
- For etigilimab infusions:
    - For first infusion measure vital signs within 60 minutes before infusion, every 15 (±5 minutes) during the infusion and 30 (±10 min) and 90 (±15) minutes after the end of the infusion.

  - For subsequent infusions, measure vital signs within 60 minutes before infusion, during infusion if clinically indicated and 30 (±10) minutes after the end of the etigilimab infusion.
- For nivolumab infusions vital signs should be taken per institutional guidelines.

### 8.3.5. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 8.1) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and corrected QT intervals.

### 8.3.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose hold), then the results must be recorded in the CRF.

### 8.3.7. Immunogenicity Assessments

Antibodies to etigilimab will be evaluated in serum samples collected from all subjects according to the SoA. Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to etigilimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to etigilimab and/or further characterize the immunogenicity of etigilimab.

The detection and characterization of antibodies to etigilimab will be performed using a validated assay method by a lab vendor under the supervision of the sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for etigilimab serum concentration to enable interpretation of the antibody data. Antibodies may be further

characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s).

Samples may be stored for a maximum of 1 year following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to etigilimab.

## 8.4. Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of etigilimab as specified in Table 3. Other samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Genetic analyses will not be performed on these blood or serum samples. Subject confidentiality will be maintained. At visits during which samples for the determination of serum concentration of etigilimab will be taken, 1 blood draw of sufficient volume can be used.

## 8.5. Pharmacogenomics

A 6-mL blood sample for DNA isolation will be collected from subjects who have consented to participate in the pharmacogenomics component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

DNA samples may be used for research related to etigilimab and nivolumab. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate) in relation to etigilimab and nivolumab or oncology clinical endpoints.

The final disposition of samples will be conducted per local regulations. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

## 8.6. Biomarkers and Biopsies

Blood and tumor samples will be obtained for biomarker evaluation from all eligible subjects prior to treatment and on treatment as detailed in the SoA. Samples will be processed for the determination of changes in signaling markers downstream of the TIGIT-PVR/PVRL2 axis, Tregs, and potential predictive biomarkers.

**Blood biomarkers**: A predose sample of 33 mL will be drawn at screening, on Study Days 1, 8, 22, and 36, every 6 weeks after Day 36 for subjects continuing on study drug, and at treatment termination to evaluate changes in plasma proteins eg, IL17, IL2, IFNγ, etc., TIGIT and immune-related gene expression and possible T-cell clonality by mRNA detection (eg, CD226, T-cell genes) and changes in peripheral blood mononuclear cell populations (PBMCs) and activation by flow cytometry.

**Tumor tissue:** Tumor tissue is required for enrollment. If archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue has not been collected preferably within 6 months of

screening, but no longer than 1 year, or is not available, either fresh core or punch needle biopsy is required at study entry (3 fresh cores/punches preferred whenever possible).

**Pre-treatment biopsy**: Baseline tumor tissue samples consisting of core needle biopsies of deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies of cutaneous, subcutaneous, or mucosal lesions will be obtained for all subjects. Subjects undergoing core needle biopsy should have accessible lesion(s) that permit a total of at least 2 biopsies (pretreatment and on-treatment) without unacceptable risk of major procedural complication (one pretreatment and an optional one on-treatment biopsy will be performed; minimum diameter, 18 gauge). If possible, at least 3 cores will be collected. One or 2 cores will be shipped to central laboratory formalin fixed in ethanol and an additional core will be fresh frozen.

**On-treatment biopsy**: An optional subsequent biopsy will be performed if the subject consents to the procedure. The biopsy will be performed approximately 8 weeks (± 5 days) following the first administration of etigilimab if not medically contraindicated. In the event that the second biopsy cannot be performed approximately 8 weeks after the first administration of etigilimab, the Medical Monitor should be notified to discuss alternative timing for the second biopsy. An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. If possible, at least 3 cores will be collected. One or 2 cores will be shipped to central lab formalin fixed in ethanol and an additional core will be fresh frozen.

Requirements and procedures for pre-treatment and on-treatment biopsy collection are identical. The expression of TIGIT, PVR, PVRL2, FOXP3 and other immune markers (eg, protein and/or RNA) may be assessed in tumor specimens. The expression levels of additional proteins and genes (eg, immune gene signatures) may be evaluated and correlated with clinical benefit. Additionally, DNA testing (eg, TMB, mismatch repair genes, TIGIT pathway related genes etc.) of the tumor tissue may be performed on subjects using the tumor specimens collected.

**Cell-free DNA**: A 10 mL blood sample for cell-free tumor DNA assessments will be collected pre-dose on Study Day 1, Day 36, Day 78 and treatment termination. Analysis of genes relevant to TIGIT, disease genes, mutation burden, and mismatch repair etc. may be performed.

### 8.7. Skin Biopsy

If a skin rash occurs during study treatment, an optional biopsy and pictures of the skin rash will be performed. The expression of immune infiltrate may be assessed by hematoxylin and eosin staining and/or IHC.

### 8.8. Deviation Reporting

The following protocol deviations will be recorded and summarized in the final report:
1) enrollment violations, 2) dosing violations, 3) concomitant therapy violations, and
4) continuation of therapy when treatment should have been discontinued.

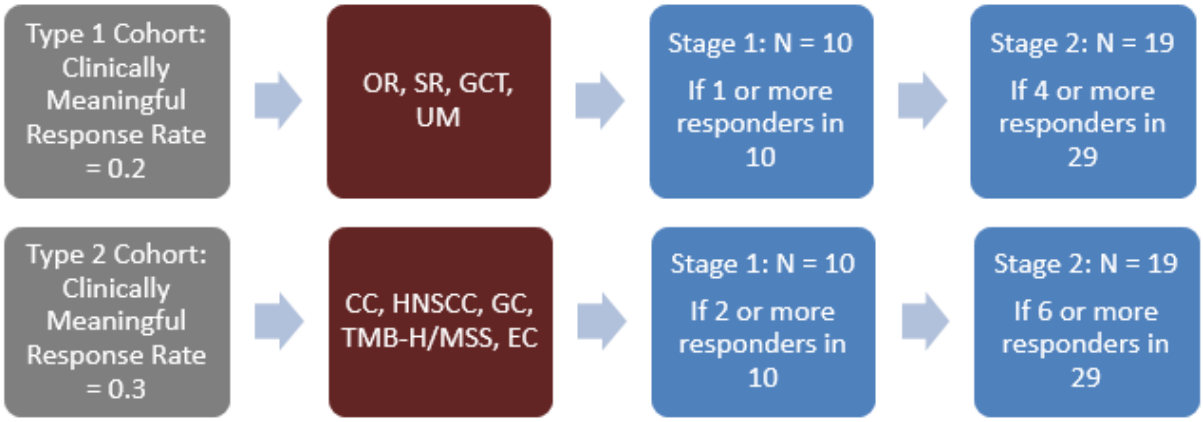
# 9. STATISTICAL CONSIDERATIONS

Data collected in this study will be presented descriptively using summary tables, figures, and data listings. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Missing values will not be imputed unless otherwise stated.

## 9.1. Sample Size Determination

This is a Phase 1b/2 open-label basket study of etigilimab (MPH313) ([redacted] mg dose for subjects ≥50 kg, [redacted] mg/kg dose for subjects <50 kg) IV administered Q2W with nivolumab 240 mg Q2W to evaluate preliminary anti-tumor activity, safety and tolerability, PK parameters, immunogenicity, and biomarkers in up to 9 cohorts of subjects with endometrial carcinoma, HNSCC, cervical cancer, ovarian cancer, gastric cancer and gastroesophageal junction adenocarcinoma, TMB-H/MSS cancer, sarcoma, germ cell tumors, and uveal melanoma. Each cohort will be evaluated using a Simon Two-Stage design appropriate to the clinically meaningful response rate for the indication as depicted in Figure 5 below. Interim futility monitoring for each individual cohort using the clinically meaningful response rate criteria per cohort will be carried out in accordance with the optimal Simon Two-Stage design when up to 10 subjects have sufficient data (either discontinued study drug treatment or having at least one post-baseline imaging assessment) for ORR and DoR evaluation by RECIST v1.1. For each cohort, the second stage may be opened for enrollment only after discussion with the IDMC and the sponsor. The sponsor may have an independent assessment of responses to verify investigator-reported responses. The responses based on independent assessments, if available, will be used for sensitivity analysis with sponsor and will make recommendations regarding study conduct, including whether to continue, modify, or stop the study.

**Figure 5 Simon Two-stage Study Design**




**Abbreviations:** CC = cervical cancer; EC = endometrial cancer; GC = gastric cancer and gastroesophageal junction adenocarcinoma; GCT = germ cell tumors; HNSCC = head and neck squamous cell carcinoma; OC = ovarian cancer; SR = sarcoma; TMB-H = tumor mutational burden-high; UM = uveal melanoma

### Type 1 Cohort

The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative that the true response rate is at least 0.2. In the first stage, 10 subjects will be enrolled and enrollment in this cohort will be halted until the response data are mature. If there are fewer than 1 responder in these 10 subjects, further enrollment in the cohort may be stopped after review of efficacy and safety data, and discussion by Sponsor with the IDMC. Otherwise, once 1 or more responders in stage 1 are observed, 19 additional subjects may be enrolled for a total of 29. The null hypothesis will be rejected and the treatment will be declared effective and worthy of further testing if 4 or more responders are observed in 29 subjects. This design yields a type I error rate of 0.0468 and power of 80.11% when the true response rate is 0.2.

### Type 2 Cohort

The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative that the true response rate is at least 0.3. In the first stage, 10 subjects will be enrolled and enrollment in this cohort will be halted until the response data are mature. If there are fewer than 2 responders in these 10 subjects, enrollment in the cohort may be stopped after review of efficacy and safety data, and discussion by Sponsor with the IDMC. Otherwise, once 2 or more responders in stage 1 are observed, 19 additional subjects may be enrolled for a total of 29. The null hypothesis will be rejected and the treatment will be declared effective and worthy of further testing if 6 or more responders are observed in 29 subjects. This design yields a type I error rate of 0.0471 and power of 80.51% when the true response rate is 0.3.

## 9.2. Populations for Analyses

The intent-to-treat (ITT) analysis set is defined as all subjects who signed an informed consent form and were enrolled into the study.

The Safety analysis set is defined as all subjects who received any amount of study drug. All safety analyses will be performed using the Safety analysis set.

The Response-Evaluable analysis set is a modified ITT analysis set defined as all subjects with measurable disease at baseline who received study treatment and had at least one post-baseline response assessment or discontinued treatment due to disease progression (including death due to disease progression) within 16 weeks (+ a 2-week window) of the first dose of study treatment. All efficacy analyses will be performed using the Response-Evaluable analysis set.

## 9.3. Statistical Analyses

All statistical analyses for this study will be undertaken by a contract research organization under the supervision of sponsor personnel. Any data analysis carried out independently by the investigator should be submitted to the sponsor prior to publication or presentation.

All data will be listed. All trial endpoints will be described using summary statistics. Data will be summarized using descriptive statistics for continuous data (safety laboratory data, pharmacodynamic and relevant biomarker data), and contingency tables for categorical data

(demographics and other baseline characteristics, efficacy measurements, safety measurements and all relevant PK measurements.

For statistical analyses and summaries, baseline is defined as the available data from the last recorded measurement prior to first administration of study drug.

Details of statistical analysis and data reporting will be provided in a SAP document finalized prior to database lock. Additional analyses may be added in the SAP and tables, listings and figures shells will also be provided.

The SAP will be developed and finalized before database lock and will describe the selection of subjects to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the study endpoints.

### 9.3.1. Efficacy Analyses

Efficacy analyses will be performed separately for each cohort. RECIST 1.1 criteria will be used for the primary endpoint evaluation (Eisenhauer et al., 2009), and iRECIST will be used for the exploratory endpoint response evaluation (Seymour et al., 2017). The iRECIST endpoints are analyzed using the same statistical methodology and the results will be presented in the same ways for the corresponding RECIST 1.1 endpoints.

The primary efficacy endpoint is the ORR defined as the proportion of subjects who achieve confirmed CR or PR per RECIST v1.1. The best overall response is the best response recorded from the start of the treatment until PD. The smallest measurements recorded since the treatment started will be used as the reference for PD. Subjects with CR or PR are considered to have obtained objective response. Subjects with not-evaluable response (NE) are counted as non-responders. Exact 95% CI will be constructed for the ORR for each cohort.

Subjects with CR, PR or SD are considered to have achieved disease control. Disease control rate is defined as the proportion of subjects who have achieved CR, PR, and SD. Duration of response only applies to subjects whose best overall response is CR or PR and is defined as the number of days from the first documentation of objective tumor response to the date of first PD or death due to underlying cancer.

Duration of stable disease is measured from the start of the treatment (the first treatment date for non-randomized studies, the randomization date for randomized studies) until the date when the criteria for overall disease progression are first met.

Duration of response is the time from first evaluation showing CR or PR (response confirmation required at subsequent tumor assessment no earlier than 4 weeks after first evaluation showing CR or PR) to the time of the first subsequent evaluation showing PD or death. Only subjects who experience a confirmed CR or PR will be analyzed for DoR. Subjects who do not experience PD or death will be censored per the censoring rules in the statistical analysis plan.

Progression-free survival is defined as the number of days from Day 1 in Cycle 1 to the first documented progression or death due to any cause. Only deaths that occurred within 30 days of the last progression assessed.

Overall survival is defined as the time from the first dose of study drug to death due to any cause.

Overall survival, PFS, and DoR will be summarized for each group using Kaplan-Meier methodology. Censoring rules will be detailed in the statistical analysis plan.

- For analysis of OS, all subjects will be followed for survival for up to 2 years, until withdrawal of consent, loss to follow up, or death, whichever occurs first. At the time of analysis of OS, any subjects who remain alive will be censored at the last date they were known to be alive.
- PFS is the time from the start of study treatment to the first evaluation showing PD or death, whichever occurs first. Subjects who do not experience PD or death will be censored per the censoring rules in the statistical analysis plan.

### 9.3.2. Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher and will be graded according to the NCI-CTCAE, v 4.03 or higher.

Summaries of AEs will be based on TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment etigilimab or nivolumab, whichever is earlier, to 100 days after the last dose of etigilimab or nivolumab (whichever is dosed last) or until starting another treatment.

TEAEs will be summarized by treatment group and by the frequency of subjects experiencing TEAEs corresponding to MedDRA system organ classes and preferred terms.

Separate tabulations will also be produced for TEAEs assessed as related to study drug(s), TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥Grade 3 in severity. Treatment-emergent serious AEs and SAEs related to study drug(s) will also be tabulated.

Laboratory results (hematology, serum or plasma chemistry, and coagulation) and the corresponding change from baseline values will be summarized by group and scheduled timepoint. A shift table, tabulation for baseline to each scheduled assessment and the worst post treatment value according to the CTCAE grade, will be provided for selected clinical laboratory tests. Laboratory results together with the normal ranges and CTCAE grade will be listed. Laboratory values that are below or above the normal ranges will be flagged.

Vital signs and ECGs and the corresponding changes from baseline will be summarized by group and scheduled timepoint.

### 9.3.3. Pharmacokinetic Analyses

The PK analysis set will include all Phase 1b subjects with sufficient plasma concentration data to allow the characterization of the PK parameters. Plasma etigilimab concentration data at each assessment timepoint will be summarized and listed and will be plotted across time. Pharmacokinetic parameters will be calculated using non-compartmental techniques from plasma concentrations and will include the following parameters: maximum concentration

observed, clearance, elimination half-life, and area under the curve. Pharmacokinetic parameters will be summarized descriptively for each group.

### 9.3.4. Immunogenicity Analyses

The immunogenicity analysis set will include all subjects with at least one evaluable post-treatment immunogenicity sample. Blood samples for evaluation of ADA will be collected to determine the relationship between ADA and etigilimab PK parameters.

### 9.3.5. Exploratory Analyses

Blood samples for evaluation of pharmacodynamics biomarkers, immune biomarkers, and exploratory predictive biomarkers will be collected from all subjects to determine their correlation with ORR and DCR.

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# 11. APPENDICES

## APPENDIX 1: ABBREVIATIONS AND TRADEMARKS

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ADA | anti-drug antibody |
| AE | adverse event |
| AFP | alpha 1-fetoprotein |
| ALT (SGPT) | alanine aminotransferase<br>(serum or plasma glutamic pyruvic transaminase) |
| aPTT | activated partial thromboplastin time |
| AST (SGOT) | aspartate aminotransferase<br>(serum or plasma glutamic oxaloacetic transaminase) |
| BAP1 | BRCA 1-associated protein-1 |
| BOR | best observed response |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CC | cervical cancer |
| CD | cluster differentiation |
| CPI | checkpoint inhibitor |
| CR | complete response |
| CRC | colorectal cancer |
| CRF | case report form |
| CT | computed tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| DCR | disease control rate |
| DFR | disease-free survival |
| DLT | dose-limiting toxicity |
| DoR | duration of response |
| EBRT | external beam radiotherapy |
| EC | endometrial carcinoma |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| eg | exempli gratia (or ‘for example’) |
| FDA | Food and Drug Administration |
| FDG PET | fluorodeoxyglucose positron emission tomography |
| FFPE | formalin-fixed, paraffin-embedded |
| GC | gastric cancer |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GEJ | gastroesophageal junction adenocarcinoma |
| GLP | Good laboratory practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HBV | hepatitis B virus |
| HBsAg | hepatitis B surface antigen |
| HDCT | high-dose chemotherapy |
| HCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HNSCC | head and neck squamous cell carcinoma |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| ie | id est (or 'that is') |
| IEC | independent ethics committee |
| IFN | interferon |
| IgG | immunoglobulin G |
| IHC | immunohistochemistry |
| IL | interleukin |
| INR | international normalized ratio |
| IRB | institutional review board |
| ITIM | tyrosine-based inhibition motifs |
| ITT | intent-to-treat |
| IV | intravenous |
| LD | longest diameter |
| MCV | mean corpuscular volume |
| MCH | mean corpuscular hemoglobin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMR | mismatched repair |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| MSI | microsatellite instability |
| MSS | microsatellite stable |
| NA | not applicable |
| NCI | National Cancer Institute |
| NE | not evaluable |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| NK | natural killer |
| NSCLC | non-small cell lung cancer |
| ORR | overall response rate |
| PBMC | peripheral blood mononuclear cell |
| PD | progressive disease |
| PD-1 | programmed death-1 |
| PDL-1 | programmed death ligand-1 |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PR | partial response |
| PT | prothrombin time |
| PVR | poliovirus receptor |
| Q2W | every 2 weeks |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RPKM | reads per kilobase per million |
| RSEM | RNA-Seq by Expectation-Maximization |
| SAE | serious adverse event |
| SCLC | small-cell lung cancer |
| SD | stable disease |
| SoA | Schedule of Activities |
| TCR | T-cell receptor |
| TCGA | The Cancer Genome Atlas |
| TEAEs | treatment-emergent adverse events |
| TIGIT | T-cell immunoreceptor with Ig and ITIM domains |
| TMB-H | tumor mutational burden-high cancer |
| Tregs | regulatory T-cells |
| TSH | thyroid-stimulating hormone |
| TILs | tumor infiltrating lymphocytes |
| ULN | upper limit of normal |
| VEGF | vascular endothelial growth factor |
| WBC | white blood cell |
| WOCBP | woman of childbearing potential |

## APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 3.1 and 3.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 4 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | Platelet count |
| | Red blood cell (RBC) count |
| | Hemoglobin |
| | Hematocrit |
| | RBC indices mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) |
| | White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils |
| Clinical Chemistry | Blood urea nitrogen (BUN) |
| | Potassium |
| | Sodium |
| | Calcium |
| | Phosphorus |
| | Magnesium |
| | Chloride |
| | Bicarbonate |
| | Alkaline phosphatase |
| | Aspartate aminotransferase (AST) /serum glutamic-oxaloacetic transaminase (SGOT) |
| | Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT) |
| | Total bilirubin |
| | Total protein |
| | Albumin |
| | Lactate dehydrogenase |
| | Creatinine |
| | Glucose |

| Laboratory Assessments | Parameters |
|---|---|
| Urinalysis | Specific gravity |
| | pH |
| | Glucose |
| | Protein |
| | Ketones |
| | Blood |
| | Microscopic examination (if blood or protein is abnormal) |
| Thyroid Function Tests | Thyroid stimulating hormone (TSH) |
| | Free T3 |
| | Free T4 |
| Coagulation | International normalized ratio (INR) |
| | Prothrombin time (PT) |
| | Activated partial prothrombin time (aPTT) |
| Other | Serum pregnancy test |

Investigators must document their review of each laboratory safety report.

## APPENDIX 3: STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within >28 days from the previous ICF signature date.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

These study results will be generated once the study is complete and can be made available to the investigators. Information will also be available upon request for IRB/IEC Annual Reports.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
    - Records and documents pertaining to the conduct of this study and the distribution of investigational product, including signed ICF, laboratory test results, study medication inventory records, and regulatory documents, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept for 2 years after the study is discontinued and the FDA and other applicable regulatory authorities are notified. sponsor will notify the Principal Investigator of these events. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents include primary documents such as medical records, CT scans, ECG scans, etc.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

# APPENDIX 4: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

## Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. |

| **Events Meeting the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect** |
| **f. Other situations:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

Definition of AESI

Adverse events of special interest (AESIs) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

| **AESIs for etigilimab** |
|---|
| Some AEs, despite their severity or outcome, will be expedited due to the relevance for participant safety or study treatment safety profile. These events should be reported to the sponsor/designee within 24 hours. This is to enable follow-up to be performed on all these reported adverse events that have not been reported as serious adverse events (SAEs). The AESIs for etigilimab are:<br>• **Infusion reactions,**<br>• **Immune-related adverse events**<br>AESIs that are considered to be clinically significant by the PI and/ or medical team will also be submitted to the independent DMC for review. |

Recording AE / AESI and SAE

| **AE, AESI and SAE Recording** |
|---|
| • When an AE/AESI /SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant AE/AESI/SAE information in the CRF.<br>• It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or their representatives in lieu of completion of the AE/AESI/SAE CRF page.<br>• There may be instances when copies of medical records for certain cases are requested by the sponsor or their representatives. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor or their representatives.<br>• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/AESI/SAE. |

| **Assessment of Intensity** |
|---|
| • The investigator will make an assessment of Grade for each AE, AESI and SAE reported during the study according to the NCI Common Terminology Criteria for Adverse Events version 5 (CTCAE v 5) or higher. |

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/AESI/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/AESI/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/AESI/SAE and has provided an assessment of causality.
- There may be situations in which an SAE /AESI has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE / AESI data.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE / AESI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE, AESI and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or their representatives to elucidate the nature and/or causality of the AE, AESI or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or their representatives with a copy of any post-mortem findings including the autopsy report and histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE / AESI data to the sponsor within 24 hours of receipt of the information.

Reporting of SAE to Sponsor

| **SAE / AESI Reporting to Sponsor via email** |
|---|
| • The primary mechanism for reporting SAE / AESI to Sponsor or its representatives will be the report form via email:<br>Email: Syneos Health Safety and Pharmacovigilance safetyreporting@syneoshealth.com and Mereo Biopharma mph313safetyalerts@mereobiopharma.com<br>• If the email is unavailable please report via fax +1-877-464-7787<br>• The site will report the SAE /AESI data via email report as soon as it becomes available.<br>• If a site receives a report of a new SAE /AESI from a study subject or receives updated data on a previously reported SAE /AESI an updated SAE /AESI form should be submitted to the same email addresses above.<br>• Further contacts for SAE /AESI reporting can be found in the Study Binder. |

## APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Males Subjects

1. Male subjects with female partners of child-bearing potential are eligible to participate if they agree to the following:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent for duration of study and for 6 months after study completion or from last dose
    - Female partner is using a highly effective contraceptive method
2. For non-genotoxic IMPs with demonstrated or suspected human teratogenicity / fetotoxicity at subtherapeutic exposure levels {where it is theoretically possible that relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid) to prevent exposure of an embryo/fetus
3. Agree to use a male condom plus an additional method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential

4. Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for duration of study and for 6 months after study completion or from last dose
5. Refrain from donating sperm for duration of study and for 6 months after study completion or from last dose

**Table 5 Highly Effective Contraceptive Methods That Are User Dependent**

| |
|---|
| *Failure rate of <1% per year when used consistently and correctly.* |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>• oral<br>• intravaginal<br>• transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• oral<br>• injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• bilateral tubal occlusion |
| Vasectomized partner<br>*(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)* |
| Sexual abstinence<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)* |
| NOTES:<br>a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.<br>b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 6 months after the last dose of study drug |

Female Subjects

Female subjects of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 5 above.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a highly sensitive negative serum pregnancy test
- Additional pregnancy testing will be performed at Treatment Termination after the last dose of study drug and as required by local clinical guidance
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed and assayed in a certified laboratory

**Collection of Pregnancy Information of Male subjects with partners of reproductive potential who become pregnant**

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Sponsor within 24 hours of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Sponsor
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

**Female Subjects who become pregnant**

Any female subject who becomes pregnant while participating will discontinue study drug or be withdrawn from the study.

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to Sponsor within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on subject and neonate, which will be forwarded to Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study drug by the investigator, will be reported to Sponsor. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

## APPENDIX 6: ECOG PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | |
|---|---|
| **Grade** | **Descriptions** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. 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 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

## APPENDIX 7: RECIST CRITERIA VERSION 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

ELIGIBILITY

Only subjects with measurable or evaluable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

**Measurable Disease** – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

**Measurable Lesions** – lesions that can be accurately measured in at least one dimension with the minimum size of:

- 10 mm by CT scan or MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 15 mm for nodal disease in short axis
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)
- Malignant lymph node: 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up only the short axis is to be followed.

**Non-Measurable Lesions** – all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, and nodal disease that is 10 to <15 mm in short axis.

Special Considerations Regarding Lesion Measurability: Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Measurement of Lesions

- All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Methods of Measurement

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at each subsequent response assessment. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.
- For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- CT is currently the best currently available and reproducible method to measure target lesions selected for response assessment. The CT scan slice thickness should be 5 mm or less. When the CT scans have a slice thickness that is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound (US) should not be used to measure tumor lesions. The utilization of endoscopy and laparoscopy for objective tumor evaluations not advised.
- Fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to determine a new lesion if the lesion was absent at baseline on FDG-PET
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]) and be representative of all involved organs, but in addition should lend themselves accurate repeated measurements.
- A sum of the LD for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added to the sum.
- If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded at 0 mm.
- If extranodal target lesions fragment, the LDs of the fragmented portions are added in the sum. If targets lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
- For a subject with SD or PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a subject with CR, reappearance of a lesion is considered PD.
- New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor. If a new lesion is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed from the date of the first scan.
- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each or in rare case unequivocal progression should be noted at each subsequent response assessment.

RESPONSE CRITERIA

Evaluation of Target Lesions

| | |
|---|---|
| Complete Response (CR): | Disappearance of all target lesions. Any pathological lymph node (whether target or nontarget) must have reduction in short axis to <10 mm |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD): | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. |

Evaluation of Non-Target Lesions

| | |
|---|---|
| Complete Response (CR): | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (ie, <10 mm short axis). |
| Non-CR/Non-PD | Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD): | Unequivocal progression of the existing non-target lesions. The appearance of one or more new lesions is also considered progressive disease. |

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the investigator should prevail.

Evaluation of Overall Response

**Table 6 Evaluation of Overall Response**

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status. If described in the clinical protocol, FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring

## REPORTING OF RESULTS

All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) not evaluable for response: specify reason such as early death from malignant disease, early death from toxicity, tumor assessments not repeated/incomplete, or other (specify).

## RECIST 1.1 and iRECIST

| | RECIST 1.1 | iRECIST |
|---|---|---|
| Definitions of measurable and non-measurable disease; numbers and site of target disease | Measurable lesions are 10 mm or more in long diameter (15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease considered not target (must be 10 mm or longer in short axis for nodal disease) | No change; however, NEW lesions are evaluated as per RECIST 1.1 but are recorded separately on the CRF (but not included in the sum of lesions for target lesions identified at baseline) |
| R, PR or SD | Cannot have met criteria for PD prior to CR, PR or SD | May have had iUPD (1 or more instances), but not iCPD, prior to iCR, iPR or iSD |
| Confirmation of CR, PR | Only required for non-randomised trials | As per RECIST 1.1 |
| Confirmation of SD | Not required | As per RECIST 1.1 |
| New lesions | Results in PD. Recorded but not measured | Results in iUPD but iCPD is only assigned based on this category if at next assessment<br>• Additional NL appear or<br>• Increase in size of NLs (≥5 mm for sum of NLT or any increase in NLNT)<br>NLs, where none have previously been recorded can also confirm iCPD |
| Independent blinded review and central collection of scans | Recommended in some circumstances | Collection of scans (but not independent review) recommended for all trials |
| Confirmation of PD | Not required (unless equivocal) | Required |
| Consideration of clinical status | Not included in assessment | Clinical stability (see definition) is considered in whether treatment is continued after iUPD |

NT = non-target, T = target; NL = new lesions; NLT = new lesion target; NLNT = new lesion non target; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; SOM= sum of measures. iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease

## Assigning time-point response for iRECIST

| **Time-point response** | | | | |
|---|---|---|---|---|
| **Target Lesions*** | **Non-Target Lesions*** | **New Lesions*** | **Time Point Response** | |
| | | | **No prior iUPD**** | **Prior iUPD**; ***** |
| iCR | iCR | No | iCR | iCR |
| iCR | Non-iCR/Non-iUPD | No | iPR | iPR |
| iPR | Non-iCR/Non-iUPD | No | iPR | iPR |
| iSD | Non-iCR/Non-iUPD | No | iSD | iSD |
| iUPD with no change OR decrease from last TP | iUPD with no change OR decrease from last TP | Yes | NA | NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number; If no change in NLs (size or number) from last TP, remains iUPD |
| iSD, iPR, iCR | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD) |
| iUPD | Non-iCR/Non-iUPD; iCR | No | iUPD | Remains iUPD unless iCPD confirmed based on:<br>• further increase in SOM of at least 5 mm, otherwise remains iUPD |
| iUPD | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based on further increase in:<br>• previously identified T lesion iUPD in SOM ≥5 mm and / or<br>• NT lesion iUPD (prior assessment - need not be unequivocal PD) |
| iUPD | iUPD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on further increase in<br>• previously identified T lesion iUPD SOM ≥5 mm and / or<br>• previously identified NT lesion iUPD (need not be unequivocal) and /or<br>• size or number of new lesions previously identified |
| Non-iUPD/PD | Non-iUPD/PD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on<br>• increase in size or number of new lesions previously identified |
| * Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP. | | | | |

iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progression; iCPD = immune confirmed progression; NL = new lesion; NLT = new lesion target; NLNT = new lesion non target; T = target; TP = timepoint; NA = not applicable; NE = not evaluable / evaluated

## Assigning best overall response for iRECIST

| **Best overall response** | | | | | |
|---|---|---|---|---|---|
| TPR1 | TPR2 | TPR3 | TPR4 | TPR5 | iBOR |
| iCR | iCR, iPR, iUPD, NE | iCR, iPR, iUPD, NE | iUPD | iCPD | iCR |
| iUPD | iPR, iSD, NE | iCR | iCR, iUPD, NE | iCR, iPR, iSD, iUPD, iCPD, NE | iCR |
| iUPD | iPR | iPR, iSD, iUPD, NE | PR, iSD, iUPD, NE, iCPD | iPR, iSD, iUPD, NE, iCPD | iPR |
| iUPD | iSD, NE | iPR | iPR, iSD, iUPD, NE | PR, iSD, iUPD, iCPD, NE | iPR |
| iUPD | iSD | iSD, iUPD, NE | iSD, iUPD, iCPD, NE | iSD, iUPD, iCPD, NE | |
| iUPD | iCPD | Anything | Anything | Anything | iCPD |
| iUPD | iUPD (no iCPD) | iCPD | Anything | Anything | iCPD |
| iUPD | NE | NE | NE | NE | iUPD |
| Examples only – many more scenarios exist but follow the same principles<br>Table assumes a randomised study where confirmation of CR or PR is not required<br>For patients with non-target disease only at baseline, only iCR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation | | | | | |

iCR =immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progression; iCPD = immune confirmed progression; NL = new lesion; NLT = new lesion target; NLNT = new lesion non target; T = target; TP = timepoint; NA = not applicable; NE = not evaluable / evaluated

Source:

As part of paper presented at the EORTC-NCI-AACR 2016 Meeting (Munich)

Later published as part of Seymour, L., et al., iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol, 2017. Mar; 18(3): e143-e152.

## APPENDIX 8: ADVERSE EVENT MANAGEMENT

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the Medical Monitor or designee. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

# GI Adverse Event Management Algorithm

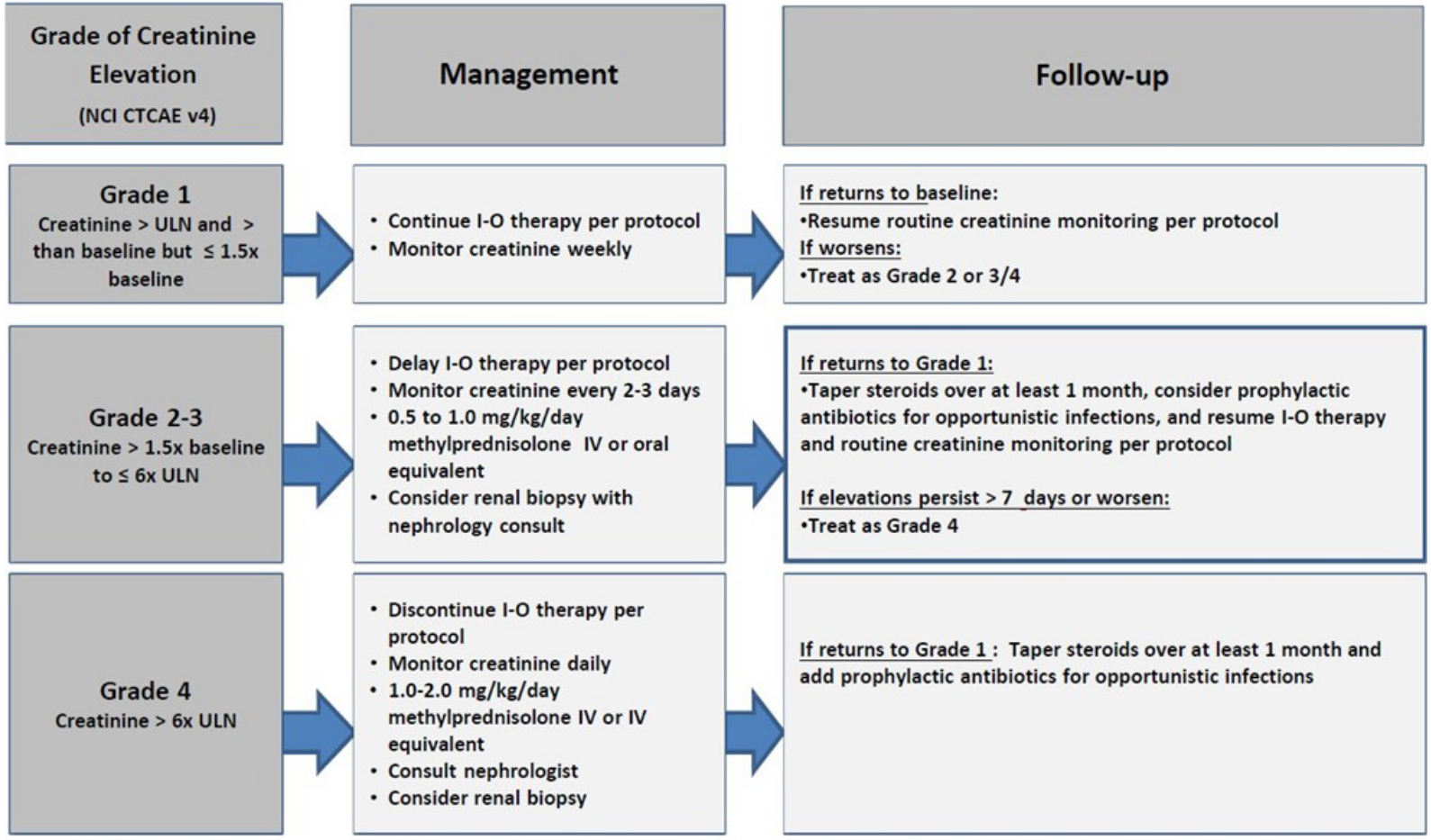
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

| Grade of Diarrhea/ Colitis (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>Diarrhea:< 4 stools/day over baseline;<br>Colitis: asymptomatic | • Continue I-O therapy per protocol<br>• Symptomatic treatment | • Close monitoring for worsening symptoms.<br>• Educate patient to report worsening immediately<br>If worsens:<br>• Treat as Grade 2 or 3/4 |
| **Grade 2**<br>Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | • Delay I-O therapy per protocol<br>• Symptomatic treatment | If improves to grade 1:<br>• Resume I-O therapy per protocol<br>If persists > 5-7 days or recur:<br>• 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent<br>• When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol.<br>If worsens or persists > 3-5 days with oral steroids:<br>• Treat as grade 3/4 |
| **Grade 3-4**<br>Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL<br>Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs<br>G4: life-threatening, perforation | • Discontinue I-O therapy per protocol<br>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consider lower endoscopy | If improves:<br>• Continue steroids until grade 1, then taper over at least 1 month<br>If persists > 3-5 days, or recurs after improvement:<br>• Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis |

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Renal Adverse Event Management Algorithm

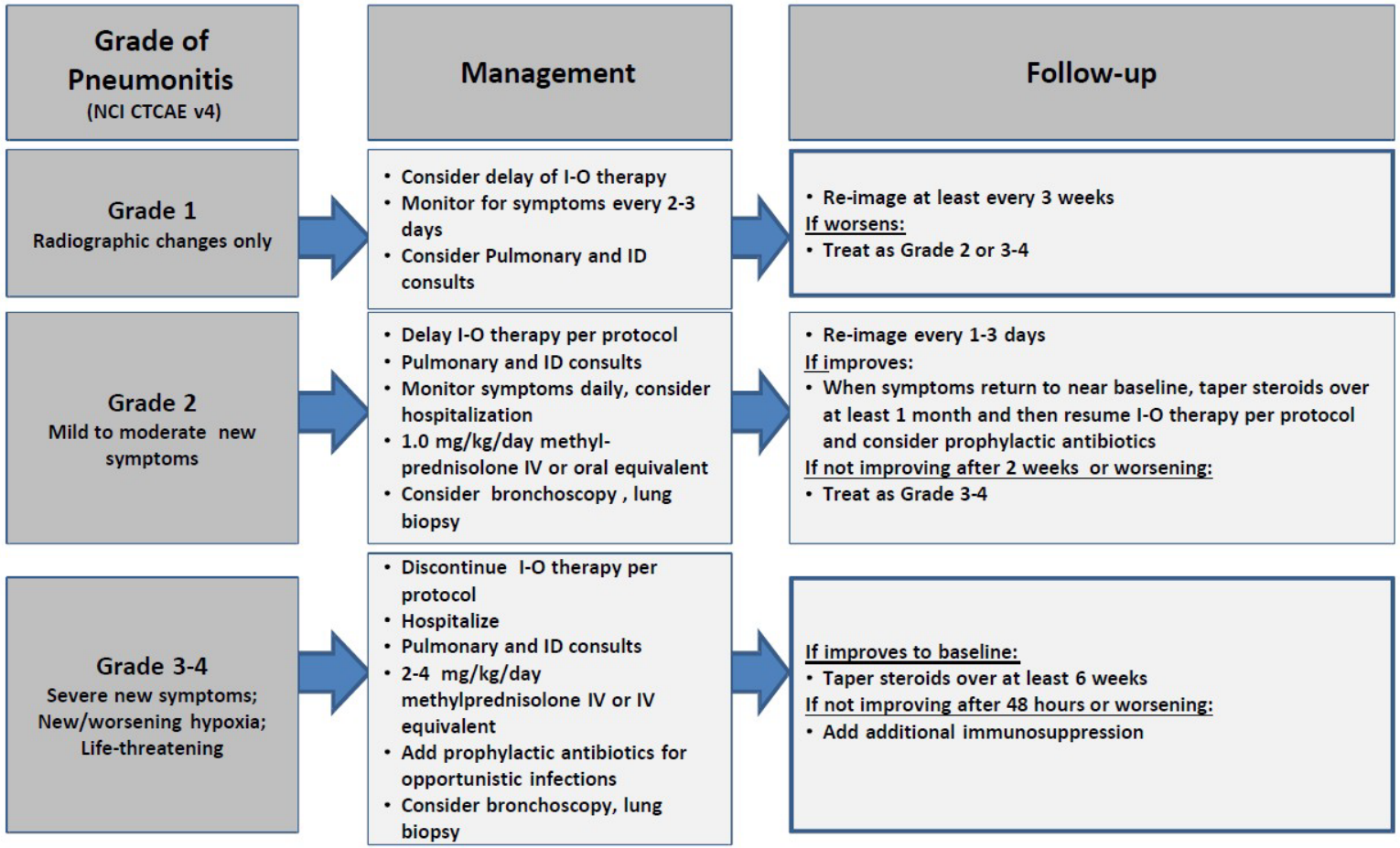
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Pulmonary Adverse Event Management Algorithm

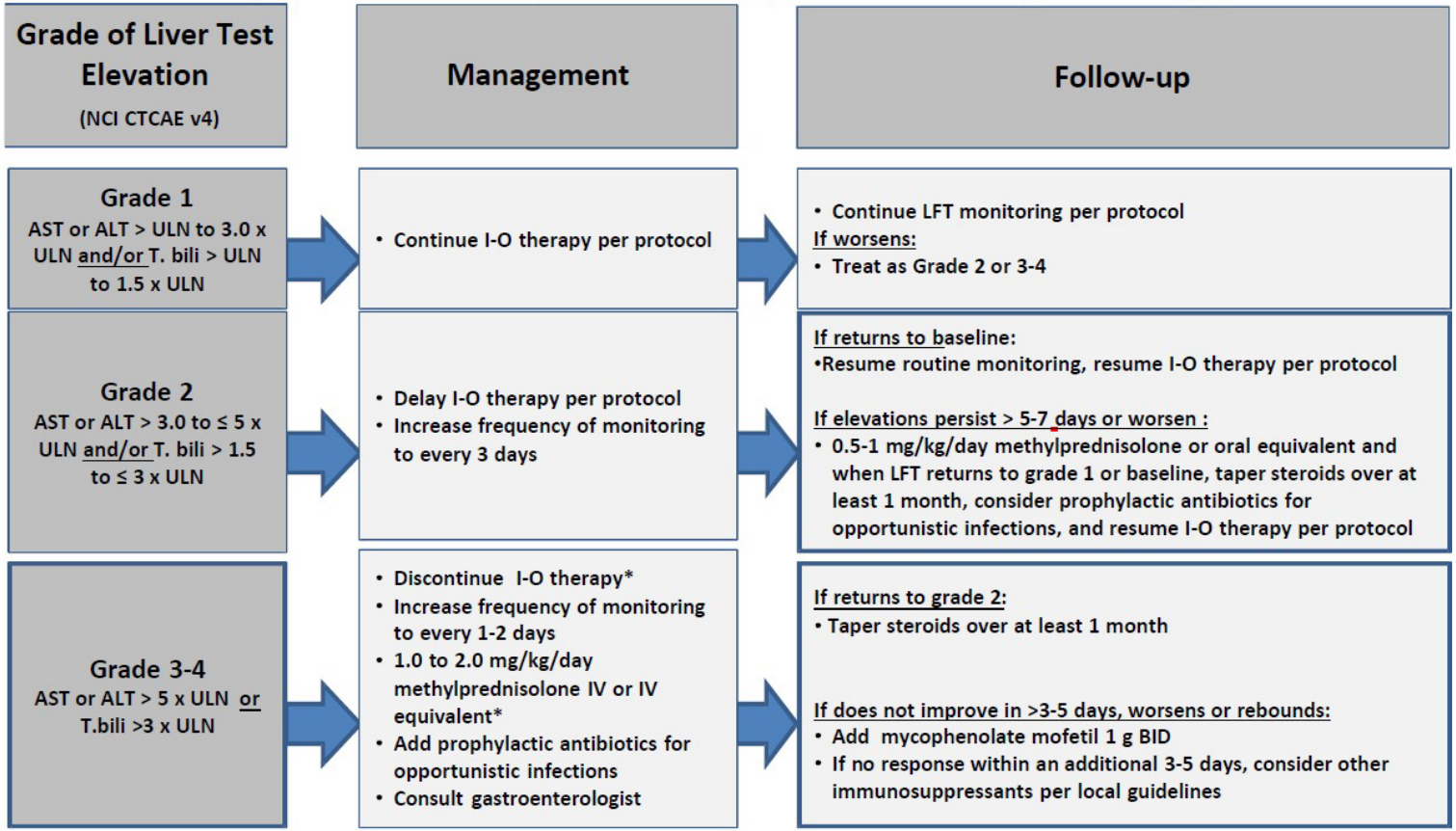
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

# Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

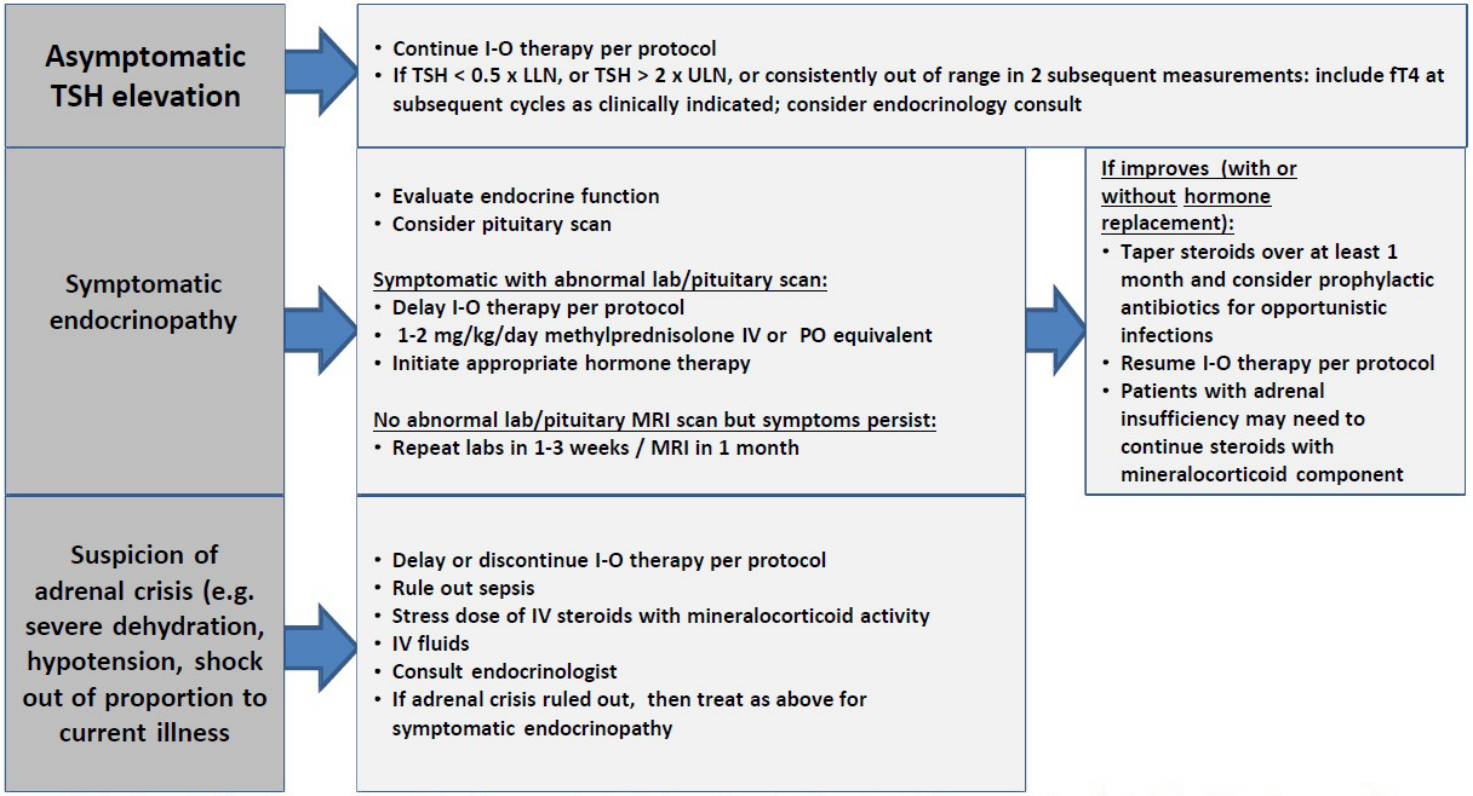



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

# Endocrinopathy Adverse Event Management Algorithm

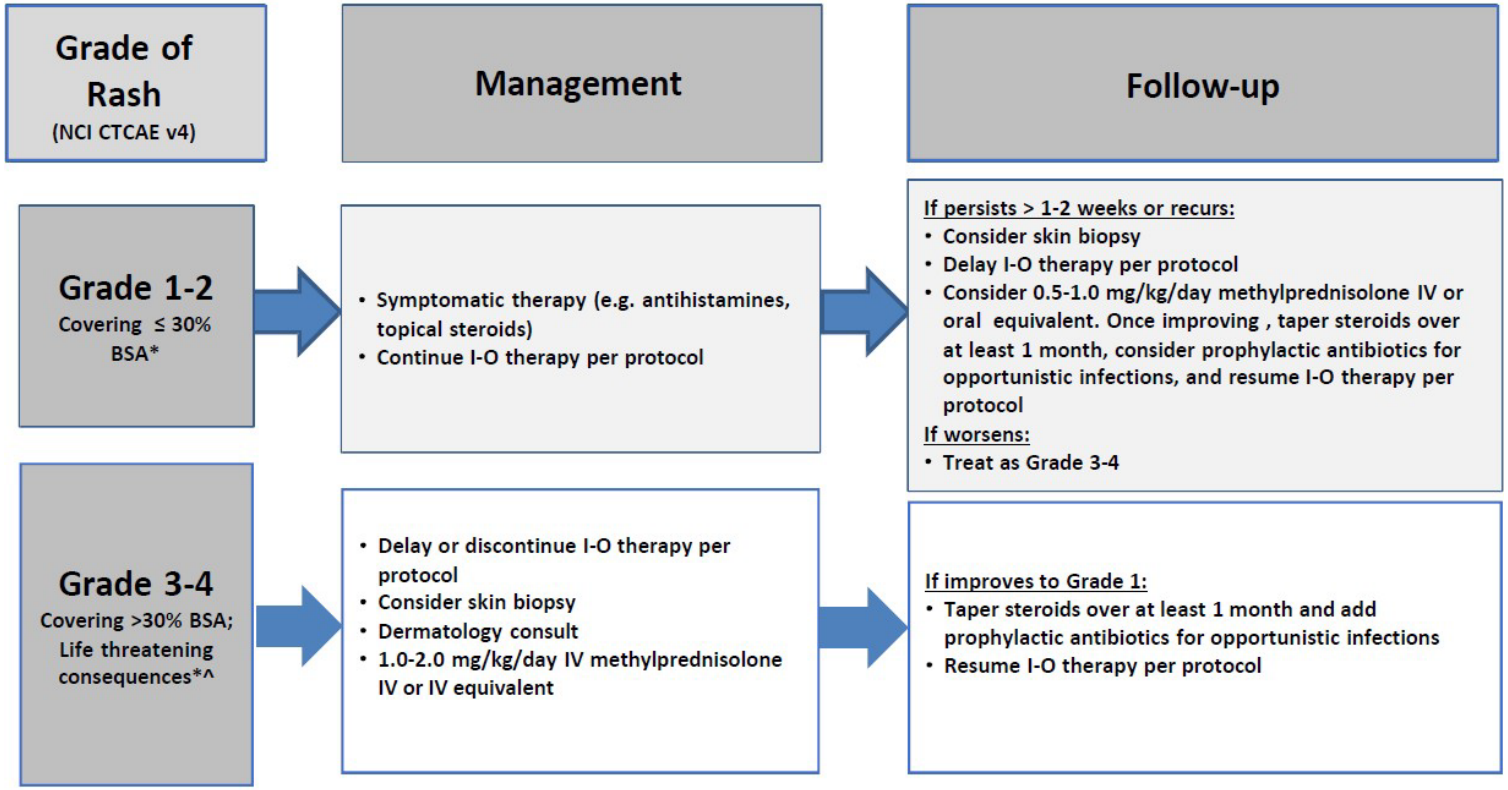
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



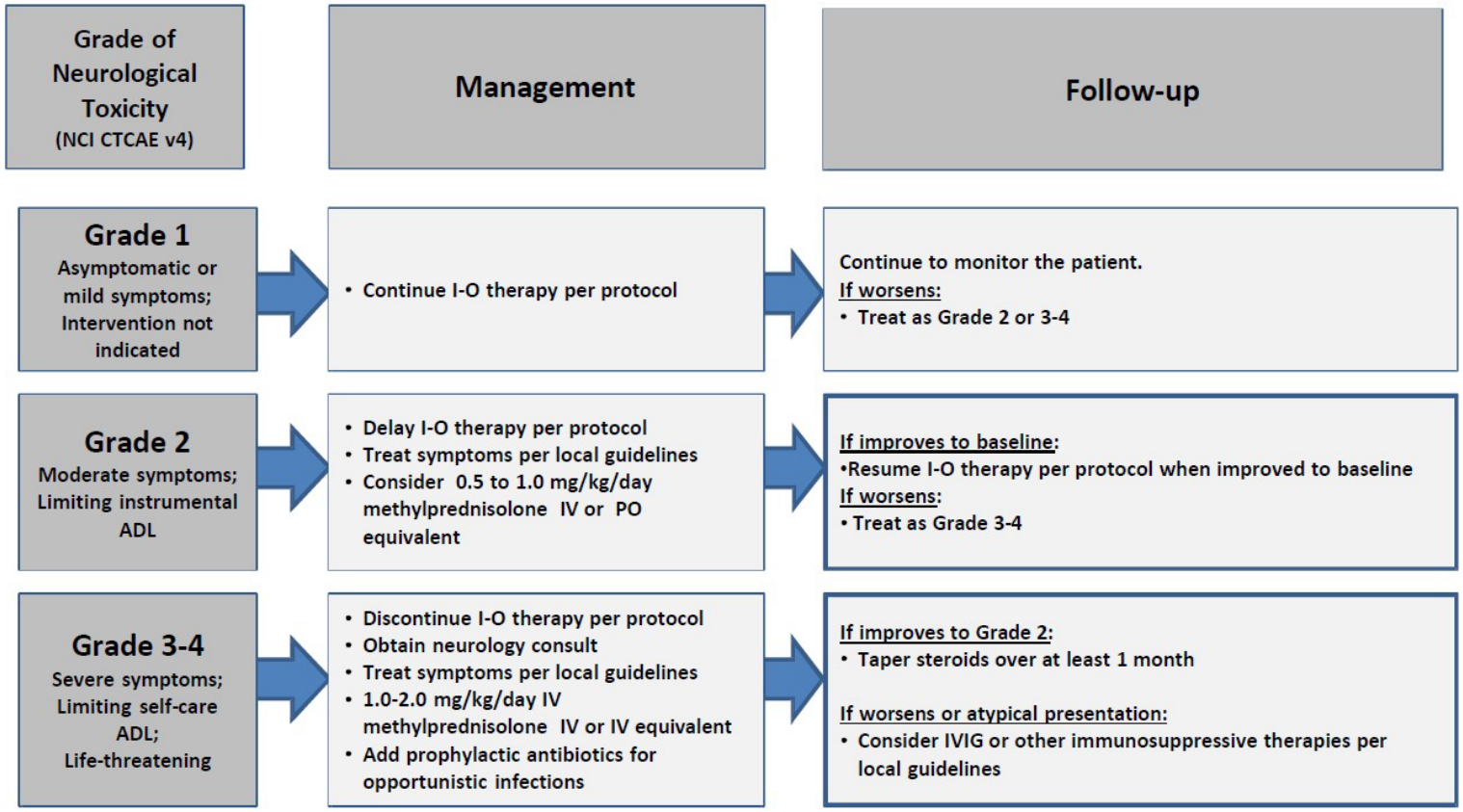

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

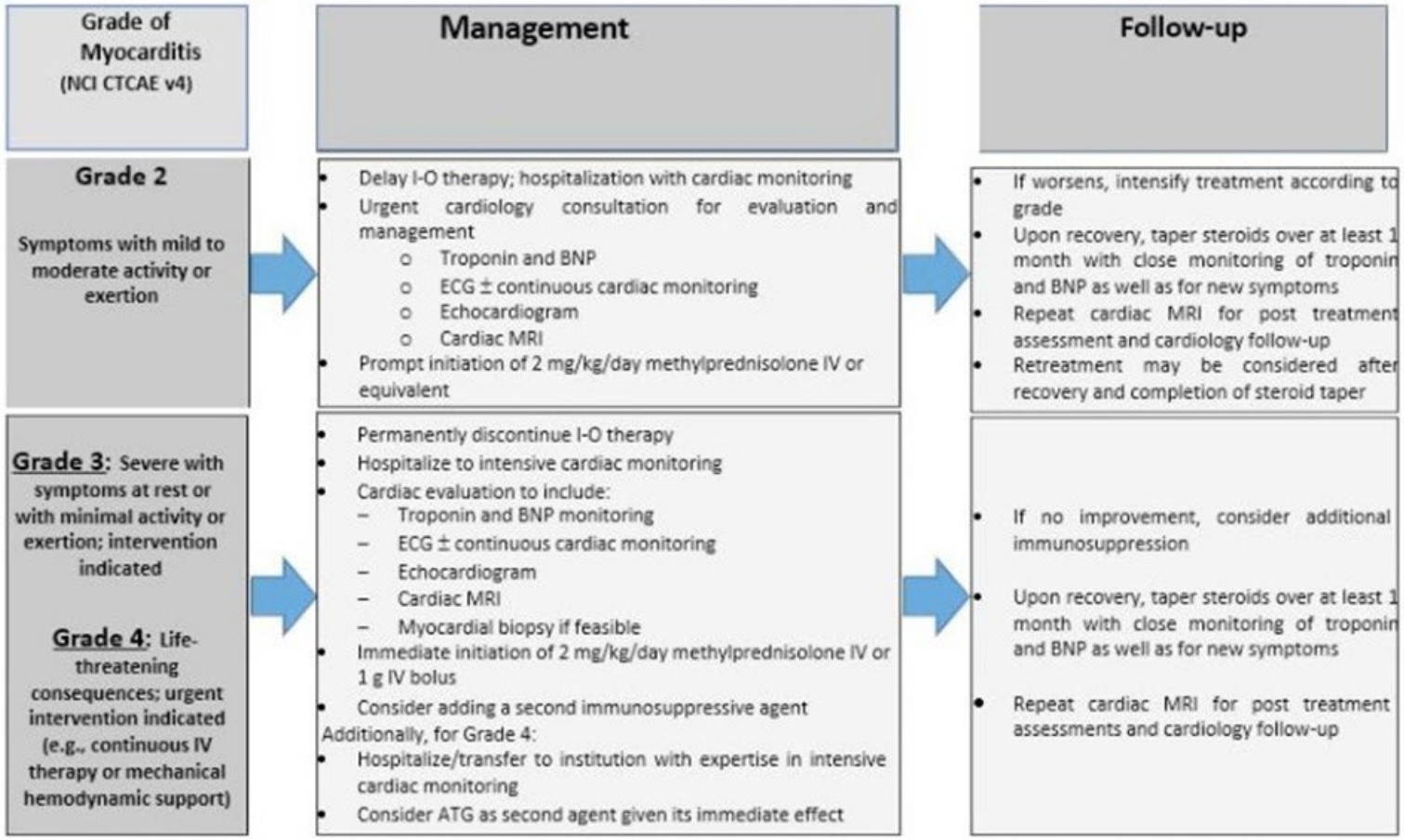
# Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Myocarditis Adverse Event Management Algorithm




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

## Additional Guidelines for Management of CTCAE-based immune-related hepatic adverse events (Puzanov 2017)

| Hepatitis (AST, ALT and Total Bilirubin) | | |
|---|---|---|
| Grade | CTCAE Description* | |
| 1 | AST, ALT >ULN -3xULN; total bilirubin >ULN-1.5xULN | • Continue study drug<br>• Continue Liver function panel once weekly |
| 2 | AST, ALT >3- < 5xULN; total bilirubin >1.5 - 3xULN | • Hold study drug<br>• Rule out viral hepatitis, autoimmune disease, biliary obstruction, new metastasis or thrombosis<br>• Start prednisone 0.5-1 mg/kg/day (or equivalent dose of methylprednisolone) with 4 week taper<br>• Monitor liver function panel twice a week<br>• Liver biopsy is optional<br>• Resume study drug as per Section 5 |
| 3 and 4 | AST, ALT >5xULN; total bilirubin >3xULN | • Permanently discontinue Study Drug<br>• Monitor liver function panel every 1–2 days<br>• Start prednisone 1–2 mg/kg/day<br>  • If refractory after 3 days, consider mycophenolate<br>• If liver enzymes improve, taper corticosteroid over 4 weeks<br>• Consider liver biopsy |
| * https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf | | |

# APPENDIX 9: PROTOCOL SYNOPSIS

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| **Name of Sponsor:** | Mereo BioPharma 5, INC |
| **Name of Product:** | Etigilimab (MPH313) - A humanized immunoglobulin G1 kappa monoclonal antibody |
| **Title of Study:** | A Phase 1b/2 Open-Label Study of the Efficacy and Safety of Etigilimab (MPH313) Administered in Combination with Nivolumab to Subjects with Locally Advanced or Metastatic Solid Tumors (ACTIVATE) |
| **Development Phase:** | 1b/2 |

| **Overall Design** | |
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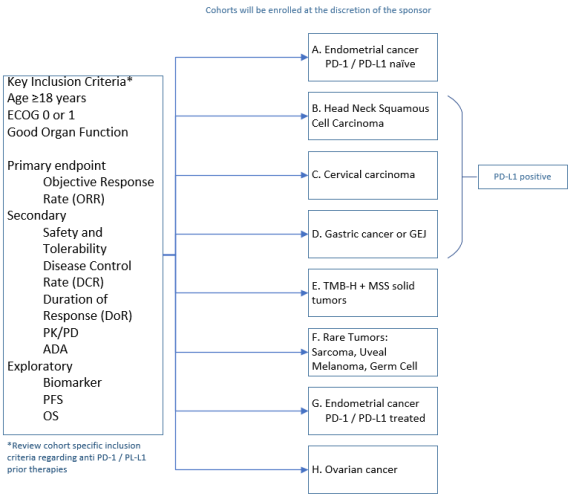
| **Schematic:** |  |
| **Written description** | This is an open-label, multicenter, Phase 1b/2 basket study designed to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etigilimab in combination with nivolumab in subjects with recurrent, locally advanced and/or metastatic solid tumors who are not candidates for available, curative standard of care therapies. In cohorts enrolling tumor types for whom anti-PD-1 antibody therapy is approved treatment for recurrent, locally advanced or metastatic disease, subjects may be enrolled prior to treatment with anti-PD-1 antibody therapy. Subjects will be assigned to receive etigilimab ([redacted] mg every 2 weeks for subjects ≥50 kg, [redacted] mg/kg dose every 2 weeks for subjects <50 kg) in combination with nivolumab (240 mg every 2 weeks) and will continue until protocol-defined discontinuation criteria are met. Cohorts will be enrolled at the discretion of the sponsor. Selected cohorts will be open for the first 20 subjects enrolled without increasing the total number of subjects proposed for the trial. During the conduct of this open label study an Independent Data Monitoring Committee (IDMC) will be established and will review study data on an ongoing basis. |
| **Screening period** | All screening tests must be performed within 28 days preceding Day 1 (defined as the first day of study drug administration), unless otherwise indicated. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window may be used and do not have to be repeated if they meet protocol specifications. The screening period will include medical history and demographic data collection, physical examination including vital signs, laboratory assessments including hematology, serum chemistry and urinalysis, electrocardiogram (ECG), collection of blood for immunogenicity, PK, and |

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| | tumor marker assessments, and collection of blood and formalin-fixed paraffin-embedded (FFPE) or fresh tumor samples for biomarker assessments. | | |
| **Treatment period** | Subjects will be assigned to receive etigilimab ([redacted] mg every 2 weeks for subjects ≥50 kg, [redacted] mg/kg dose every 2 weeks for subjects <50 kg) in combination with nivolumab (240 mg every 2 weeks) and will continue until protocol-defined discontinuation criteria are met. | | |
| **Follow-up period** | All subjects who have discontinued study drug treatment will return to the clinic for a treatment termination visit within 30 days after the last dose of etigilimab or nivolumab, whichever occurs last. Following etigilimab and nivolumab study treatment discontinuation, all subjects will be followed for survival and subsequent anti-cancer therapy via telephone calls, subject medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the sponsor unless the subject requests to be withdrawn from follow-up. | | |
| **Number of subjects:** | **Screened: 135** | **Enrolled: 125** | **Completed: 115** |
| **Planned number of sites:** | **20 (10 in US, 5 in UK and 5 in Spain)** | | |
| **Planned Subject Population for Study** | | | |
| **Inclusion Criteria** | | | |
| **Subjects who have** | **Cohort A**<br>Histologically confirmed diagnosis of endometrial carcinoma (EC);<br>Note: carcinosarcoma (malignant mixed Mullerian tumor), endometrial leiomysarcoma and endometrial stromal sarcomas are excluded.<br>Recurrent, advanced, and/or metastatic disease without potential for local curative surgery or radiation.<br>Radiographic evidence of progression after 1 prior systemic platinum-based chemotherapy regimen for EC with at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 that is suitable for repeat measurement including:<br>• non-nodal lesion that measures ≥10 mm in the longest diameter<br>• radiographic evidence of subsequent growth after locoregional therapy or external beam radiotherapy (EBRT).<br>Up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting. There is no restriction regarding prior hormonal therapy.<br>Treatment with prior anti-programmed death (PD)-1/anti-programmed death ligand (PD L)1/2 antibodies is not allowed **Cohort B.**<br>Histological or cytological evidence of advanced and/or recurrent or metastatic head and neck squamous cell carcinoma (**HNSCC**) or for the first-line treatment of subjects with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (combined positive score [CPS] >1%). Diagnosis of squamous cell carcinoma of the oral cavity, nasal cavity, paranasal sinuses, nasopharynx oropharynx, hypopharynx. or larynx are permitted. Primary or recurrent disease for which no curative or established palliative treatments are amenable:<br>• Subjects without prior anti-PD-1/anti-PD-L1/2 antibody treatment are eligible.<br>Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are eligible provided they have had (i) documented best observed response (BOR) of stable disease (SD) or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥6 weeks interval since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment<br>**Cohort C**<br>Histologically confirmed cervical cancer<br>Recurrent, advanced and/or metastatic disease with disease progression on or after one or more lines of chemotherapy, without potential for local curative treatment options including systemic chemotherapy, surgery or radiation and PD-L1-expressing tumors (CPS >1%). | | |

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| | Note: Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a systemic therapy regimen.<br>Treatment with prior anti-PD-1/anti-PD L1/2 antibodies is not allowed.<br>**Cohort D**<br>Histological or cytological evidence of recurrent advanced and/or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS >1%), with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.<br>Subjects without prior anti-PD-1/anti-PD-L1/2 antibody treatment are eligible.<br>Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are eligible provided (i) they have had documented BOR of SD or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥6 weeks interval since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment<br>**Cohort E**<br>Histological or cytological evidence of unresectable or metastatic tumor mutational burden-high (TMB-H) and microsatellite stable (MSS) solid tumors (TMB as defined by an FDA-approved test, e.g. Foundation Medicine >10 mutations/megabase or an Laboratory Developed Test (approved by the sponsor (e.g. Guardant Health), that have progressed following prior treatment and who have no satisfactory alternative treatment options. Subjects without prior treatment with anti-PD1 antibody treatment are eligible. Subjects who have received prior anti-PD-1/PD-L1/2 treatment are eligible with at least 6 weeks since their last dose of these prior treatments. Subjects must have had a previous SD or better in response to an anti-PD1/PDL-1/2 therapy. Subjects with the following TMB-H and MSS solid tumors will enroll into the tumor specific cohorts noted below after discussion with the sponsor:<br>• Cohort A: Endometrial cancer PD-1/PD-L1/2 naïve<br>• Cohort C: Cervical carcinoma<br>• Cohort F: Rare tumors (sarcoma, uveal melanoma, germ cell carcinoma)<br>• Cohort H: Ovarian cancer<br>**Cohort F Rare Tumors**<br>• Germ cell tumors<br>Histologically or cytologically confirmed seminoma or non-seminoma testicular germ cell tumors<br>Recurrent, advanced and/or metastatic disease, including new lesions, persistently elevated β-human chorionic gonadotropin (HCG) or alfa 1-fetoprotein (AFP) or increase in consecutive elevated serum tumor markers (β-HCG or AFP) done at least one week apart after prior high-dose chemotherapy (HDCT).<br>Subjects deemed not to be candidates for benefit from potentially curative HDCT may also be eligible including those with:<br>• Inadequate renal function for HDCT<br>• relapse >2 years after last therapy<br>• inadequate stem cell collection to move forward with HDCT<br>• significant medical or psychosocial comorbidities that are felt to be a contraindication to HDCT by the treating investigator.<br>Subjects with serum tumor marker ≥S2 HCG and AFP (levels ≥1000 for AFP and ≥5000 for HCG are excluded).<br>Subjects who have received prior anti-PD1/anti-PD-L1/2 antibodies are excluded.<br>• Sarcoma |

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| | Histological diagnosis (with archival or new biopsy sample available for pathology review) of locally advanced/unresectable and/or metastatic soft tissue sarcoma histopathological subtypes as noted below, who have radiological evidence of measurable disease and are not candidates for any curative surgery of multimodality therapy:<br>• De-differentiated liposarcoma (n=10)<br>• Undifferentiated pleomorphic sarcoma (UPS) (n=10)<br>• Alveolar soft part sarcoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma (grade 2 or higher), OR pleomorphic dermal sarcoma (total n=5)<br>Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies as standard of care are excluded.<br>• Uveal Melanoma<br>Histologically confirmed recurrent uveal melanoma with disease progression beyond prior approved standard of care therapy administered in the advanced setting (prior surgical resection of liver metastases, local radiation therapy and adjuvant systemic therapy are acceptable) are eligible.<br>Subjects who have received prior anti-PD1/anti-PD-L1/2 antibodies are excluded.<br>**Cohort G**<br>Histologically confirmed diagnosis of endometrial carcinoma (EC);<br>Note: carcinosarcoma (malignant mixed Mullerian tumor), endometrial leiomyosarcoma, and endometrial stromal sarcomas are excluded.<br>Subjects must have recurrent, advanced, and/or metastatic disease and must not be candidates for local curative surgery and radiation or intolerant to known standard of care systemic chemotherapy.<br>Radiographic evidence of progression after >1 and no more than 3 prior systemic anti-cancer therapy regimens for EC, (neoadjuvant, adjuvant, and maintenance treatment are considered part of one treatment line).<br>At least 1 measurable target lesion according to RECIST 1.1 that is suitable for repeat measurement including (i) non-nodal lesion that measures ≥10 mm in the longest diameter (ii) radiographic evidence of subsequent growth after locoregional therapy or external beam radiotherapy (EBRT).<br>Prior treatment with any treatment targeting vascular endothelial growth factor (VEGF)-directed angiogenesis, any anti-PD-1, anti-PD-L1/2 agent is allowed.<br>• Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies are also eligible provided (i) they have had documented Best Observed Response (BOR) of SD or better in response to an anti-PD1/PD-L1/2 therapy, AND (ii) ≥ 3 months interval prior to first study drug administration (C1D1) since their last dose of prior anti-PD-1/anti-PD-L1/2 treatment<br>**Cohort H**<br>Histologically confirmed high grade serous and endometrioid ovarian cancer, fallopian tube cancer or primary peritoneal cancer<br>Must have received a front-line platinum-based regimen per standard of care after primary or interval debulking surgery and have documented radiological disease recurrence<br>Must have measurable disease by RECIST 1.1 as determined by the local investigator/radiology assessment including 2 sites of disease/biopsy accessible disease. Subjects with less than 2 sites will need approval of the sponsor prior to enrollment. Note: Maintenance treatment following front-line treatment is permitted and counted together as part of the front-line treatment.<br>Subjects who have received prior anti-PD-1/anti-PD-L1/2 antibodies as treatment are excluded. |

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| **Prior Cancer Treatments** | Radiation therapy must be completed >3 weeks prior to first study drug administration (C1D1). Participants must have recovered from all radiation-related toxicities and/or complications prior to enrollment.<br>Palliative radiotherapy is allowed if completed at least 2 weeks prior to first study drug administration. Subjects must have recovered from all radiation-related toxicities and/or complications prior to enrollment.<br>Subjects must have measurable disease outside the radiation field to be eligible; subjects with progression in a previously radiated field will also be eligible.<br>All toxicities attributed to prior anticancer therapy, with the exception of peripheral neuropathy, alopecia, vitiligo, active thyroiditis, and fatigue, must have resolved to Grade 1 (per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 5 or higher) or baseline of prior treatment prior to enrollment. Peripheral neuropathy must have resolved to Grade 2 (per NCI CTCAE version 5 or higher). |
| **Aged** | ≥18 years |
| **ECOG performance status** | Eastern Cooperative Oncology Group (ECOG) of 0 or 1 |
| **Disease status** | Have measurable disease based on RECIST 1.1 as determined by the local investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. |
| **Tumor tissue availability** | Confirmed availability of representative tumor specimens in paraffin blocks is required for enrollment with an associated pathology report including PD-L1 status for PD-L1 positive cohorts.<br>Latest available archival tumor sample eg, within 6 months to 1 year prior to screening is strongly preferred. In instances where archival tissue is not available, a pre-dose biopsy will be required for submission with 3 core samples from an 18-gauge needle or larger. Only tissue from a surgical resection or a core needle, punch, or excisional/incisional biopsy sample collection will be accepted. Fine needle aspirate samples are not acceptable. Sponsor medical review is required if a fresh tumor biopsy cannot be provided during screening due to potential risk to subject from procedure.<br>For endometrial cancer (Cohorts A and G) archival or fresh biopsy specimen for determination of mismatched repair (MMR) status is required if historical MMR results are unavailable.<br>For study participants with sarcoma, archival tumor sample must be available for pathology review. If no archival material is available, a fresh biopsy should be performed to obtain tissue. |
| **Hematologic and end organ function** | Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):<br>a. Absolute neutrophil count ≥1500 cells/μL.<br>b. Platelet count ≥100,000/μL (without transfusion within 14 days prior to Cycle 1, Day 1).<br>c. Hemoglobin ≥9.0 g/dL (without transfusion of packed red blood cells (RBCs) or erythropoietic treatment within 14 days prior to Cycle 1, Day 1).<br>d. Total bilirubin ≤1.5 × upper limit of normal (ULN) unless elevated due to Gilbert's syndrome.<br>e. Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤3.0 × ULN with the following exception:<br>– Subjects with documented liver metastases: AST and/or ALT ≤5.0 × ULN.<br>– Total bilirubin <1.5 × ULN (subjects with Gilbert's syndrome may be enrolled with sponsor approval).<br>f. Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (aPTT) ≤1.5 × ULN and INR |

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| | ≤1.5 × ULN in subjects not on anticoagulant therapy; subjects receiving therapeutic anticoagulation should be on a stable dose with PT, INR, and aPTT within the intended therapeutic range.<br>g. Creatinine ≤1.5 × ULN or measured or calculated creatinine clearance ≥45 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:<br>(140-age) × (weight in kg) × (0.85 if female) 72 × (serum creatinine in mg/dL). |
| **Contraception** | • **Male Subject:**<br>A male subject must agree to use a highly effective contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 6 months after the last dose of study treatment and refrain from donating sperm during this period.<br>• **Female Subject:**<br>A female subject is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:<br>o Not a woman of childbearing potential (WOCBP) as defined in Appendix 5<br>OR<br>o A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 6 months after the last dose of study treatment. |
| **Informed Consent** | Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. |
| **Exclusion criteria** | |
| **Medical conditions** | • Severe allergic or anaphylactic reaction to any monoclonal antibody therapy, murine protein, or known hypersensitivity to any excipient in the study drugs.<br>• Major surgery within 4 weeks prior to screening.<br>• Subjects who have received radiotherapy within <1 week of starting study treatment, or who have unresolved associated AEs.<br>• Following known active viral infections:<br>o Known HIV infection.<br>o Active Hepatitis B or Hepatitis C infection at the time of screening for the study. Active Hepatitis B is defined as a known positive HbsAg result. Active Hepatitis C is defined as a known positive Hep C Ab result and known quantitative hepatitis C (HCV) RNA results greater than the lower limit of detection of the assay.<br>o Subjects with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA must be obtained in these subjects prior to randomization. Subjects with positive Hepatitis B serology who are immune due to vaccination, resolved wild-type infection or passive immunization due to immunoglobulin therapy will be eligible.<br>o Subjects with past HCV infection and positive for HCV antibody are eligible only if PCR is negative for HCV RNA.<br>o History of active non-infectious pneumonitis or history of pneumonitis that required steroids or current pneumonitis.<br>• Ongoing systemic bacterial, fungal, or viral infections at screening.<br>NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met. |

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| | • Female subjects who are pregnant or breastfeeding. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1 Day 1.<br>• Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia.<br>• Subjects with active, known, or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with minor autoimmune disease after discussion with the Medical Monitor.<br>• History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to screening.<br>• Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the risk to the subject associated with his or her participation in the study.<br>• History of any Grade 3 or 4 immune-related adverse event (AE) toxicity from prior immunotherapy that resulted in treatment discontinuation.<br>• Has primary central nervous system (CNS) malignancy or known untreated/active CNS metastases and/or carcinomatous meningitis.<br>o Subjects with previously treated, asymptomatic brain metastases may participate provided they meet the following criteria: clinically stable for at least 4 weeks and have no 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.<br>o Subjects with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease.<br>o Subjects with CNS symptoms should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, subjects with spinal cord compression must be excluded. |

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| **Prior medications** | • Prior treatment with CD137 agonist, -CTLA-4 and anti- TIGIT antibodies for all cohorts. Any prior anti-PD-1 and anti-PD-L1 therapeutic antibodies is excluded for Cohorts A, C, F and H only.<br>• Immune-related adverse events that lead to discontinuation of prior immune therapies including anti-PD-1 or PDL-1 therapy.<br>• Treatment with systemic immunostimulatory agents (including but not limited to interferon (IFN)α, IL2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1.<br>• Systemic anti-cancer chemotherapy, biologic therapy, or other investigational agent within <5 times the half-life of the agent or <28 days (whichever is shorter) of starting study drug with the following exceptions:<br>o Hormone-replacement therapy or oral contraceptives.<br>o Herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week before Cycle 1, Day 1.<br>o Subjects with castrate resistant prostate cancer should be allowed to remain on luteinizing hormone-releasing hormone analogues for medical castration.<br>o Previously initiated chronic bisphosphonate or denosumab therapy for bone metastases may be continued during study participation.<br>• Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.<br>• Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1:<br>Subjects receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.<br>• Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study. Inactivated influenza vaccination is permitted during influenza season only.<br>• History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. |
| **Prior Procedures** | • Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.<br>• Subjects who received investigational (not authorized or approved by relevant Health Authorities) COVID-19 vaccine or therapies prior to screening are not eligible without discussion with sponsor.<br>• History of additional prior malignancy with the exception of cured skin, bladder, prostate, cervical, or other carcinoma in situ with no evidence of active disease for at least 1 year. |

| Study Objectives and Endpoints | |
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| To make a preliminary assessment of the antitumor activity of etigilimab in combination with nivolumab in subjects with pre-specified locally advanced or metastatic solid tumors based on RECIST v1.1 criteria. Each cohort will be evaluated independently. | • Objective response rate (ORR) |
| Evaluate the safety and tolerability of etigilimab administered in combination with nivolumab. | • Count and % of subjects who experience at least 1 adverse event (AE) and abnormal safety laboratory parameters<br>• Adverse events of special interest (AESIs; infusion reactions, immune-related adverse events)<br>• Relationship of PK and safety |
| To evaluate preliminary anti-tumor activity of etigilimab in combination with nivolumab according to RECIST v1.1. Each cohort will be evaluated independently. | • Disease control rate (DCR; is the proportion of subjects whose BOR is CR, PR, or SD)<br>• Duration of Response (DoR)<br>• Duration of stable disease |
| To characterize the PK of etigilimab in a sub-set of subjects who have advanced, relapsed, or refractory solid tumors in combination with nivolumab. | • PK levels of etigilimab in combination with nivolumab. |
| To characterize the immunogenicity of etigilimab in a subset of subjects who have advanced, relapsed, or refractory solid tumors in combination with nivolumab. | • Anti-drug antibodies (ADA) to etigilimab; Impact of developed etigilimab ADAs on PK levels of etigilimab. |
| **EXPLORATORY** | |
| To assess exploratory pharmacodynamic biomarkers following etigilimab treatment in combination with nivolumab. | Pharmacodynamic biomarkers will be assessed to determine their correlation with response to etigilimab treatment as follows:<br>• Changes in peripheral blood mononuclear cell populations and activation.<br>• TIGIT and immune-related gene expression by messenger RNA (mRNA) detection (eg, CD226, TIGIT, T-cell genes).<br>• Plasma proteins (eg, interleukin 17 [IL17], interleukin 2 [IL2], interferon gamma [IFNγ]. |
| To assess potential predictive biomarkers for correlation with response to etigilimab treatment and exploratory biomarkers with treatment response. | • To correlate levels of TIGIT, PVR, TMB, PD-L1, and other immune markers with anti-tumor activity endpoints.<br>• BAP1 (BRCA1 associated protein-1) tumor mutations with etigilimab treatment response. |
| To evaluate preliminary anti-tumor activity of etigilimab in combination with nivolumab according to iRECIST.<br>Each cohort will be evaluated independently. | • ORR (proportion of iCR [complete response] plus iPR [partial response] subjects)<br>• DoR (iRECIST)<br>• Progression-free survival (PFS) using RECIST v1.1 and iRECIST<br>• Overall survival (OS) |

| Study Treatments | |
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| **Treatment under evaluation** | Etigilimab IV on Day 1 of 14-day cycles<br>[redacted] mg if subject is ≥50 kg<br>[redacted] mg/kg if subject is <50 kg |
| **Standard of care** | Nivolumab 240 mg IV every 2 weeks (Q2W) on Day 1 of the first 14-day cycle except for Cycle 1 when it will be administered on Day 3 to separate potential confounding infusion reactions. |
| **Treatment Durations** | In the absence of unacceptable toxicities or investigator-determined disease progression, subjects will be offered continued study until progression, death, unacceptable toxicities or other reasons. |

## Statistical Methods

This is a Phase 1b/2 Open-Label Basket Study of etigilimab (MPH313) ([redacted] mg dose for subjects ≥50 kg, [redacted] mg/kg dose for subjects <50 kg) IV administered Q2W with nivolumab 240 mg Q2W to evaluate preliminary anti-tumor activity, safety and tolerability, PK parameters, immunogenicity, and biomarkers in up to 9 cohorts of subjects with EC, HNSCC, cervical cancer, ovarian cancer, gastric cancer and gastroesophageal junction adenocarcinoma, TMB-H/MSS cancer, sarcoma, germ cell tumors, and uveal melanoma) Each cohort will be evaluated using a Simon Two-Stage design appropriate to the clinically meaningful response rate for the indication. Interim futility monitoring for each individual cohort using the clinically meaningful response rate criteria per cohort will be carried out in accordance with the optimal Simon Two-Stage design when up to 10 subjects have sufficient data (either discontinued study drug treatment or having at least one post-baseline imaging assessment) for ORR and DoR evaluation by RECIST v1.1. For each cohort, the second stage may be opened for enrollment only after discussion with the IDMC and the sponsor.

**Type 1 Cohort**

The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative that the true response rate is at least 0.2. In the first stage, 10 subjects will be enrolled and enrollment in this cohort will be halted until the response data are mature. If there are fewer than 1 responder in these 10 subjects, further enrollment in the cohort may be stopped after review of efficacy and safety data, and discussion by Sponsor with the IDMC. Otherwise, once 1 or more responders in stage 1 are observed, 19 additional subjects may be enrolled for a total of 29. The null hypothesis will be rejected and the treatment will be declared effective and worthy of further testing if 4 or more responders are observed in 29 subjects. This design yields a type I error rate of 0.0468 and power of 80.11% when the true response rate is 0.2.

**Type 2 Cohort**

The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative that the true response rate is at least 0.3. In the first stage, 10 subjects will be enrolled and enrollment in this cohort will be halted until the response data are mature. If there are fewer than 2 responders in these 10 subjects, enrollment in the cohort may be stopped after review of efficacy and safety data, and discussion by Sponsor with the IDMC. Otherwise, once 2 or more responders in stage 1 are observed, 19 additional subjects may be enrolled for a total of 29. The null hypothesis will be rejected and the treatment will be declared effective and worthy of further testing if 6 or more responders are observed in 29 subjects. This design yields a type I error rate of 0.0471 and power of 80.51% when the true response rate is 0.3.

The Intent-to-Treat (ITT) analysis set is defined as all subjects who signed an informed consent form and were enrolled into the study.

The Safety analysis set is defined as all subjects who received any amount of study drug. All safety analyses will be performed using the Safety analysis set.

The Response-Evaluable analysis set is a modified ITT analysis set defined as all subjects with measurable disease at baseline who received study treatment and had at least one post-baseline response assessment or discontinued treatment due to disease progression (including death due to disease progression) within 16 weeks (+ a 2-week window) of the first dose of study treatment. All efficacy analyses will be performed using the Response-Evaluable analysis set.

Efficacy analyses will be performed separately for each cohort. RECIST 1.1 criteria will be used for primary endpoint evaluation (Eisenhauer et al., 2009), iRECIST will be used for exploratory endpoint response

evaluation (Seymour et al., 2017). The iRECIST endpoints are analyzed using the same statistical methodology and the results will be presented in the same ways for the corresponding RECIST 1.1 endpoints.

The primary efficacy endpoint is the objective response rate (ORR) defined as the proportion of subjects who achieve confirmed CR or PR per RECIST v1.1. The best overall response is the best response recorded from the start of the treatment until PD. The smallest measurements recorded since the treatment started will be used as the reference for PD. Subjects with CR or PR are considered to have obtained objective response. Subjects with not-evaluable response (NE) are counted as non-responders. Exact 95% confidence intervals will be constructed for the ORR for each cohort.

Disease control rate: Subjects with CR, PR or SD are considered to have achieved disease control. Disease control rate is defined as the proportion of subjects who have achieved CR, PR, and SD. Duration of Response only applies to subjects whose best overall response is CR or PR and is defined as the number of days from the first documentation of objective tumor response to the date of first PD or death due to underlying cancer.

Duration of stable disease is measured from the start of the treatment (the first treatment date for non-randomized studies, the randomization date for randomized studies) until the date when the criteria for overall disease progression are first met. Duration of stable disease is defined as follows for the following cohort will also be considered for Simon-2 Stage futility monitoring in the rare cancer cohort for subjects with germ cell tumors only.

Progression-free Survival

PFS is defined as the number of days from Day 1 in Cycle 1 to the first documented progression or death due to any cause. Only deaths that occurred within 30 days of the last progression assessed.

OS, PFS, and DoR will be summarized for each group using Kaplan-Meier methodology. Censoring rules will be detailed in the statistical analysis plan.

- For analysis of OS, all subjects will be followed for survival for up to 2 years, until withdrawal of consent, loss to follow-up, or death, whichever occurs first. At the time of analysis of OS, any subjects who remain alive will be censored at the last date they were known to be alive.
- PFS is the time from the start of study treatment to the first evaluation showing PD or death, whichever occurs first. Subjects who do not experience PD or death will be censored per the censoring rules in the statistical analysis plan.

DoR is the time from first evaluation showing CR or PR (response confirmation required at subsequent tumor assessment no earlier than 4 weeks after first evaluation showing CR or PR) to the time of the first subsequent evaluation showing PD or death. Only subjects who experience a confirmed CR or PR will be analyzed for DoR. Subjects who do not experience PD or death will be censored per the censoring rules in the statistical analysis plan.

The Safety analysis set is defined as all subjects who received any amount of study drug. All safety analyses will be performed using the Safety analysis set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher and will be graded according to the NCI-CTCAE, v 4.03 or higher.

Summaries of AEs will be based on treatment-emergent AEs (TEAEs). A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment etigilimab or nivolumab, whichever is earlier) to 100 days after the last dose of etigilimab or nivolumab (whichever is dosed last) or until starting another treatment.

TEAEs will be summarized by treatment group and by the frequency of subjects experiencing TEAEs corresponding to MedDRA system organ classes and preferred terms.

Separate tabulations will also be produced for TEAEs assessed as related to study drug(s), TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥Grade 3 in severity. Treatment-emergent serious adverse events (SAEs) and SAEs related to study drug(s) will also be tabulated.

Laboratory results (hematology, serum or plasma chemistry and coagulation) and the corresponding change from baseline values will be summarized by group and scheduled timepoint. A shift table, tabulation for baseline to each scheduled assessment and the worst post treatment value according to the CTCAE grade, will be provided for selected clinical laboratory tests. Laboratory results together with the normal ranges and CTCAE grade will be listed. Lab values that are below or above the normal ranges will be flagged.

Vital signs and ECGs and the corresponding changes from baseline will be summarized by group and scheduled timepoint.

The PK analysis set will include all Phase 1b subjects with sufficient plasma concentration data to allow the characterization of the PK parameters. Plasma etigilimab concentration data at each assessment timepoint will be summarized and listed and will be plotted across time. Pharmacokinetic parameters will be calculated using non-compartmental techniques from plasma concentrations and will include the following parameters: maximum concentration observed, clearance, elimination half-life, and area under the curve. Pharmacokinetic parameters will be summarized descriptively for each group.

The immunogenicity analysis set will include all subjects with at least one evaluable post-treatment immunogenicity sample. Blood samples for evaluation of anti-drug antibodies (ADA) will be collected to determine the relationship between ADA and etigilimab PK parameters.

Blood samples for evaluation of pharmacodynamics biomarkers, immune biomarkers, and exploratory predictive biomarkers will be collected from all subjects to determine their correlation with ORR and DCR.

**Independent Data Monitoring Committee:**
An Independent Data Monitoring Committee (IDMC), consisting of at least 3 members with expertise in their field of practice as well as in the conduct of clinical studies, will hold regularly scheduled data review meetings. The IDMC will consist of at least 3 members with expertise in their field of practice as well as in the conduct of clinical studies. The committee members will be free of significant conflicts of interest. The IDMC will hold regularly scheduled data review meetings at pre-specified intervals as defined in the IDMC charter. The IDMC will also be available on an ad hoc basis e.g. to provide guidance related to any emerging safety signals or if requested by the sponsor.

**Independent Response Committee:**
The sponsor may have an independent assessment of responses to verify investigator-reported responses. The responses based on independent assessments, if available, will be used for sensitivity analysis.

# APPENDIX 10: SUMMARY OF VERSIONS AND CHANGES

## Summary of Versions

| Protocol | Version | Date | Summary of Change |
|---|---|---|---|
| Original | 1.0 | 11 September 2020 | Not Applicable |
| Amendment 1 | 2.0 | 20 October 2020 | Added etigilimab weight-based dosing, dose adjusting guidelines for weight-based dosing, clarified the schedule for PK and ADA sample collection, limited the time that diluted etigilimab can remain in solution to 4 hours prior to administration, defined protocol deviations that will be reported in the Clinical Study Report, and made other administrative changes. |
| Amendment 2 | 3.0 | 26 March 2021 | Refinement of basket study design and modification of cohort inclusion criteria for study population. Clarification around inclusion requirements. Adjustments to treatment hold and discontinuation criteria. Inclusion of iRECIST criteria as exploratory endpoint.<br>General corrections and administrative changes. |
| Amendment 3 | 4.0 | 29 June 2022 | Frequency of IDMC meetings clarified to be consistent with the language in the IDMC charter, supporting flexibility based on rate of accrual and amount of new data for review with the IDMC. |

| Protocol Amendment 3 V4.0 Changes | Sections Applied | Rationale |
|---|---|---|
| Removal of language that was inconsistent with IDMC Charter | Section 1.3, Study Design; and Appendix 9; Protocol Synopsis | Flexibility needed as captured in IDMC charter based on rate of accrual and amount of new data for review with the IDMC |

## APPENDIX 11: SPONSOR'S ELECTRONIC PROTOCOL SIGNATURE PAGE

Signature Page for MPH313-1-02_Protocol_V4.0_29Jun2022 v4.0

| | |
|---|---|
| Reason for signing: Approved | Name: [redacted]<br>Function: [redacted]<br>Date of signature: 29-Jun-2022 12:01:28 GMT+0000 |

| | |
|---|---|
| Reason for signing: Approved | Name: [redacted]<br>Function: [redacted]<br>Date of signature: 29-Jun-2022 12:19:26 GMT+0000 |

Signature Page for VV-TMF-65634 v4.0