Phase 1b Clinical Trial of Eribulin Mesylate and the PD-L1 Monoclonal Antibody, Avelumab, in Cisplatin Ineligible or Platinum Resistant Metastatic Urothelial Cell Cancer Patients

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VERSION DATE: 11JUL2019

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

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Location of Facility (City and State)

PLASE EMAIL COMPLETED FORM TO BTCRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	Phase 1b Clinical Trial of Eribulin Mesylate and the PD-L1 Monoclonal Antibody, Avelumab, in Cisplatin Ineligible or Platinum Resistant Metastatic Urothelial Cell Cancer Patients
PHASE	Phase Ib
OBJECTIVES	Primary Objective: 1. To assess the safety of combining Eribulin mesylate with Avelumab 2. To assess the response rates (Complete Response [CR]+Partial Response [PR]) Secondary Objectives: 1. To assess the disease control rate [DCR] (DCR=CR+PR+Stable Disease [SD]) at 3,6, 12 months 2. To estimate Progression Free Survival (PFS) rate at 12 months 3. To estimate Overall Survival (OS) rate at 12 months 4. To estimate median PFS 5. To estimate median OS 6. To assess the duration of response Exploratory Objectives: 1. To compare the expression of PD-L1 (programmed cell death ligand 1) by immunohistochemistry (IHC) in tumor and tumor infiltrating cells at baseline and after exposure to 2 doses of Eribulin mesylate. Optional biopsy will be done after 2 doses for expansion cohort. 2. To assess the correlation between PD-L1 expressions by IHC in tumor and tumor infiltrating cells with response rates. 3. To explore the correlation between PD-1(programmed cell death 1) expression on T-cells in peripheral blood with exposure to Eribulin mesylate x 2 doses. (PBMC to be drawn at baseline and again after 2 doses of Eribulin mesylate) 4. To explore other immune markers in the blood and markers in tumor that correlate with response- such as gamma interferon in plasma, immune markers- interleukins, T-regs and mutational sequencing on tumor, tumor mutation burden. 5. To explore the correlation of urine based biomarkers with clinical outcome
STUDY DESIGN	This is a phase I study to assess the maximum safe dose of combining Eribulin mesylate with Avelumab. N=24 patients A standard "3+3" design will be used to determine the maximum tolerated dose (MTD) of Eribulin mesylate with Avelumab (as shown in the table below). There are a total of 3 dose levels (level -1, 0, and +1) in the study, of which 2 levels will be actually used (0 to +1, or 0 to -1). For each dose level, we will need 3 or 6 patients. The maximum tolerated dose is the dose of Eribulin mesylate combined with Avelumab with dose limiting toxicity of 0-1 of 6 patients in the first cycle of combination therapy. After MTD has been

<table>
<tr><td></td><td>determined, an additional 12-patient expansion cohort will be enrolled at the MTD to evaluate the efficacy of this combination.
<table>
<tr><th>Dose Cohort</th><th>n</th><th>Eribulin mesylate</th><th>Avelumab</th><th>Cycle Length</th></tr>
<tr><td>-1</td><td>3-6</td><td>0.7mg/m^2 on days 1, 15</td><td>10mg/kg on days 1, 15</td><td>28 days</td></tr>
<tr><td><u>0: Starting cohort</u></td><td>3-6</td><td>1.1mg/m^2 on days 1,15</td><td>10mg/kg on days 1, 15</td><td>28 days</td></tr>
<tr><td>+1</td><td>3-6</td><td>1.4mg/m^2 on days 1,15</td><td>10mg/kg on days 1, 15</td><td>28 days</td></tr>
</table></td></tr>
<tr><td>KEY ELIGIBILITY CRITERIA</td><td>All patients must meet the following criteria:
1. Written informed consent and HIPAA authorization for release of personal health information. NOTE: HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0-2 at the time of enrollment.
4. Life expectancy of >12 weeks.
5. Stage IV patients with either locally advanced node positive or metastatic-M1 urothelial cancer of bladder and upper tract. Patients with local or distant recurrence of disease after definitive standard therapy (radiation OR surgery) are also eligible.
6. Histologically proven (pure or mixed) urothelial carcinoma of bladder or upper tract with any percentage of transitional cell component. Adenocarcinoma, squamous cell differentiation, or other atypical histology (such as plasmacytoid or sarcomotoid) will be allowed on the study; small cell histology will be excluded.
7. Presence of measurable disease per RECIST v1.1 for solid tumors.
8. Patients must be treatment naïve AND cisplatin ineligible OR must be platinum resistant.
9. Patients who are treatment naïve must be <u>cisplatin ineligible, defined as</u> the presence of one or more of the following:
a. Impaired renal function (GFR ≥ 30 but ≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation.
b. Grade ≥ 2 hearing loss (hearing loss measured by audiometry of 25 dB at two contiguous frequencies)
c. Grade ≥ 2 peripheral neuropathy (Please note that for enrollment on this trial patients must have peripheral neuropathy grade 2 or lower)
d. ECOG Performance Status of 2
e. NYHA Class III-IV CHF
10. For treatment naïve patients: Use of chemotherapy in neoadjuvant or adjuvant form is allowed provided the time period between last dose of treatment and enrollment is >12 months and subjects must have recovered</td></tr>
</table>

from all reversible toxic effects of the regimen (other than alopecia) to ≤Grade 1 or baseline.

11. For platinum resistant patients: Patients must have progressed during or within 12 months after a completing a cisplatin OR carboplatin based chemotherapy regimen. In addition, subjects must have recovered from all reversible toxic effects of the regimen (other than alopecia) to ≤Grade 1 or baseline. Patients who become intolerant to platinum based chemotherapy could also be enrolled on the study provided they have had no clinical response to platinum therapy.
12. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Platelet	≥ 100 K/mm^3
ANC	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Renal	
Calculated creatinine clearance • ≥30 cc/min using the Cockcroft-Gault formula (Cockcroft and Gault 1976) • or by equivalent criteria such as measured GFR by hospital's laboratory • or by 24-hour urine collection for determination of creatinine clearance: **Males:** Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) **Females:** Creatinine CL (mL/min) = Weight (kg) x (140 – Age) x 0.85 / 72 x serum creatinine (mg/dL)	
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN)
AST	≤ 2.5 × ULN
ALT	≤ 2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5× ULN for patients who are not on any anticoagulants. • Patients who are on warfarin will require switching to a short acting anticoagulant e.g., oral apixaban, lovenox injection etc. Prior to entry on the trial their INR should be <2.0. • Patients who are not medically able to switch (ex. artificial heart valve) may remain on their current regimen if the INR is stable and there is no concern for active ongoing bleeding. • Patients who are already on short acting anticoagulants will be allowed to enroll on the study provided their INR <2.0.

	13. Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. 14. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use a highly effective method of contraception from the time of informed consent until 90 days after treatment discontinuation. 15. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study. 16. Availability of baseline tumor tissue (fresh biopsy or archival) prior to enrollment on the clinical trial. TURBT specimens are preferred but tissue from lymph node or visceral areas are also acceptable. If archival tissue is not available, the subject must be willing to consent to a fresh biopsy for research prior to registration for protocol therapy. If archival tissue is not available and there are no sites amenable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis. 17. Palliative radiation therapy prior to or during the treatment is allowed if indicated. However, if prior to start of treatment, radiation therapy must complete at least 7 days prior to cycle 1 day 1 of treatment.
STATISTICAL CONSIDERATIONS	**Statistical Methods and Analysis Plan:** Descriptive statistics will be used in the study to analyze patient's characteristics and demographics. In particular, patient age, race, weight, ECOG performance status will be described. For the dose-finding component of this trial, the incidence and type of DLTs (dose limiting toxicity) will be tabulated and reported at the dose level. Other toxicity information will be summarized via frequency tables by type and grade of toxicity. For the efficacy component of the study, the primary endpoints are the response status (CR+PR) on treatment. It is a binary variable. Another binary outcome variable is the Disease Control status (CR+PR+SD) at 3, 6, 12 months. These binary outcomes will be summarized using point estimate values of the relative frequencies and their 95% confidence intervals. Exact binomial tests will be used to compare the response rate and disease control rate from the study sample to the existing values from historical cohorts. We also have PFS status and OS status at 12 months as our outcome variables. The PFS and OS will be analyzed using the Kaplan–Meier estimator with particular emphasis for 12-month survival rate. The survival (PFS and OS) time will be graphical displayed by the Kaplan-Meier survival curve. The median survival time and its 95% CI will be reported. Another outcome in the secondary objective is the duration of response, which is a continuous variable. It will be summarized using numerical (point estimate and confidence interval of the mean values) and graphical (histogram/boxplot) methods.

	The bivariate relationship between the outcome variables and some key clinical and demographic variables, such as tumor stage, ECOG status, smoking status, and gender, etc. will be examined by Fisher's exact test, Log-rank test, and ANOVA models when appropriate. For the factors that show marginally significant relationship (for example, $p<0.1$), their relationship with the outcome variable will be reexamined by using some multiple regression methods, such as multiple logistic regression, multiple Cox proportional hazard regression, and multiple linear regression depending on the type of outcome variable. For the exploratory objectives, the expression of PD-L1, PD-1, and some other immune markers in the blood and tumor will be compared between baseline and after treatment. The comparisons will be made using nonparametric Wilcoxon Signed-rank test for continuous markers and McNemar's test for markers that can be categorized into high/low values. The correlation PD-L1 expression and response rate will be examined using Fisher's exact test. All analyses will be performed using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA). The statistical significance level to be used is 0.05. **Statistical Power and Sample Size Considerations:** The dose-finding component consists of three dose levels (-1, 0, +1) with the starting dose level at level 0. It requires a maximum of 12 patients. We treat the efficacy-study component of the study as a pilot study so a formal statistical power calculation will not be performed. The main goal of this efficacy study is to generate some initial data for the clinical outcomes and detect the patterns in the results. Then a formal statistical power calculation can be performed. We believe an additional 10 patients for the efficacy-study component should be sufficient to achieve our needs. All patients in the dose-finding stage will be rolled over and combined with the patients in the expansion cohort for the evaluation of efficacy. With a consideration of about 10% patient drop-out rate throughout the study, a total of about 24 patients will be enrolled.
TOTAL NUMBER OF SUBJECTS	N = 24
ESTIMATED ENROLLMENT PERIOD	18 months
ESTIMATED STUDY DURATION	30 months

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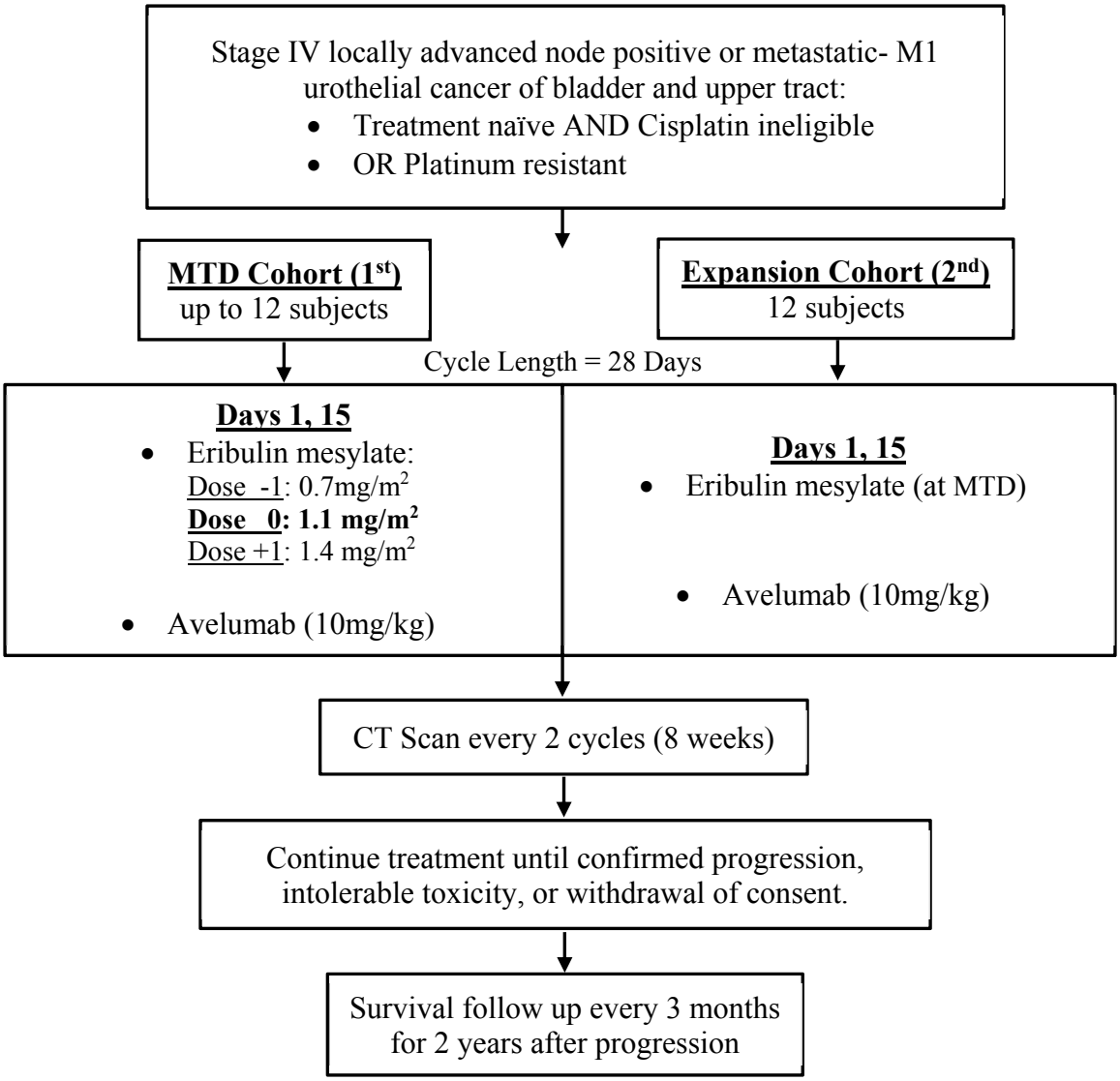
SCHEMA


Stage IV locally advanced node positive or metastatic- M1 urothelial cancer of bladder and upper tract:
• Treatment naïve AND Cisplatin ineligible
• OR Platinum resistant
MTD Cohort (1st)
up to 12 subjects
Expansion Cohort (2nd)
12 subjects
Cycle Length = 28 Days
Days 1, 15
• Eribulin mesylate:
Dose -1: 0.7mg/m2
Dose 0: 1.1 mg/m2
Dose +1: 1.4 mg/m2
• Avelumab (10mg/kg)
Days 1, 15
• Eribulin mesylate (at MTD)
• Avelumab (10mg/kg)
CT Scan every 2 cycles (8 weeks)
Continue treatment until confirmed progression, intolerable toxicity, or withdrawal of consent.
Survival follow up every 3 months for 2 years after progression

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Bladder cancer accounts for an approximately 5% of all new cancers and it is the 4th most common cancer in men. It is estimated that bladder cancer will account for approximately 79,030 new cases and 16,870 deaths in year 2017 [1]. The 5-year relative survival rate for bladder cancer is 77% but the 5-year relative survival rate for stage IV patients is very poor, 15%.

Metastatic urothelial cell cancer (mUCC) has poor prognosis with an OS of around 9-15 month and there is dearth of systemic therapy for this population. Cisplatin based treatment (GC [Gemcitabine and cisplatin] OR MVAC [methotrexate vinblastine, adriamycin, cisplatin]) [2] remains the standard of care as 1st line therapy for mUCC. The median survival of 14.0 months has been observed with treatment with GC and 15.2 months for MVAC with median progression-free survival (PFS) of 7.7 months for GC and 8.3 months for MVAC[2]. However, responses are not durable and these chemotherapies are associated with significant toxicities. Most importantly, there are significant numbers of patients who are not fit for cisplatin based chemotherapy either due to renal impairment or other co-morbidities, necessitating the need for developing novel combinations for mUCC. It is estimated that about 28% of patients will have low creatinine clearance <60ml/min making them unfit for cisplatin and this percentage increases to >40% with increasing age of >70 years [3]. Recent studies have shown immunotherapy, PD-1 directed therapy, to be an effective treatment in stage IV platinum refractory patients but still the ORR is limited to 15-19.6% [4, 5]. A study demonstrated a 23% objective response rate with a median OS of 15.9 months with Atezolizumab (monoclonal PD-L1 antibody) amongst untreated patients with locally advanced or metastatic UCC who were cisplatin ineligible [6]. Similarly, other immunotherapeutic agents such as Nivolumab is also showing efficacy as monotherapy in cisplatin ineligible patients in the upfront setting in clinical trials. However as of March 2017, there is no definitive standard of care for cisplatin ineligible patients. Carboplatin based chemotherapy or single agent gemcitabine are some alternative options for mUCC patients who are cisplatin ineligible, however their efficacy is modest in this setting. In general, any non-cisplatin regimen is considered an inferior therapy for mUCC patients. Treatment with carboplatin based chemotherapy has a median OS of 9 months with 1 year OS of 37% amongst mUCC patients which appears to be much lower that the cisplatin based therapy or that observed in clinical trials with immunotherapeutic agents.

Eribulin mesylate mesylate is a microtubule inhibitor that is already approved by FDA for use in refractory metastatic breast cancer and is showing promising results in mUCC. A phase II data reported by Dr. Quinn et al. in ASCO annual meeting 2015, showed Eribulin mesylate monotherapy to be effective in mUCC with an ORR of 32% [7]. The median OS on this study was 9.6 months and some of these patients have stable disease for >12 weeks with tolerable toxicity profile.

Avelumab is a fully human IgG1 antibody directed against PD-L1. It binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. There is data for activity of avelumab as monotherapy in various solid tumors including mUCC as listed below in section 1.3A. A phase 1b study showed avelumab to be an effective therapy in mUCC in 2nd line setting- an ORR of 18.2% (2 CRs and 6 PRs; 4 were ongoing) [9]. Stable disease was seen in 38.6% and disease-control rate was 56.8%. The OS was reported as 50.9% at 12 months. The results were provocative, showing activity in mUCC.

On August 16, 2018, FDA issued a warning to update the use of Pembrolizumab and Atezolizumab in cisplatin ineligible patients, given the results of recent phase 3 studies showing inferior outcome in patients who received immunotherapy alone vs. those who got platinum based chemotherapy.

Pembrolizumab is now indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

In addition, use of Atezolizuamb in cisplatin ineligible patients was restricted for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or
- Are not eligible for any platinum-containing therapy regardless of level of tumor PD-L1 expression.

However, the criteria for carboplatin ineligibility is NOT clear. Given the above update, the investigators feel strongly that we need to amend the current protocol to also include patients who have failed cisplatin or carboplatin based chemotherapy. Since our trial is not using single agent checkpoint inhibitor, we will continue to enroll patients who are cisplatin ineligible.

In this proposed phase 1b study we will evaluate the safety and efficacy of combining Avelumab with Eribulin mesylate in mUCC in cisplatin ineligible and platinum resistant mUCC patients.

1.2 Investigational Treatments

1.2.1 Avelumab

Because of the known role of programmed death ligand 1 (PD-L1) in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/programmed death 1 (PD-1) interaction presents a highly promising strategy for cancer immunotherapy. Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

The antitumor activity of avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor CD8+ T cell responses. To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all of the nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores anti-tumor CD8+ T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. There is emerging evidence that PD-L1 tumor expression may be an important factor to achieve an objective response upon blockade of the PD-1/PD-L1 axis [8].

Given the important role of PD-L1 in the suppression of T-cell responses, and the mode of action of avelumab which blocks the interaction between PD-L1 and its receptors, avelumab is being developed as a potential therapy for subjects with various tumors.

1.2.1.1 Physical, chemical, and pharmaceutical properties and formulation:

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (iv) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab.

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution be used immediately. If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature or up to 24 hours at 2°C to 8°C.

1.2.1.2 Nonclinical pharmacology:

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo.

Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-γ) production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1.

As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 μg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses.

The in vivo anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX], and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination with avelumab capable of causing complete regression of established tumors probably

through generating anti-tumor immune memory.

Various immunomonitoring assays were incorporated into the in vivo studies. Treatment with avelumab resulted in a consistent increase in the percentage of CD8+ PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (T_{EM}) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in CD8+ PD-1+ T cells, CD8+ T_{EM} cells, and antigen-specific T cell responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting.

1.2.1.3 Nonclinical pharmacokinetics and metabolism:

Full pharmacokinetic (PK) profiles were evaluated in mice and cynomolgus monkeys, since these species have similar binding affinity to PD-L1 to humans, and therefore these species are likely to have similar target-mediated clearance. Additional toxicokinetic (TK) data were obtained during the course of repeated toxicity studies with avelumab in mice, rats, and cynomolgus monkeys, with molecules MSB0010294 and MSB0010682 being the precursors to the final molecule avelumab. The anti-PD-L1 antibodies from research batches and precursor molecules tested in single-dose PK studies in mice and cynomolgus monkeys demonstrated pronounced nonlinear PK characteristics in mice and cynomolgus monkeys in single-dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Similar terminal half-lives (t1/2) ranging from 58 to 70 hours at doses between 20 and 140 mg/kg were observed in toxicity studies in mice and monkeys.

Since avelumab represents a foreign protein to the immune system of animals, anti-avelumab antibodies in rodents and nonhuman primates were observed and have been considered in interpreting the nonclinical data, with higher doses generally resulting in lower immunogenicity incidence. This is potentially due to the interference of avelumab trough concentrations with the measurement of antidrug antibody (ADA), and did not affect exposure or impact the conclusions of the toxicity studies. The immunogenicity incidence against the human antibody avelumab in animals is not deemed predictive for human subjects.

The clearance from the clinical population PK model is well predicted by allometric scaling from the cynomolgus monkey, confirming its suitability as the primary nonclinical PK species.

1.2.1.4 Nonclinical toxicology:

The toxicological profile of avelumab was evaluated in vivo in mice, rats, and cynomolgus monkeys. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) as well as tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues were performed.

On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. In repeat dose toxicity studies in CD-1 mice with avelumab IV bolus injections, mortality occurred mainly after the 3rd administration. Due to severe post-dose anaphylactic reactions after repeated administration of avelumab in mice and the low

binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) was followed and confirmed with Health Authorities.

In cynomolgus monkeys neither in the pilot 4-week IV repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week iv repeat-dose toxicity study, a no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established.

No reproductive toxicity studies were conducted. However, the reproductive and developmental toxicity potentially associated with avelumab treatment is considered adequately established based on available data, from repeat-dose studies and public sources and in view of the pursued indications and targeted indications (life threatening cancer diseases, advanced-stage cancer subjects). Considering that disruption of PD-1/PD-L1 communication has been reported to significantly increase the risk of fetal loss during pregnancy, the potential for adverse outcomes on embryofetal development cannot be excluded and adequate protections must be in place to prevent risk of pregnancies.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in phytohemagglutinin (PHA) prestimulated PBMCs. There was no evidence of phototoxicity on evaluation of UV absorption.

Overall, the nonclinical safety profile established for avelumab is considered adequate to support the use of avelumab in the planned therapeutic indication in humans.

1.2.1.5 Clinical safety:

Avelumab is currently in clinical development across Phases I, II, and III. The Investigator's Brochure includes safety data from the clinical trials that are being conducted to date with Avelumab. As of the date of the current Investigator Brochure, there are no completed clinical trials to report.

The safety data summarized for the Investigator's Brochure include data from all subjects treated with 10 mg/kg every 2 weeks from studies EMR100070-001 (1650 subjects) and EMR100070-003 Part A (88 subjects) as pooled safety dataset with a data cutoff of 09 June 2016. The pooled data included subjects treated in all tumor expansion cohorts, including nonsmall cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, UC, ovarian cancer, renal cell carcinoma, squamous cell cancer of the head and neck, and MCC. Safety data are also summarized for 51 subjects in the ongoing Phase I Trial EMR100070-002. For all other ongoing studies, an overview of the serious adverse events (SAEs) with a data cut off of 17 December 2016 is provided in the Investigator's Brochure.

EMR 100070-001 is a Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This trial consists of 2 parts. In the dose escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks) with a 3 + 3 algorithm design for determination of the maximum tolerated dose (MTD) of avelumab; in the treatment expansion phase, subjects in

different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until confirmed progression, unacceptable toxicity, or any reason for withdrawal occurs. As of 09 June 2016, 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively). The 3 + 3 dose escalation part is complete and a MTD was not reached. A dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of MoAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis) have been identified as important risks for avelumab. Guidelines for the management of immune-mediated adverse reactions and infusion-related reactions are implemented in all ongoing clinical studies with avelumab.

1.2.1.6 Clinical efficacy:

The clinical efficacy information for all tumor types has been summarized in the Investigator's Brochure.

Avelumab has been evaluated in 2nd line therapy in patients with metastatic urothelial carcinoma (mUC; NCT01772004) [9]. The results were reported in ASCO annual meeting 2016. Per ASCO abstract- By Oct 7, 2015, 44 pts (27 with visceral metastasis) were treated with avelumab (median 14 weeks and followed for a median of 11 months [range 10-13]). Median number of prior therapies was 2 (range 1-6). The most common (≥10%) adverse event reported were- infusion-related reaction (20.5%), fatigue (20.5%), asthenia (11.4%), and nausea (11.4%). Grade ≥3 adverse events were asthenia, myositis, decreased appetite, and elevated CPK or AST (each 1 event) and no treatment-related deaths occurred. ORR was 18.2% (8 patients; 95% CI: 8.2, 32.7) with 2 CRs and 6 PRs; 4 were ongoing. Stable disease was observed in 17 patients (38.6%); disease-control rate was 56.8%. PD-L1 expression was evaluable in a total of 35 patients. Using a ≥5% cutoff for tumor cells staining, 12/35 [34.3%] were PD-L1+; ORR was 50.0% in PD-L1+ patients (6/12; 95% CI: 21.1, 78.9) vs. 4.3% in PD-L1- patients (1/23; 95% CI: 0.1, 21.9). PFS rate at 24 wks was 58.3% (95% CI: 27.0, 80.1) in PD-L1+ patients vs. 16.6% (95% CI: 4.2, 36.0) in PD-L1-. ORR in pts +/- baseline visceral metastasis was 18.5% (5/27) and 17.6% (3/17), respectively. OS at 12 months was 50.9% (95% CI: 32.6, 66.6) for the overall population.

1.2.1.7 Rationale for Efficacy:

Clinical Phase I/II trials with MoAbs targeting either PD-L1 or PD-1 have shown promising hints for clinical efficacy, i.e., objective tumor response in indications such as NSCLC, melanoma, and ovarian cancer [8, 10].

Avelumab has 2 main mechanisms of action for exerting its anti-tumor effects:

- PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.

- Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has ADCC potential. Upon binding to PD-L1 on tumor cells and binding with their Fc part to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1, avelumab offers unique therapeutic potential compared with MoAbs targeting PD-1.

1.2.1.8 Rationale for Dose Selection:

A dose of 10 mg/kg of avelumab, intravenous (iv) once every 2 weeks, was selected for the expansion cohorts of Phase I trials, the Phase II pivotal trial (EMR 100070-003), and the ongoing Phase III trials based on the preliminary pharmacokinetic (PK), target occupancy, and preliminary clinical safety data collected in the clinical trials.

1.2.1.8.1 Pharmacokinetics and Target Occupancy

Available PK data from EMR 100070-001 show that the concentration at the end of dose interval (C_{min}) increased more than proportionally to dose between 1 to 10 mg/kg, but proportionally for doses above 10 mg/kg. Consistently the $t_{1/2}$ also increased with the dose. However, the geometric mean values for t1/2 were similar for 10 mg/kg and 20 mg/kg dose levels, 94.6 hours (3.96 days) and 99.1 hours (4.1 days) respectively. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and a high PD-L1 TO is likely achieved at the trough concentration for doses of 10 mg/kg and 20 mg/kg.

The 10 mg/kg dose once every 2 weeks achieved the high target occupancy (mean TO > 90%) of PD-L1 in PBMC during the whole dose interval as determined from ex vivo studies. Based on the in vitro TO data and the observed trough serum avelumab levels, TO was predicted to reach or exceed 95% throughout the entire dose interval for more subjects in 10 mg/kg dose group than those in 3 mg/kg dose group from the dose escalation cohorts of Study EMR100070-001.

1.2.1.8.2 Clinical Safety Data Related to Dose:

As of 09 June 2016, 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 1738 subjects in the pooled safety dataset part (Study EMR100070-001 and EMR100070-003 Part A) had received 10 mg/kg avelumab.

In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring Committee (SMC) suggests an acceptable safety profile of avelumab administered at the 10 mg/kg every 2 weeks dose and schedule. In the pooled safety dataset (Study EMR100070-001 in solid tumors and EMR100070-003 in MCC) with a data cut-off on 09 June 2016, treatment-related TEAEs were observed in 1164 (67.0%) subjects in the pooled safety dataset. The most frequently observed treatment-related TEAEs (with an incidence of ≥5%) of any grade were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%). Grade ≥ 3 treatment-related TEAEs were observed in 177 subjects (10.2%) in the pooled Safety dataset. The most frequently reported Grade ≥ 3 treatment-related TEAEs were fatigue, lipase increased (17 subjects each;

1.0%), GGT increased, infusion related reaction (10 subjects; 0.6%), AST increased (8 subjects; 0.5%), pneumonitis (7 subjects; 0.4%), anaemia, blood CPK increased (6 subjects each; 0.3%), diarrhea, asthenia (5 subjects each; 0.3%), autoimmune hepatitis, ALT increased, amylase increased, hyponatraemia, hypophosphataemia (4 subjects each; 0.2%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus), other immune-related AEs (myositis and myocarditis) have been identified as important risks of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

In summary, available data from the dose escalation part of Study EMR100070-001 showed that avelumab at doses up to 20mg/kg IV every 2 weeks was well tolerated, and data from the pooled dataset (Study EMR100070-001 and Study EMR100070-003) confirmed the dose of 10 mg/kg intravenously every 2 weeks was considered to have an acceptable safety profile.

1.2.1.8.3 Efficacy

Avelumab 10 mg/kg once every 2 weeks has demonstrated meaningful clinical activity across various tumor types and treatment settings. Regardless of the tumor type, responses with avelumab were observed early during treatment and appear durable in nature, including ongoing responses >1 year in several of the cohorts. Overall, many responders were still ongoing response at the time of database lock.

Based on the above analyses, a dose of 10 mg/kg IV once every 2 weeks was considered to have a favorable risk benefit profile and thus represents an appropriate dose for further investigation in registration studies of avelumab.

1.2.1.8.4 Additional dose regimen

The exposure-response relationship, however, is complex for oncology agents and challenging to characterize with data from just one dose level/regimen as described in literature [11, 12]. Therefore, one additional dose regimen, 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks, is being investigated in subjects with NSCLC which is supported by following analyses.

- An apparent exposure-efficacy response relationship was observed in NSCLC subjects treated with 10 mg/kg once every 2 weeks with higher exposure ($C_{trough,ss}$) associated with a better efficacy based on 1L NSCLC cohort of Study EMR100070-001.
- Preliminary observations from the 1L NSCLC cohort of EMR100070-001 showed that approximately 80% of reported responses occurred within 12 weeks of treatment initiation, and the majority of responses appeared to be durable.

It is not expected that the exposure at 10 mg/kg once every week would substantially impact the manageable safety profile currently observed with 10 mg/kg once every 2 weeks dosing. The exposure-irAE relationship curve appeared to be shallow for shorter treatment durations (≤ 18 weeks). Median exposures (Cmax,ss and AUCss) are not expected to exceed those for previously administered regimens including 20 mg/kg once every 2 weeks.

In conclusion, a dose of 10 mg/kg IV once every 2 weeks was considered to have a favorable risk benefit profile and thus represents an appropriate dose for further investigation in registration studies of

avelumab. An additional dosing regimen of 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks is also being investigated to determine whether higher exposure can lead to better efficacy.

1.2.2 Eribulin mesylate

Halichondrin B, a large polyether macrolide isolated from a marine sponge, exhibits potent anticancer effects in both in vitro and in vivo models of cancer [13-15]. The anticancer activity of HalB resides in its macrocyclic lactone moiety eribulin mesylate, a structurally simplified synthetic analog encompassing the biologically-active macrocyclic portion of HalB, exhibits similar or identical anticancer properties to HalB in preclinical models [16, 17] The structure of eribulin mesylate is a simplified macrocyclic ketone in which the entire C39-C54 polyether sidechain is removed, the C1 lactone ester is replaced by ketone, C31 methyl is replaced by methoxy, and the tricyclic C29-C38 system is replaced by a single five-membered ring [16].

Eribulin mesylate exerts its antiproliferative effects via a tubulin-based antimitotic mechanism. Currently available data indicate that its mechanism of action is similar or identical to that of HalB [16, 18] Like HalB, eribulin mesylate was shown to be a potent inhibitor of tubulin polymerization into microtubules as well as microtubule dynamics in vitro and in whole cells [16, 19, 20] Nonclinical data show that sub- to low-nmol/L levels of eribulin mesylate inhibit cancer cell proliferation via induction of irreversible cell cycle blocks at G_2/M, disruption of mitotic spindles, and initiation of apoptosis [16, 18, 19].

Among tubulin-targeted agents, eribulin mesylate is a mechanistically unique inhibitor of microtubule dynamics, leading to inhibition of microtubule growth in the absence of effects on microtubule shortening at microtubule plus ends, and formation of nonproductive tubulin aggregates [20]. Eribulin mesylate binds specifically to high affinity binding sites on the growing plus ends of microtubules. This unique pattern of eribulin mesylate's inhibitory effects on microtubule dynamics, combined with its distinct binding profile to microtubules, is not shared by other known tubulin-targeted agents [21, 22]

Accumulating evidence indicates that microtubules and microtubule dynamics have important roles for not only mitosis, but also locomotive functions of cells with controlled directionality involving tumor invasion [23, 24] and tumor angiogenesis [25] Chanez et al. [26] reported that microtubule plus-end interacting proteins including EB1 and ch-TOG/XMAP215 play important regulatory roles for cell migration upon binding to microtubule plus-ends, and subnanomolar levels of eribulin mesylate induced a dose-dependent depletion of ch-TOG accompanied by the inhibition of cellular migration [26]. Eribulin mesylate also depleted EB1 from microtubule plus-ends [26, 27] a potential oncogene working for cancer migration and proliferation [28, 29] Carbonaro et al. have reported that microtubules contribute to the activation of HIF-1α at both the translational and nuclear accumulation stages [30-32]; this upregulates the gene expression of molecules that promote aggressive phenotypes of cancer cells and tumor angiogenesis. These resent findings indicate that targeting microtubule dynamics should be useful for suppressing tumor malignancy as well as direct killing of cancer cells.

Human tumor xenograft studies in mice (ovary, lung, breast, colon, pancreatic cancers, melanoma and sarcoma) demonstrate tumor regressions, remissions, and an increased lifespan at dose levels at or below the maximum tolerated dose (MTD) [16, 33, 34](Periodic Safety Update Report for Halaven, 2014). In vivo animal model data predict that eribulin mesylate will have greater efficacy than the taxanes and that increased antitumor activity can be achieved with fewer adverse effects. In addition, the potential for

common side effects and drug–drug interactions with eribulin mesylate are less than or equal to existing therapies. Currently, there is no evidence for paclitaxel-like hypersensitivity with eribulin mesylate. Although eribulin mesylate is a P-gp drug efflux pump substrate, it retains full in vitro activity against cancer cells that are taxane-resistant due to β-tubulin mutations [35] suggesting that eribulin mesylate may show clinical effectiveness in subjects with refractory tumors that are taxane-resistant based on β-tubulin mutations.

Preclinical in vitro studies demonstrated that eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness [36] In mouse xenograft models of human breast cancer, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype [37]

In summary, eribulin mesylate is a non-taxane inhibitor of microtubule dynamics that specifically binds to a small number of high affinity sites at the plus ends of microtubules. Eribulin mesylate suppresses the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates, resulting in irreversible mitotic blockage and subsequent cell death by apoptosis. When tested in a variety of animal models of human cancer, these molecular- and cell-based anticancer activities of eribulin mesylate result in significant antitumor effects including tumor growth inhibition, regressions, remissions and increased life span. Current nonclinical data predict anticancer efficacy greater than the taxanes, achieved with fewer adverse effects. In addition to having primary anticancer effects associated with classical cytotoxicity, eribulin mesylate also affects tumor phenotype and the surrounding microenvironment, thus rendering residual tumors less aggressive and less likely to metastasize.

Eribulin mesylate is approved for the treatment of patients with MBC and liposarcoma (see prescribing information for further details). Development of eribulin is ongoing for other tumor types.

Eribulin mesylate was first approved on 15 Nov 2010 in the United States for the treatment of patients with MBC and has subsequently been approved worldwide, with the indications being extended to earlier lines of chemotherapy for MBC and for liposarcoma.

1.2.2.1 Pharmacokinetic Parameters

The PK of eribulin mesylate is characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean half-life of approximately 40 hours. It has a large V_{ss}, 43–114 L/m^2) and low CL (1.16–2.42 L/h/m^2). Protein binding of eribulin mesylate in human plasma is low. The plasma protein binding of eribulin mesylate (100–1000 ng/mL) ranged between 49% and 65% in human plasma.

Eribulin mesylate is not a P-gp inhibitor at clinically relevant concentrations. Potential inhibitory activity of eribulin mesylate on P-gp-mediated-digoxin transport was assessed with Caco-2 human colonic carcinoma cell monolayers. In the presence of eribulin mesylate, P-gp-mediated transport of digoxin was reduced in a concentration-dependent manner with an estimated IC_{50} of >10 μmol/L (7300 ng/mL). This IC_{50} value represents 10-fold the highest mean C_{max} observed in the Phase 1 clinical pharmacology studies. Thus, inhibition of P-gp by eribulin mesylate is unlikely to be clinically relevant.

CYP3A4 was identified as the major enzyme responsible for eribulin metabolism in human liver microsomes. Metabolism represents a minor component in eribulin clearance. Following administration

of a 2-mg [^{14}C] eribulin acetate dose to subjects, eribulin plasma concentrations were approximately 100% of the total drug derived radioactivity, indicating minimal eribulin metabolism. Renal elimination is a minor route for eribulin mesylate excretion, with less than 10% of the drug excreted unchanged in urine; the majority is excreted unchanged in feces. Although it cannot be directly measured in subjects, biliary excretion may also represent a substantial contribution to eribulin mesylate clearance.

1.2.2.1.1 Effects on Tumor Vascular Remodeling and reversal of EMT in Pre-Clinical Models

Gene expression analysis of subcutaneous MX-1 human breast cancer xenografts grown in mice showed that mRNA levels of several human epithelial-mesenchymal transition (EMT)-related genes were higher than control 3 days after intravenous administration of 0.3, 1, and 3 mg/kg of eribulin mesylate (P57). In addition, eribulin mesylate treatment induced higher protein levels of epithelial marker E-cadherin, while simultaneously lowering protein levels of mesenchymal markers N-cadherin, vimentin, and E-box-binding homeobox 1 (ZEB1) in MX-1 xenograft sections (7 days after administration of eribulin mesylate) (P58 and P59). Finally, effects of eribulin mesylate on the tumor microenvironment were investigated by assessing angiogenesis- and EMT-related pathway components in host (mouse) tissues. Results indicated that intravenous treatment of mice bearing MX-1 and MDA-MB-231 human breast cancer xenografts with eribulin mesylate (0.3, 1, and 3 mg/kg) significantly downregulated expression of many murine angiogenesis- and EMT-related genes (P57). In addition, eribulin mesylate treatment also decreased protein levels of murine VEGF present in the tumors (P60 and P61). Thus, combining analyses of both human and murine genes and proteins, eribulin mesylate was shown to exert significant global effects on both angiogenesis- and EMT-related pathway components of both human tumor cells and murine host cells within the complex context of the tumor microenvironment.

1.2.2.2 Clinical Experience with Eribulin Mesylate

Eribulin mesylate was first approved on 15 Nov 2010 in the United States for the treatment of patients with MBC and has subsequently been approved worldwide, with the indications being extended to earlier lines of chemotherapy for MBC and for liposarcoma. Eribulin mesylate should be given at a dose of 1.4 mg/m2 (equivalent to 1.23 mg/m2 eribulin [expressed as free base]) which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle of the ready to use solution. Approval has been obtained in the 62 countries. The trade name in all countries is Halaven.

A total of 1622 SAE reports are included in the pharmacovigilance database as of the cutoff date 14 November 2016. The data includes cumulative SAEs from completed and ongoing studies (unaudited data) for all Eisai sponsored interventional clinical studies in subjects who received eribulin mesylate. Of the 1622 reports, 677 were reported as related to eribulin mesylate and 945 were reported as not related to eribulin mesylate. The most common adverse reactions (≥25%) in metastatic breast cancer were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common adverse reactions (≥25%) in liposarcoma and leiomyosarcoma were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. The most common (≥5%) Grade 3-4 laboratory abnormalities in liposarcoma and leiomyosarcoma were neutropenia, hypokalemia, and hypocalcemia.

NCI Protocol No.7435 is a Phase 1/2 study conducted to evaluate the safety and efficacy of eribulin mesylate monotherapy in patients with mUCC [7]. This study was originally designed as a Phase 2 study in patients with advanced UC who had not received any chemotherapy for advanced or recurrent disease; there was a safety lead-in Phase 1 component for patients with renal impairment. With 159 pts the overall response rate was 35% with a median PFS of 4.0 months and median OS of 9.2 months.

Common toxicities seen were reversible neutropenia, reversible thrombocytopenia, fatigue, grade 1 transaminase increase and grade 1-2 sensory neuropathy. Overall, the most common Grade 3 and 4 TEAEs (≥5%) in order of descending frequency were neutrophil count decreased (56.1%), white blood cell decreased (43.9%), hyponatremia (15.3%), anemia (13.4%), lymphocyte count decreased (13.4%), hypophosphatemia (11.5%), fatigue (8.3%), urinary tract infection (7.0%), thromboembolic events (6.4%) and hypertension (5.7%). In summary, eribulin mesylate provides clinical benefit for the treatment of patients with locally recurring breast cancer and MBC as well as in subjects with mUCC previously treated with chemotherapeutic regimens. Eribulin mesylate has an acceptable safety profile. The risk of toxicity with eribulin mesylate mesylate is comparable or less than that for other agents currently used in this population. Proposed precautions and dose adjustments will allow the toxicity of eribulin mesylate mesylate to be managed appropriately. Eribulin mesylate mesylate is provided as a ready-to-use formulation that is easily administered without the need for premedications to prevent hypersensitivity. It is therefore concluded that the benefit-risk ratio of eribulin mesylate mesylate continues to be favorable.

1.3 Rationale for Combining Eribulin Mesylate with Avelumab

Eribulin mesylate is a microtubule inhibitor that is already approved by FDA for use in refractory metastatic breast cancer and liposarcoma and is showing promising results in mUCC. A phase II data reported by Dr. Quinn et al. in ASCO annual meeting 2015, showed Eribulin mesylate to be effective in mUCC with an ORR of 32% [7]. The median OS on this study was 9.6 months and some of these patients have stable disease for >12 weeks with tolerable toxicity profile.

Avelumab is is a fully human IgG1 antibody directed against PD-L1. It binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. There is data for activity of avelumab as monotherapy in various solid tumors including mUCC as listed in section 1.3A. A phase 1b study showed avelumab to be an effective therapy in mUCC in 2nd line setting- an ORR of 18.2% (2 CRs and 6 PRs; 4 were ongoing)[9]. Stable disease was seen in 38.6% and disease-control rate was 56.8%. The OS was reported as 50.9% at 12 months. The results were provocative showing activity in mUCC.

Chemotherapy can induce immunogenic response that can prime the tumor cells to immune checkpoint blockade and can help mount a synergistic anti-tumor response in various cancers [38]. Chemotherapeutic agents can cause enhancement of antigen presentation, a decrease in T-reg, an increase in expression of co-stimulatory molecules such as B7-1, and can downregulate the expression of inhibitory molecules such as PD-L1 thus promoting the immune-mediated killing effect on the cancer cells [39]. Studies are being conducted to study the effects of combining cisplatin-based chemotherapy with immunotherapy. However cisplatin-based chemotherapy causes significant toxicity and is contraindicated in patients with renal impairment. Eribulin mesylate was studied in a phase II study in mUCC with acceptable toxicity and can be given safely in patients with mild to moderate renal impairment with GFR>20.

There is an ongoing study of combining Eribulin mesylate with PD-1 mAB, pembrolizumab in breast cancer but the similar approach has not been used in bladder cancer. The data from the phase Ib/II study of combination of pembrolizumab and eribulin in triple negative breast cancer (TNBC) was presented at the 2016 San Antonio Breast Cancer Symposium. The study enrolled a total of 89 patients with

metastatic TNBC who previously received 0 to 2 prior therapies. Eribulin was administered at 1.4 mg/m2 on days 1 and 8 and pembrolizumab was given at a flat dose of 200 mg every 3 weeks. At the July 12, 2016, data cutoff, 39 patients were evaluable for efficacy. The median duration of treatment was 3.9 months with eribulin (95% CI, 1.0-8.3) and 3.7 months with pembrolizumab (95% CI, 0.8-9.0). There was 1 compete response (CR; 2.6%) and 12 partial responses (PR; 30.8%). The stable disease rate was 28.2% and the durable SD rate (SD for ≥24 weeks) was 7.7%. The clinical benefit rate (CBR; CR + PR + durable SD) was 41%. In those with PD-L1-positive disease, the ORR was 29.4% (95% CI, 11.1-51.1). The CBR was 35.3%. In those with PD-L1-negative disease (n = 18), the ORR was 33.3% (95% CI, 14.1-54.6) and the CBR was 44.4%. The 1 CR in the study was seen in a group of 4 patients with unavailable PD-L1 status. The response rates were the similar between those who were PD-L1-positive and those who were PD-L1-negative. (http://www.onclive.com/conference-coverage/sabcs-2016/pembrolizumab-eribulin-combo-shows-promise-for-tnbc#sthash.Hiv20SDD.dpuf)

In this proposed phase 1b study we would like to evaluate the safety and efficacy of combining Avelumab with Eribulin mesylate in mUCC in cisplatin ineligible and platinum resistant mUCC patients. Since we are using eribulin to enhance the immunogenic response, we believe that it can be used at a dosage frequency, similar to avelumab, q2 weekly. The standard dose of eribulin (1.4mg/m^2 days 1, 8 every 21 days) has been compared to biweekly regimen in a multicenter phase 2 study in metastatic breast cancer patients. The clinical benefit ratio was 31% in biweekly arm vs. 21.1% in standard scheduling arm and no serious events were reported in either arms [40]. An additonal biweekly study conducted in the US (NCT02481050) has been completed and is pending data presentation at SABCS 2017.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

1. MTD cohort: To estimate the safety of combining Eribulin mesylate with Avelumab
2. Expansion cohort: To assess the response rates (Complete Response [CR]+Partial Response [PR]).

2.1.2 Secondary Objectives

1. To estimate the DCR (CR+PR+Stable Disease [SD]) at 3, 6, and 12 months
2. To estimate Progression Free Survival (PFS) rate at 12 months
3. To estimate Overall Survival (OS) rate at 12 months
4. To estimate the median PFS.
5. To estimate the median OS
6. To assess the duration of response

2.1.3 Correlative/Exploratory Objectives

1. To explore the correlation between expression of PD-L1 by IHC in tumor and tumor infiltrating cells at baseline and after exposure to 2 doses of Eribulin mesylate. Biopsy would done after 2 doses for expansion cohort.
2. To explore the correlation between PD-L1 expressions by IHC in tumor and tumor infiltrating cells with response rates.

3. To explore the correlation between PD-1 expression on T-cells in peripheral blood with exposure to Eribulin mesylate x 2 doses. (PBMC to be drawn at baseline and again after 2 doses of Eribulin mesylate)
4. To explore other immune markers in the blood and markers in tumor that correlate with response- such as gamma interferon in plasma, immune markers- interleukins, T-regs and mutational sequencing on tumor, tumor mutational burden.
5. To explore the correlation of urine based biomarkers with clinical outcome.

2.2 Endpoints

2.2.1 Primary Endpoint

- *To assess the safety of combining avelumab with Eribulin mesylate in that DLT (dose limiting toxicity) rate is lower than than 33%.*
- *To assess the response rates (Complete Response [CR]+Partial Response [PR]) to treatment by modified RECIST 1.1. CR or PR would need to be confirmed on subsequent imaging*

2.2.2 Secondary Endpoints

- *To estimate the DCR (CR+PR+Stable Disease [SD]) at 3, 6 and 12 months.* DCR will be defined for this study as rates of patients achieving CR, PR or SD post completion of Eribulin mesylate+Avelumab at 6 months and at 12 months. Response will be determined by modified RECIST 1.1.
- *To estimate Progression Free Survival (PFS) rate at 12 months.* Progression free survival rate at 12 months is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 at 12 months from the start of treatment, D1 of Eribulin mesylate+Avelumab.
- *Estimate the OS rate at 12months.* OS is defined as time from start of treatment, D1, to the date of death due to any cause.
- *Estimate the median PFS.* PFS is defined as a measurement from the date of initiation of avelumab+ eribulin, D1 until the criteria for disease progression is met as defined by modified RECIST 1.1
- Estimate the median OS.
- *To assess the duration of response.* Duration of response is defined as the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0-2 at the time of enrollment.
4. Life expectancy of >12 weeks.
5. Stage IV patients with either locally advanced node positive or metastatic-M1 urothelial cancer of bladder and upper tract. Patients with local or distant recurrence of disease after definitive standard therapy (radiation OR surgery) are also eligible.
6. Histologically proven (pure or mixed) urothelial carcinoma of bladder or upper tract with any percentage of transitional cell component. Adenocarcinoma, squamous cell differentiation, or other atypical histology (such as plasmacytoid or sarcomotoid) will be allowed on the study; small cell histology will be excluded.
7. Presence of measurable disease per RECIST v1.1 for solid tumors.
8. Patients must be treatment naïve AND cisplatin ineligible OR must be platinum resistant.
9. Patients who are treatment naïve must be cisplatin ineligible, defined by the presence of one or more of the following:
   a. Impaired renal function (GFR ≥ 30 but ≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation.
   b. Grade ≥ 2 hearing loss (hearing loss measured by audiometry of 25 dB at two contiguous frequencies)
   c. Grade ≥ 2 peripheral neuropathy (Please note that for enrollment on this trial patients must have peripheral neuropathy grade 2 or lower)
   d. ECOG Performance Status of 2
   e. NYHA Class III-IV CHF (Please note that for enrollment on this trial patients must have Ejection Fraction of >35% measured on ECHO or MUGA)
10. For treatment naïve patients: Patients must be treatment naïve for metastatic disease. Use of chemotherapy in neoadjuvant or adjuvant form is allowed provided the time period between last dose of treatment and enrollment is >12 months and subjects must have recovered from all reversible toxic effects of the regimen (other than alopecia) to ≤Grade 1 or baseline.
11. For platinum resistant patients: Patients must have progressed during or within 12 months after completing a cisplatin OR carboplatin based chemotherapy regimen. In addition, subjects must have recovered from all reversible toxic effects of the regimen (other than alopecia) to ≤Grade 1 or baseline. Patients who become intolerant to platinum based chemotherapy could also be enrolled on the study provided they have had no clinical response to platinum therapy.

12. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to study registration.

System	Laboratory Value
Hematological	
Platelet	≥ 100K/mm^3
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Renal	
Calculated creatinine clearance • ≥ 30 cc/min using the Cockcroft-Gault formula (Cockcroft and Gault 1976) • or by equivalent criteria such as measured GFR by hospital's laboratory • or by 24-hour urine collection for determination of creatinine clearance: **Males:** Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) **Females:** Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) x 0.85	
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5× ULN for patients who are not on any anticoagulants. • Patients who are on warfarin would require switching to either a short acting anticoagulant such as oral apixaban or lovenox injection. Prior to entry on the trial their INR should be <2.0. • Patients who are not medically able to switch (ex. artificial heart valve) may remain on their current regimen if the INR is stable and there is no concern for active ongoing bleeding. • Patients who are already on short acting anticoagulants would be allowed to enroll on the study provided their INR <2.0.

13. Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.
14. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use a highly effective method of contraception from the time of informed consent until 90 days after treatment discontinuation.

15. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.
16. Availability of baseline tumor tissue (fresh biopsy or archival) prior to enrollment on the clinical trial. TURBT specimens are preferred but tissue from lymph node or visceral areas are also acceptable. If archival tissue is not available, the subject must be willing to consent to a fresh biopsy for research prior to registration for protocol therapy. If archival tissue is not available and there are no sites amenable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis.
17. Palliative radiation therapy prior to or during the treatment is allowed if indicated. However, if prior to start of treatment, radiation therapy must complete at least 7 days prior to cycle 1 day 1 of treatment.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Participation in another clinical study with an investigational product within 2 weeks prior to registration.
2. Any previous treatment with a PD1 or PD-L1 inhibitor, including Avelumab.
3. Previous systemic immunotherapy. Previous use of intravesical BCG is acceptable.
4. Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen are not eligible for this trial.
5. Receipt of the last dose of anti-cancer therapy (chemotherapy, tumor embolization, monoclonal antibodies, investigational agents) for local recurrence or metastatic disease within 14 days prior to study registration and within 4 weeks for intravesical BCG or mitomycin C.
6. Mean QT interval corrected for heart rate (QTc) ≥470 ms on electrocardiogram (ECG) using Fridericia's Correction.
7. Current or prior use of immunosuppressive medication within 28 days before study registration, with the exceptions of: a) intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection) b) systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid, c) steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
8. Any unresolved toxicity (≥CTCAE grade 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss). Alopecia, sensory neuropathy grade ≤ 2, or other grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
9. Active or prior documented autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. NOTE: Subjects with diabetes type I, vitiligo, hypo- or hyperthyroid diseases, or psoriasis not requiring immunosuppressive systemic treatment are eligible. Patients with a history of completely resolved childhood asthma or atopy are also eligible.
10. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
11. History of and/or confirmed pneumonitis.
12. History of primary immunodeficiency.

13. History of organ transplantation including allogeneic stem-cell transplant.
14. History of hypersensitivity to Avelumab or Eribulin mesylate, including known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3).
15. Uncontrolled intercurrent illness including, but not limited to:
    a. ongoing or active infection requiring systemic therapy
    b. active peptic ulcer disease or gastritis, or active bleeding diatheses,
    c. psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
16. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. Patients who are worse than class 2B are not eligible for this trial (must be class 2B or better).
17. Any subject known to have evidence of acute or chronic hepatitis B (positive HBV surface antigen), hepatitis C (perform HCV RNA if anti-HCV antibody screening test positive), or human immunodeficiency virus (HIV). Note: testing will be performed if applicable per physician discretion. The following exceptions will apply:
    a. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
    b. Subjects with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
    c. HIV-infected subjects on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
18. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of starting treatment with Avelumab. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
19. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control. For this study male or female patients of reproductive potential need to employ highly effective and acceptable forms of contraception throughout their participation in the study and for 90 days after last dose of study drug.
20. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
21. Brain metastases or history of leptomeningeal carcinomatosis.
22. Subjects with uncontrolled seizures.

4. SUBJECT REGISTRATION

All subjects must be registered through BTCRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an On Study date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within 7 days of registration.

Subjects who do not begin study treatment: If a subject signs consent, is registered to the study, and later is not able to begin the planned study treatment, for whatever reason, the subject will be considered a screen failure and will be replaced. The reason for removal from study will be clearly indicated in EDC system. The subject will then be treated off study, per physician's discretion.

Subjects who are incorrectly enrolled but have not initiated treatment should be withdrawn from the study and will be labeled as screen failure.

Subjects who have been enrolled in error and have initiated treatment should be discussed with the sponsor-investigator. It will be at the discretion of sponsor-investigator to decide about the safety of continuing treatment for that patient. If the sponsor-investigator decides to exclude the patient from the study, that subject will not be counted for any statistical analyses. Please note that these subjects must be excluded from the phase I study analyses and treatment on the clinical trial should be discontinued.

5. TREATMENT PLAN

This is a single arm, open-label phase Ib study of combining eribulin mesylate with avelumab. The initial 9-12 patients (MTD cohort) will be enrolled to determine safety of avelumab in combination with eribulin mesylate. Upon determination of maximum tolerated dose (MTD), 12 additional patients will be enrolled in an expansion cohort (efficacy cohort) to assess response rates (CR +PR).

5.1 Dose Escalation Plan

A standard "3+3" design will be used to determine the MTD of eribulin with avelumab.

- Three subjects will be enrolled at dose level 0. If none of the 3 subjects experience a dose limiting toxicity (DLT) during the first cycle of therapy, an additional 3 subjects will be enrolled at dose level +1. If all three subjects in dose level+1 complete the first cycle of therapy without DLT, 3 more subjects will be enrolled to ensure only 0-1 of 6 subjects have a DLT. There will be no further escalation beyond dose level+1.
- Alternatively, if 1 of the first 3 subjects experiences a DLT at the dose level 0, the cohort will be expanded to 6 subjects. If only 1 of the total 6 subjects in a dose level 0 experience a DLT, the study will proceed to dose level+1 as described above.
- If there are 2 DLTs experienced during first cycle of therapy at dose level +1, the eribulin dose will be de-escalated to dose level 0. Dose level 0 will then be expanded to 6 subjects (if applicable). If there were previously 2 DLTs experienced during the first cycle of therapy at dose level 0, the dose of eribulin will be de-escalated to dose level-1. Three subjects will be enrolled at dose level -1 and if none experience any DLT, additional 3 subjects will be enrolled to ensure no more than 0-1 of 6 subjects experience DLTs. This dose would be considered the MTD for this combination. However, if there are 2 or more DLTs at dose level -1, the combination will be considered unsafe for further development.

The maximum tolerated dose is the dose of eribulin combined with avelumab with dose limiting toxicity of 0-1 of 6 patients in the first cycle of combination therapy. After the MTD has been determined, an additional 12 patients will be enrolled in an expansion cohort at the MTD to evaluate the efficacy of this

combination. Please see table of the dose cohorts below.

Dose Cohort	N	Eribulin mesylate	Avelumab	Cycle Length
-1	3-6	0.7mg/m^2 on days 1, 15	10mg/kg on days 1, 15	28 days
0: Starting cohort	3-6	1.1mg/m^2 on days 1,15	10mg/kg on days 1, 15	28 days
+1	3-6	1.4mg/m^2 on days 1,15	10mg/kg on days 1, 15	28 days

N=number of patients

5.2 Definition of Dose Limiting Toxicity

A DLT is defined as an adverse event or clinically significant abnormal laboratory value listed in the table below assessed as, at minimum, possibly related to study drug(s), and unrelated to disease, disease progression, inter- current illness, or concomitant medications that occurs within the first 28 days of treatment with the combination of eribulin and avelumab. NCI CTCAE version 4 should be used for all toxicity grading.

Toxicity	Criteria for DLT graded by NCI CTCAE version 4
Hematological	• Grade 4 febrile neutropenia • Grade 4 or greater thrombocytopenia on day of eribulin infusion. • Grade 3 or greater thrombocytopenia with significant hemorrhage of any duration. • Anemia, thrombocytopenia, or neutropenia of any grade which causes a treatment delay of > 2 weeks.
Cardiac	• Cardiac toxicity ≥ grade 3 • Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or troponin ≥ grade 3
Hepatobiliary	• Grade ≥2 total bilirubin for more than 7 consecutive days in absence of Gilbert's syndrome[1] • For subjects **without** baseline AST/ALT elevation: Grade ≥3 ALT or AST[3] • For subjects **with** baseline AST/ALT elevation due to disease: >5 × increase of ALT or AST from baseline[3] • For subjects **without** baseline ALP elevation: Grade 4 serum alkaline phosphatase >7 consecutive days[3] • For subjects **with** baseline ALP elevation: >20 × increase from baseline of serum alkaline phosphatase >7 consecutive days[3]
Gastrointestinal	• Grade ≥ 3 vomiting ≥72 hours despite optimal anti-emetic therapy per standard of care or institutional guidelines • Grade ≥ 3 diarrhea ≥48 hours despite optimal anti-diarrhea treatment
Renal	• Grade ≥3 serum creatinine
Fatigue	• Grade 3 fatigue lasting > 14 days
Immune related AEs[2]	• Grade 4 irAE[2] • Grade ≥3 colitis • Grade ≥2 immune-mediated neurotoxicity. • Grade 3 non-infectious pneumonitis irrespective of duration

	• Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days • For subjects **without** baseline transaminase elevation: Grade 3 liver transaminase elevation with concurrent total bilirubin > 2 × ULN for >4 consecutive days. • For subjects **with** baseline transaminase elevation: >5 × increase from baseline liver transaminase value with concurrent total bilirubin > 2 × ULN for >4 consecutive days. • Grade ≥2 immune-mediated cardiotoxicity
[1] For Gilbert's syndrome a direct bilirubin will be measured; [2]Immune-related AEs (irAE) are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. [3] In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. In addition, if the asymptomatic rise in ALT and AST or ALP is thought to be due to Neulasta then that would not be counted as DLT.	

In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Please also note that since Eribulin is a chemotherapy- myelosuppression and neutropenic fever are known side effects thus not all grade 3 or more are being counted as DLT. However all adverse events/ serious adverse events due to eribulin would be captured in the EDC system.

DLTs will be counted based on the number of subjects with a DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event. Additional subject cohorts will not be enrolled at the next dose level until all subjects at the initial dose level complete all planned treatment for 1st cycle of combined eribulin and avelumab and are able to start cycle 2 with no more than a 2-week delay. Intra-subject dose escalation is not permitted.

After determination of MTD for eribulin mesylate, an additional 12 patients will be enrolled on the expansion cohort. Subjects on the expansion cohort will be assessed for adverse events but will not be assessed for DLTs.

Total number of subjects enrolled will be 24.

5.3 Pre-medication and Hydration

5.3.1 Eribulin Mesylate Pre-medication

Premedication with odanseteron 8 mg (or an alternative such as Compazine 10mg) oral 30 minutes prior to administration of eribulin mesylate is recommended.

5.3.2 Avelumab Pre-medication

Premedication with an antihistamine along with acetaminophen is mandatory 30 to 60 minutes (± 10 min) prior to the first 4 infusions of avelumab (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

5.3.3 Other Premedication and Hydration

Other premedication and hydration prior to avelumab and eribulin mesylate will be administered according to institutional standards, per treating physician discretion. Stronger antiemetics such as fosprepitant, granisetron, palanosetron etc. are allowed if clinically indicated, per physician discretion. Steroids should not be given as a premedication.

5.4 Eribulin mesylate Administration

Eribulin mesylate is given as an IV push over 2 to 5 minutes or per local practice. Eribulin mesylate will be administered *prior to* avelumab.

5.5 Avelumab Administration

Avelumab is administered as a 1-hour iv infusion (± 10 min), diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. Avelumab will be administered 1 hour (± 10 min) *after* completion of eribulin mesylate and observed for 30 minutes after the avelumab infusion for potential infusion-related reactions. The pre/post avelumab observation times may be increased, based on clinical judgement, without incurring a deviation.

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Eribulin mesylate (1st)	**Level -1**: 0.7mg/m^2	IV push	Days 1 and 15	28 days
	Level 0 (start): 1.1mg/m^2			
	Level +1: 1.4mg/m^2			
Avelumab (2nd)[3]	10mg/kg (fixed dosing)	Intravenously (IV) over 1 hour **after** completion of Eribulin mesylate	Days 1 and 15	28 days

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] A window of +/- 3 working days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[3] Patient must be observed for 30 minutes after each avelumab infusion for potential infusion-related reactions.

5.6 Concomitant Medications

5.6.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Investigators may prescribe other concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" in section 5.3.2. In addition, blood and platelet transfusions are allowed per standard of care. Palliative radiation therapy is allowed prior to or during the course of treatment per physician discretion.

Best supportive care (including antibiotics, nutritional support, growth factor support (except if the patient is undergoing palliative RT), correction of metabolic disorders, optimal symptom control, and pain management [including palliative surgery, etc.]) should be given when necessary to the patients.

Concomitant use of bisphosphonates- such as zoledronic acid or use denosumab along with calcium and vitamin D is permitted.

Concomitant use of short acting anticoagulation treatment such as apixaban, rivoroxaban, fondaparinux or lovenox is permitted during the course of treatment.

5.6.2 Prohibited Concomitant Medications

Avelumab is not expected to have drug- drug interactions (DDI) with other drugs because it is primarily metabolized through catabolic pathways and is not expected to affect the expression of CYP450 enzymes.

The following medications are prohibited during treatment.

1. Any concurrent chemotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable by local surgery.
2. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related adverse events or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for select indications, at the discretion of the sponsor-investigator (e.g., asthma, chronic obstructive pulmonary disease, radiation, nausea, etc. a temporary course of steroid up to a maximum of 1mg/d for 7 days will be allowed). Topical steroids are not contraindicated.
3. Live attenuated vaccines within 30 days of treatment (ie, 30 days prior to the first dose), during treatment with avelumab and eribulin mesylate and for 30 days post discontinuation of treatment. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

5.7 Supportive Care

Best supportive care (including antibiotics, nutritional support, growth factor support (except if the patient is undergoing palliative RT), correction of metabolic disorders, optimal symptom control, and pain management [including palliative surgery, etc]) should be given when necessary to the patients.

For toxicities associated with eribulin mesylate or avelumab that require symptomatic management, e.g., diarrhea, HFSR, pneumonitis etc. please refer to standard guidelines for management of symptoms and section 6.2.2.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, both treatments may be delayed ≤ 2 weeks from the expected day of the next treatment for any reason. If treatment is delayed ≤ 2 weeks, subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below.

Subjects who are initially treated with eribulin mesylate and avelumab can remain on 1 or both study drugs in the presence of clinical benefit until intercurrent illness, unacceptable toxicity, or disease progression occurs, or until the subject withdraws consent.

In the event of an adverse event leading to treatment interruption or delay of either study drug, the subject may continue treatment with the other study drug, as long as there is a clinical benefit.

Please note that any dosing interruption may increase the duration of cycle if both drugs are held. If only 1 drug is held, the cycle duration will not be increased and will continue as usual. For example, if both drugs are given continuously from D1 of each cycle, and if both treatments are held on D15 of Cycle 3 for toxicity, and resumed a week later, then that day will be recorded as C3D15. However, if only one drug, e.g., eribulin mesylate is held on D15, treatment with other drug will continue and then the dose for D15 of the eribulin mesylate will be considered as "skipped dose" and subject will resume treatment with eribulin mesylate at the next scheduled dose as usual.

6.2 Dose Levels for Dose Reductions

6.2.1 Eribulin mesylate dose modification during treatment

Eribulin mesylate's dose may need to be delayed and reduced during the course of treatment on the study. Dose interruption and dose reduction instructions for subjects who experience eribulin mesylate mesylate toxicity is listed in the table below.

<u>Recommended dose delays:</u>
Do not administer eribulin mesylate on Day 1 or Day 15 for any of the following:

1. Absolute neutrophil count (ANC) <1,000/mm^3
2. Platelets<75,000/mm^3
3. Grade 3 or 4 non-hematological toxicities

- Eribulin mesylate Day 1 dose may be delayed for a maximum of 2 weeks in an event when both drugs are being held. However, if only eribulin mesylate is delayed on Day 1, skip the dose and resume the dosing on D15.
- If toxicities do not resolve or improve to ≤ Grade 2 severity by D15, omit the dose.
- If toxicities resolve or improve to ≤Grade 2 severities by Day 15, administer eribulin mesylate at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

- Use of pegfilgrastim or filgrastim is permitted per physician discretion

Recommended dose reductions: If a dose has been delayed for toxicity and toxicities have recovered to ≤Grade 2 severities, resume eribulin mesylate at a reduced dose shown in table below. Do not re-escalate the eribulin mesylate dose after it has been reduced.

Adverse Reaction	***Recommended Dose Modification***
Permanently reduce the 1.4 mg/m^2 eribulin mesylate dose for any of the following: • ANC <500/mm^3 for >7 days • ANC <1,000/mm^3 with fever or infection • Platelets <25,000/mm^3 • Platelets <50,000/mm^3 requiring transfusion • Non-hematologic Grade 3 or 4 toxicities • Omission or delay of Day 15 eribulin mesylate dose in previous cycle for toxicity	Permanently reduce eribulin dose to 1.1 mg/m^2
Permanently reduce dose while receiving 1.1mg/m^2 for any of the following: • ANC <500/mm^3 for >7 days • ANC <1,000/mm^3 with fever or infection • Platelets <25,000/mm^3 • Platelets <50,000/mm^3 requiring transfusion • Non-hematologic Grade 3 or 4 toxicities • Omission or delay of Day 15 eribulin mesylate dose in previous cycle for toxicity	Permanently reduce eribulin dose to 0.7mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2. If unable to administer a scheduled dose of eribulin mesylate for more than 28 days of study, discuss with sponsor-investigator prior to continuing treatment.	Permanently discontinue eribulin mesylate

6.2.2 Avelumab dose modification during treatment

NOTE: There will be no dose reductions for Avelumab. Dose will be omitted for adverse events. Please follow toxicity guidelines listed below.

If toxicities necessitate >2 week treatment delay for both Eribulin and Avelumab combination, treatment will be permanently discontinued and the subject will enter the follow up phase per protocol.

6.2.2.1 Management of Immune-Related Adverse Events (NCI-CTCAE v4)

1. Gastrointestinal irAEs		
Severity of diarrhea/colitis	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline; Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide) .	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2	Withhold avelumab therapy.	If improves to Grade ≤1: Resume

Diarrhea: 4 to 6 stools per day over Baseline; iv fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Symptomatic treatment.	avelumab therapy. If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; iv fluids ≥ 24 h; interfering with ADL. Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation.	Withhold avelumab therapy for Grade 3. Permanently discontinue avelumab therapy for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroid taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis

2. Dermatological irAEs		
Grade of Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids). Continue avelumab therapy.	If Grade 2 persists > 1 to 2 weeks or recurs: Consider skin biopsy. Withhold avelumab therapy. Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroid taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy. Dermatology consult. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month. Resume avelumab therapy following steroids taper (for initial Grade 3).

3. Pulmonary irAEs		
Grade of Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab. Monitor for symptoms every 2 to 3 days. Consider Pulmonary and Infectious Disease consults.	Re-assess at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy. Pulmonary and Infectious Disease consults. Monitor symptoms daily, consider hospitalization. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for	Re-assess every 1 to 3 days If improves: When symptoms return to ≤ Grade 1, taper steroids over at least 1 month and then resume avelumab therapy following steroid taper. If not improving after 2 weeks or

	opportunistic infections. Consider bronchoscopy, lung biopsy.	worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life- threatening	Permanently discontinue avelumab. Hospitalize. Pulmonary and Infectious Disease consults. 10. to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improves to Grade ≤1: Taper steroids over at least 4 weeks. If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

4. Hepatic irAEs		
Grade of Liver Test Elevation	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring, resume avelumab therapy If elevations persist > 5-7 days or worsen : Treat at Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

5. Renal irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroid taper. If worsens: Treat as Grade 4.
Grade 4	Permanently discontinue avelumab.	If returns to Grade ≤1:

Creatinine increased > 6 x ULN	Monitor creatinine daily. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	Taper steroids over at least 1 month.

6. Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule- out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune- mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
*Local guidelines, or eg. ESC or AHA guidelines: ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

7. Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).

	hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

8. Other irAEs (not described above)		
Grade of other irAEs*	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤ 1: Taper steroids over at least 1 month.

	Specialty consult as appropriate.	
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy. Specialty consult.	
* Grade 2 or 3 asymptomatic rise in amylase/lipase- monitor and continue avelumab. Start of steroids per physician discretion for symptomatic patients, if there is suspicion for pancreatitis. Grade 4 rise in amylase or lipase- withhold treatment till it decreases to <=grade 2 or baseline. Treatment including use of steroids per physician discretion.		

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

6.2.2.2 Management of Avelumab Infusion-Related Reactions

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Management of infusion-related reactions should follow guidelines set forth in table below. In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) is mandatory prior to each dose of avelumab. Please refer to the clinical trial protocol for detailed guidance.

Table for Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening • The total infusion time for avelumab should not exceed 120 minutes
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 h	• Stop avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects must be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

iv: intravenous; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline for the subsequent infusions based on investigator's medical judgment. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from avelumab treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

6.2.2.3 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the

Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the investigator immediately.

A. Symptoms

- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

B. Management

- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert intensive care unit for possible transfer if required. For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab iv infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the investigator.

6.2.2.4 Tumor Lysis Syndrome

Since avelumab can induce ADCC, there is a theoretical risk of tumor lysis syndrome. Should this occur, subjects should be treated as per local guidelines and the management algorithm.

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If both therapies on the protocol are interrupted for ≥ 28 days.

6.4 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 28 days[2]	Screening	Treatment Cycle 1				Cycle 2+		Safety follow up	Long-term Follow up[5]
	-28 days[1]	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	30 days[2,4] post last dose	Q2 mos (±14)
REQUIRED ASSESSMENTS									
Consent, Medical hx, smoking hx, Dx and Staging[6]	X								
Physical exam, vital signs, ECOG PS[7]	X	X		X		X	X	X	
EKG and Echo (or MUGA. See 7.1.1)	X								
AEs & concomitant medications	X	X		X		X		X	X[4]
LABORATORY ASSESSMENTS									
Complete Blood Cell Count with diff (CBC)	X	X[8]	X[18]	X	X[18]	X	X	X	
Comprehensive Metabolic Profile (CMP)[9]	X	X[8]	X[18]	X	X[18]	X	X	X	
Mg, Phos, Uric Acid, LDH[9]	X	X[8]		X		X[9]	X	X	
Amylase, Lipase, GGT[9]	X	X[8]				X		X	
PT/INR and aPTT	X					Every odd[3]			
Thyroid Function (TSH, T3, T4)	X	X				Every odd[3]		X	
Pregnancy test (serum or urine) WOCBP	-7d[10]					X			
Urinalysis	X								
Hepatitis serologies, HIV screening, if applicable[17]	X								
DISEASE ASSESSMENT[11]									
Prior PD-L1 and/or genetic results, if available		X							
CT of chest; CT or MRI of abdomen and pelvis	X					Every odd[3]			X[5]
CT or MRI Brain[11]	X								
Bone/PET Scan [11]	X					Every odd[3,11]			X[5]
TREATMENT EXPOSURE									
Eribulin mesylate		X		X		X	X		
Avelumab		X		X		X	X		
CORRELATIVE STUDIES (SPECIMEN COLLECTION)									
Archival/fresh tumor tissue[12]	X					Pre C2[12]			
Blood for biomarker research[13]		X				Pre C2		X	
Urine for biomarker research[13]		X				Pre C2		X	
BANKING SAMPLES (SPECIMEN COLLECTION)									
Whole Blood[14]		X							
Unstained Slides from Tumor Block[15] (if available)		X							
Serum and Plasma[16]		X						X	
FOLLOW-UP									
Survival status, subsequent therapy									X

Key to Footnotes

1: If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.
2: A window of ±2 days will be applied to all treatment study visits; for safety follow-up visit and tumor imaging, a ±7-day window will apply. Informed consent may be obtained outside the 28-day screening window however, consent still must be obtained prior to performing any study-specific procedures.
3: To be performed every odd numbered cycle until progression, starting with cycle 3.
4: A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. irAEs and SAEs will be collected for 90 days after the end of treatment. See Section 11.2.
5: Subjects without documented disease progression who come off treatment due to other reasons will be followed for disease progression every 2 months for 2 years. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 2 years from the time of documented progression.
6: Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging.
7: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status
8: If CBC, CMP, Mag, Phos, Uric acid, LDH, amylase, lipase, GGT are done within 7 days prior to Cycle 1 Day1, it does not need repeating
9: CMP to include: albumin, alk phos, AST, ALT, amylase, bicarb, calcium, chloride, creatinine, GGT, glucose, LDH, lipase, magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen (depending on local practice), uric acid. If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin. GGT at baseline and as clinically indicated thereafter.
10: For women of childbearing potential (WOCBP): urine or serum βhCG, within 7 days prior to study registration and Day 1 of each cycle, starting with Cycle 2. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11: Tumor response assessment will be performed every odd numbered cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator. Baseline bone scan will be obtained if there is any suspicion of metastatic bone involvement. If bone scan is positive at baseline, it will be included with subsequent tumor response assessments as noted above. CT or MRI of brain should be performed at screening to evaluate for the presence of brain metastases if deemed necessary by the treating physician per standard of care. RECIST 1.1 measurements for evaluation of disease response must be captured at baseline and after every follow up imaging. PET CT is acceptable at baseline, but CT is preferred. Follow up PET imaging is not needed for the study. It could be done if deemed necessary by the treating oncologist.
12: Mandatory baseline fixed paraffin-embedded blocks/slides must be available prior to enrollment (fresh biopsy or archival). For the expansion cohort, optional fresh tumor tissue to be requested after C1, prior to C2D1.
13: Serial blood and urine samples will be collected to support biomarker research. See CLM for additional details.
14: Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.
15: Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.
16: Serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.
17: Hepatitis serologies and HIV serology if applicable per physician discretion to include: Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.
18: Only perform for MTD cohort during 1st cycle

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

Screening procedures will be performed up to 28 days before registration, unless otherwise specified. All subjects must sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history to include demographics, tobacco and alcohol use, prior treatments, and surgical history
- Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging
- Complete physical exam.
- ECOG Performance Status
- Vitals signs to include temperature, blood pressure, pulse rate, respiratory rate
- Weight and height
- 12-lead ECG.
- Echocardiogram or MUGA. If subject has a standard of care MUGA performed during the screening period, MUGA results will be used. An echocardiogram will be performed in all other circumstances.
- Baseline signs and symptoms
- Concomitant medications
- Complete blood count with differential (CBC): to include basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, total white cell count.
- Comprehensive metabolic panel (CMP): to include albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen (depending on local practice), uric acid. If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin. GGT at baseline and as clinically indicated thereafter.
- Thyroid stimulating hormone. T3 and/or T4 (free or total) will be measured per local practice if TSH is abnormal.
- [Within 7 days prior to registration] Urine hCG or serum βhCG pregnancy test for women of childbearing potential (WOCBP)
- Urinalysis: to include bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.
- Hepatitis serologies and HIV: if applicable, per physician discretion. Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, HIV antibody.

- Coagulation panel: to include prothrombin time (PT), aPTT and INR.
  CT chest, abdomen and pelvis with contrast (contrast is preferred but patients with contraindication for contrast may have non-contrast imaging); urogram at baseline if possible; MRI abdomen and pelvis are acceptable instead of CT abd/pelvis. Baseline bone scan will be obtained if there is any suspicion of metastatic bone involvement. If bone scan is positive at baseline, it will be included with subsequent tumor response assessments as noted above. CT or MRI of brain should be performed at screening if deemed necessary by the treating physician per standard of care.

  Correlative studies:
- Tumor biopsy specimen from recent TURBT (preferred) or LN core biopsy is needed. Tissue block is preferred, if available. An alternative is to submit at least 7-12 FFPE slides with tumor specimen.

7.2 On Treatment Evaluations

Each cycle of treatment with avelumab+eribulin mesylate is days 1, 15 every 28 days or 4 weekly. Cycle 1 details are listed below. For subsequent cycles, patients will be seen in clinic on days 1, 15 with labs as listed above in the calendar.

7.2.1 Cycle 1 Day 1

Note: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- If prior PD-L1/NGS results are available, they should be submitted by Cycle 1 Day 1.
- Physical exam and ECOG PS
- Vital signs: blood pressure and pulse rate will be measured prior to infusion
- Weight (repeat measurement of height is not required if done during screening)
- Adverse events; concomitant medications
- CBC with differential
- CMP
- Magnesium, phosphorus, uric acid, LDH, amylase, lipase. GGT if clinically indicated.
- Thyroid stimulating hormone. T3 and/or T4 (free or total) will be measured per local practice if TSH is abnormal.
- Urinalysis to be repeated only if clinically indicated (It will be done during the screening phase)
- Eribulin mesylate infusion
- Avelumab infusion
- Correlative and Banking samples. See Correlative Laboratory Manual for specific instructions.

7.2.2 Cycle 1 Day 8, 22 only for cohort#1 for MTD

- CBC with differential
- CMP
- Magnesium, phosphorus, uric acid, LDH. GGT if clinically indicated.

7.2.3 Cycle 1 Day 15

- Physical exam and ECOG PS
- Vital signs: blood pressure and pulse rate will be measured prior to infusion
- Weight
- Adverse events; concomitant medications

- CBC with differential
- CMP
- Magnesium, phosphorus, uric acid, LDH. GGT if clinically indicated.
- Urinalysis to be repeated only if clinically indicated (It will be done during the screening phase)
- Eribulin mesylate infusion
- Avelumab infusion
- Correlative collection of whole blood: Cycle 1 Day 1 , Cycle 2 Day 1 and 30 days post discontinuation of study. See Correlative Laboratory Manual for specific instructions.

7.2.4 Day 1 of every cycle starting with Cycle 2

- Physical exam and ECOG PS
- Vital signs: blood pressure and pulse rate will be measured prior to infusion
- Adverse events; concomitant medications
- CBC with differential
- CMP
- Magnesium, phosphorus, uric acid, LDH, amylase, lipase. GGT if clinically indicated.
- Urine hCG or serum βhCG pregnancy test for women of childbearing potential (WOCBP)
- Eribulin mesylate infusion
- Avelumab infusion

7.2.5 Every Odd Numbered Cycle Day 1 starting with Cycle 3

- Coagulation panel: to include prothrombin time (PT), aPTT and INR.
- TSH. T3 and/or T4 (free or total) will be measured per local practice if TSH is abnormal.
- CT chest, abdomen and pelvis with contrast (contrast is preferred but patients with contraindication for contrast may have non-contrast imaging); MRI abdomen and pelvis are acceptable. Tumor response assessment will be performed every odd numbered cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator. Baseline bone scan will be obtained if there is any suspicion of metastatic bone involvement. If bone scan is positive at baseline, it will be included with subsequent tumor response assessments as noted above.

7.3 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

7.4 Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 2 months for 2 years.

Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 2 years from the time of documented progression. Follow up may be performed either via a site visit or via a telephone call; a site visit will be requested if any concerns are noted during the telephone call.

8. BIOSPECIMEN STUDIES AND PROCEDURES

For correlative research purposes we will be collecting blood and tissue at specific times. We will be testing samples for somatic mutations in tumor and immune markers in tumor tissue and blood. We will be performing these tests in an institutional lab (Dr. Zheng's lab at Penn State Cancer Institute, for peripheral blood) and CLIA certified lab such as Caris Life sciences upon receipt of adequate funding. The descriptions of these are mentioned below.

8.1 PD-L1 testing in tissue

If sufficient archival tissue is not available, fresh tissue should be collected at baseline. If prior PD-L1 results are not available, they should be ordered as standard of care when possible. In addition, tissue for central testing will also be collected. See CLM for collection, labeling, and shipping instructions. Central PD-L1 biomarker analysis will be used for exploring its predictive and prognostic implications. It will not be used for clinical decision-making.

Immunohistochemistry (IHC) will be performed per already established standard, and clinical pathologists will assess all IHC. Correlations amongst IHC scores for PD-L1 in tumor and tumor infiltrating cells at baseline and after 2 doses of eribulin mesylate will be evaluated. We hypothesize that eribulin will increase the PD-L1 expression on tumor and tumor infiltrating cells, thus enhancing killing effect. The association between IHC scores at baseline, post 2 doses of eribulin (expansion cohort) and response to treatment will be evaluated as well.

Sample collection for central PD-L1 testing

- Time: Fresh biopsy at baseline (only if sufficient archival tissue is not available); optional repeat biopsy for expansion cohort after 2 doses of eribulin. In our study, baseline archival sample of tissue by TURBT or LN/ visceral disease is acceptable for PD-L1 testing.
- Samples to be collected via a core needle of 18 gauges or larger or be collected per institutional guidelines. Where institutional practice uses a smaller gauge needle, samples must be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from decalcified bone and fine needle aspirates are not appropriate for PD-L1 analysis.
- Please refer to clinical laboratory manual for further details. If adequate amount of tissue is not available, the case should be discussed with the sponsor investigator prior to enrollment.

8.2 PD-1 and plasma IFN-γ testing in peripheral blood

Peripheral blood will be collected prior to starting treatment on clinical trial, post 2 doses of eribulin.

PD-1: Expression of PD-1 on CD4+ and CD8+ T cells will be assessed by flow cytometry. Correlation between the level of PD-1 expression pre and post 2 doses of eribulin and clinical outcomes will be analyzed.

Time periods include: baseline, post 2 doses of eribulin, i.e. prior to start of Cycle 2 Day 1 and at the 30-Day Safety Follow up visit.

The blood samples need to be shipped on ice (4° C) to Dr. Zheng's lab within 24 hours for processing before saving in liquid nitrogen. See CLM for collection and shipping details.

Study Description
Peripheral blood will be collected at above time periods. Samples will be diluted 1:1 with PBS before separation of peripheral blood mononuclear cells (PBMCs) by density gradient centrifugation. Cells will be frozen and stored in liquid nitrogen. When assays are performed, frozen cells will be thawed and washed in staining buffer. Cells will be then incubated with directly conjugated monoclonal antibodies CD3-APC, CD8-APCcy7, CD4-FITC and PD-1-PE for 30 minutes at 4°C. Flow cytometry will be performed on a BD Fortessa with subsequent analysis using FlowJo Version 8.8.7 software. Analysis will be performed after gating on live singlet cells. Percentage of PD-1 positive cells among CD3+CD4+ and CD3+CD8+ T cells respectively will be evaluated.

Plasma IFN-γ: Plasma obtained from peripheral blood collected (above for PD-1 expression) will also be used to analyze IFN-y. IFN-γ concentration in plasma will be assessed by Bead-based immunoassays. In addition, intracellular IFN-γ release by T cells will be assessed by flow cytometry.

8.3 Mutational Sequencing

If sufficient archival tissue is not available, fresh tissue should be collected at baseline. If prior genetic sequencing results are not available, they should be ordered as standard of care when possible. In addition, tissue for central genetic analyses such as, but not limited to NGS, will also be collected. See CLM for collection, labeling, and shipping instructions. Central genetic analyses will be used for exploring its predictive and prognostic implications. It will not be used for clinical decision-making.

We will use sequencing results of tumors at pretreatment to explore their correlation with clinical outcome. We will explore the correlation between somatic mutational statuses- upregulation of specific mutation/pathway, tumor mutational burden with clinical outcome.

Sample collection for central genetic testing:

- The samples will be collected as stated above for PD-L1 testing. We will use the left over specimen after PD-L1 test on tissue for performing genetic testing such as NGS. Both PD-L1 central testing and central genetic testing will be done at an outside lab, such as Caris Life sciences, upon receipt of funding.

Please refer to Correlative Laboratory Manual (CLM), for specific details on correlative study procedures, handling, preserving, and shipping.

Data centrally obtained during any additional tests- such as immune markers or mutational sequencing will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict genetic risks for diseases that an individual subject does not currently have.

8.4 Urine biomarkers

Urine volume of about 30cc will be collected at baseline, pre cycle 2 and post completion of treatment and it will be stored for further testing.

We will store the urine at baseline for performing NGS (somatic mutation) on urine cell free DNA (ucfDNA) if possible. Additional tests such as urine based immune-markers would also be explored if possible. Please note that this correlative testing will be done only if additional funding is available.

8.5 Storage of Biospecimens

Samples will be stored at Hoosier Cancer Research Network Biorepository. Peripheral blood will be stored at Dr. Zheng's labs. Remaining specimens post completion of above tests will be stored for future research studies.

8.6 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.7 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. HCRN, will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.8 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following [41] [42]:

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

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

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with avelumab and eribulin will continue between the initial assessment of progression and confirmation for progression.

Modification of RECIST as described may discourage the early discontinuation of aveliumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. The efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on modified RECIST 1.1 criteria.

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

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

9.3 Target Lesions

All measurable lesions up to a maximum of 2 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) 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. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 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 (<10 mm short axis)

	Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
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)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.5 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.6 Disease Control Rate:

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.7 Time to Progression:

A measurement from the date treatment until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.8.8 Progression Free Survival

A measurement from the date of start of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.9 Overall Survival
Overall survival is defined by the date of start of treatment to date of death from any cause.

10. DRUG INFORMATION
Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding Avelumab and Eribulin mesylate.

10.1 Avelumab (Bavencio®)
The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1. This drug is currently not approved by FDA. It has shown efficacy in different tumor types including mUCC as mentioned in section 1.2.1.

10.1.1 Supplier/How Supplied
Pfizer will supply avelumab at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation
Please also refer to the prescribing information and/or to Pharmacy Manual if provided by the drug manufacturer for details on the preparation of the drug. Dosing and administration has already been addressed in the Treatment Plan section. Below provides a brief summary of dosing again.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab.

Dose of Avelumab in mg= 10mg x body weight [Kg]

10.1.3 Storage and Stability
Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution be used immediately. If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature or up to 24 hours at 2°C to 8°C.

10.1.4 Handling and Disposal
Please see Avelumab's IB recommended handling as per the drug manufacturer, including any precautions associated with handling.

10.1.5 Dispensing
Avelumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Avelumab should be stored in a secure area according to local

regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

The following contains a brief overview of the known and potential risks that may be possibly associated with the use of Avelumab. While known risk refers to a risk that has been demonstrated to occur in humans, a potential risk refers to a risk that may be anticipated from the pharmacological, toxicological or pharmacokinetic properties. Please refer to the current version of the Investigator's Brochure (IB) for a full list of adverse events.

Safety data from subjects with different tumor types treated with avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in subjects with advanced solid tumors or with similar class effects of mAb blocking the PD-1/PD-L1 axis. The infusion related reactions including drug hypersensitivity reactions and irAEs including immune-mediated pneumonitis, immune- mediated colitis, immune-mediated hepatitis including autoimmune hepatitis, immune- mediated endocrinopathies (thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis, autoimmune thyroiditis, adrenal insufficiency, new onset Type I diabetes mellitus, pituitary disorders), immune mediated nephritis and renal dysfunction, immune-mediated skin reactions (including rash, pruritus, rash generalized, rash pruritic, rash maculo-papular, erythema, pemphigoid), and other immune-mediated reactions including myocarditis, myositis, Guillain-Barré syndrome and uveitis have been identified as important risks for avelumab. Adverse reactions with fatal outcome were reported for immune-mediated hepatitis, immune-mediated pneumonitis and myocarditis. Please refer to section 6.2.2 for details of AEs including infusion related reactions and dose adjustment guidelines.

10.2 Eribulin Mesylate (Halaven®)

Eribulin mesylate is a microtubule inhibitor, which has direct cytotoxic activity. In addition, it is thought to improve tumor blood perfusion through vascular remodeling, which may indirectly contribute to reduced metastasis, invasion, and reversal of EMT in the tumor microenvironment, leading to a normoxic tumor microenvironment. This drug is currently approved for use in metastatic breast cancer.

10.2.1 Supplier/How Supplied

Eribulin mesylate will be provided by Eisai at no charge to subjects participating in this trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Preparation

Please also refer to the prescribing information and/or to Pharmacy Manual, if provided by the drug manufacturer, for details on the preparation of the drug. Dosing and administration has already been addressed in the Treatment Plan section. Below provides a brief summary of dosing again.

Before dose administration, the amount of eribulin mesylate needed for each subject must be calculated in the following manner:

1. Body surface area (BSA) will be calculated using any method that is accepted and customarily used by the investigational site, such as the Mosteller formula (BSA should be recalculated when

weight changes by ≥ 10% according to the Mosteller formula):
BSA (m^2) = ([Height ([cm] × Weight (kg))] / 3600) ^{½}
2. Scheduled dose (mg/m^2) × body surface area (m^2) = Dose (mg)
3. Dose (mg) × 2 = the number of mL of eribulin mesylate to withdraw from vials for administration.

The amount of eribulin mesylate required (as calculated above and in section 5.2) will be withdrawn from the appropriate number of vials into a syringe. This may be administered directly as an intravenous injection over 2 to 5 minutes or diluted in up to 100 mL 0.9% saline for IV infusion over 2 to 5 minutes. No special tubing is required for IV administration of eribulin mesylate.

10.2.3 Storage and Stability

Eribulin mesylate will be supplied to the study sites in glass vials containing 1.0 mg eribulin mesylate in 2.0 mL of clear, colorless, and sterile solution. Study drugs will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drugs are maintained within an established temperature range.

10.2.4 Handling and Disposal

Please see Eribulin mesylate's IB recommended handling as per the drug manufacturer, including any precautions associated with handling.

10.2.5 Dispensing

Eribulin mesylate must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Eribulin mesylate should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.2.6 Adverse Events

The following contains a brief overview of the known and potential risks that may be possibly associated with the use of Eribulin mesylate. While known risk refers to a risk that has been demonstrated to occur in humans, a potential risk refers to a risk that may be anticipated from the pharmacological, toxicological or pharmacokinetic properties. Please refer to the current version of the Investigator's Brochure (IB) for a full list of adverse events.

Eribulin mesylate is a cytotoxic chemotherapy and can cause neutropenia, anemia, thrombocytopenia, asthenia, alopecia, peripheral neuropathy, nausea, vomiting, anorexia, weight loss, diarrhea, constipation, cough, arthralgia/myalgia, headaches, pyrexia, urinary tract infection. Rare AEs include stomatitis, insomnia, depression, rash, stomatitis, xerostomia, dizziness, and muscle spasms. For details please refer to current IB. The details of possible AEs from eribulin mesylate needing dose delay or adjustments have been described in sections 6.2.1.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as 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)
- Requires inpatient hospitalization or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
    - Exposure during pregnancy or breastfeeding (even if not associated with an adverse event)
    - Occupational exposure (even if not associated with an adverse event)
    - Potential drug-induced liver injury (Hy's Law cases)

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed

consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Transient asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to BTCRC Administrative Headquarters

- SAEs will be recorded from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs that meet any of the following criteria will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
  - death

- a non-fatal SAE that occurs during the reporting period and that is assessed by the Principal Investigator as both at least possibly related to Avelumab and unexpected for Avelumab OR at least possibly related to Eribulin Mesylate
- an SAE assessed by the Principal Investigator as related to Avelumab that occurs after the SAE reporting period
- an otherwise reportable event such as exposure during pregnancy, exposure during lactation, or occupational exposure.

The site will submit the completed SAE Submission Form (see Documents/Info tab in the EDC) to BTCRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to BTCRC AHQ at safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence or fax confirmation sheet must be kept within the study file at the study site.

Once the SAE has resolved, sites must electronically submit a follow up SAE Submission Form within a reasonable timeframe to BTCRC AHQ at safety@hoosiercancer.org.

11.2.2.2 BTCRC AHQ Requirements for Reporting SAEs to Pfizer

Because the Pfizer Product used in this study is a mature marketed product with a well-established safety profile, only SAEs that fit into any of the following categories need to be reported to Pfizer. BTCRC AHQ will report the following SAEs to Pfizer within **24 hours** of receipt of the SAE Reporting Form:

(1) a death, regardless of whether it is considered related to treatment with the Pfizer Product,
(2) a non-fatal SAE that occurs during the reporting period and that is assessed by the Principal Investigator as both related to treatment with the Pfizer Product and unexpected for that Product,
(3) an SAE assessed by the Principal Investigator as related to the Pfizer Product that occurs after the SAE reporting period, or
(4) an otherwise reportable event such as exposure during pregnancy, exposure during lactation, or occupational exposure. An event should be considered "related" to the Pfizer Product if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon a single safety reference document identified by Sponsor Investigator and documented in association with the Study.

Pfizer U.S. Clinical Trial Department: Fax 1-866-997-8322

Follow-up information will be provided to Pfizer as reasonably requested.

11.2.2.3 BTCRC AHQ Requirements for Reporting SAEs to Eisai

BTCRC AHQ will report all serious suspected adverse drug reactions occurring in an individual who has been exposed to the Eisai study drug, and where the Eisai study drug is the suspected product within **1 business day** of receipt of the SAE Reporting Form.

An adverse drug reaction is defined as: A noxious and unintended response to a medicinal product related to any dose. A causal relationship between the medicinal product and the adverse response is at least a reasonable possibility.

Notification should be done by fax or email and sent to:

Eisai Product Safety
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: 1-732-791-1111
Email: ESI_Safety@eisai.com

BTCRC AHQ will notify Eisai immediately of other information of a serious and significant nature of which it becomes aware in the course of conducing the Study that reasonably suggests a change to the safety profile of the Study Drug. Follow-up information will be provided to Eisai as reasonably requested.

11.2.2.4 Sponsor-Investigator Responsibilities

BTCRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.5 BTCRC AHQ Responsibilities for Reporting SAEs to FDA

BTCRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. BTCRC AHQ will cross-reference this submission to Pfizer's (for Avelumab) and Eisai (for eribulin mesylate) parent IND at the time of submission. Additionally, BTCRC AHQ will submit a copy of these documents to both companies at the time of submission to FDA.

BTCRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, BTCRC AHQ will submit a copy of these reports to Pfizer and Eisai at the time of submission to FDA.

11.2.2.6 IND Safety Reports Unrelated to this Trial

Pfizer and Eisai will provide BTCRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. BTCRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. BTCRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from BTCRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a single arm, open-label study phase Ib with extension study of combining Eribulin with Avelumab. There are two components in this study: the dose-finding component (Phase Ib part) will be conducted to determine the safety of combining Eribulin with Avelumab, the efficacy component (the extension cohort) will estimate the 12-month response rate, the DCR, as well as other clinical endpoints (post completion of the proposed treatment).

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

1. The dose-finding component (MTD cohort):
To assess the safety of combining Eribulin with Avelumab in that the DLT would be less than 33.3%. Documenting DLTs during the combined eribulin+avelumab 1st cycle=28 day period. Subjects will be monitored for DLTs for 4-weeks.

2. The efficacy study component (expansion cohort):
To estimate the response rates (CR+ PR) with modified RECIST 1.1.

12.2.2 Definition of Secondary Endpoints

1. *To assess the DCR (CR+PR+SD) at 3, 6 and 12 months*. DCR will be defined for this study as rates of patients achieving CR, PR or SD, on eribulin+avelumab treatment at 3, 6, and 12 months. Response will be determined by modified RECIST 1.1
2. *To estimate Progression Free Survival (PFS) rate at 12 months.* Progression free survival rate at 12 months is defined as the probability that a patient remains free of progression of disease (SD+CR+PR) by modified RECIST 1.1 at 12 months from the start of treatment, D1 of eribulin mesylate+avelumab.
3. *Estimate the OS rate at 12months.* OS is defined as time from start of treatment, D1, to the date of death due to any cause.
4. *Estimate the median PFS.* PFS is defined as a measurement from the date of initiation of avelumab+ eribulin, D1 until the criteria for disease progression is met as defined by modified RECIST 1.1
5. Estimate the median OS.
6. *To evaluate duration of response.* Duration of response is defined as the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented.

12.3 Sample Size and Accrual

The dose-finding component consists of three dose levels (-1, 0, +1) with the starting dose level at level 0. It requires a maximum of 12 patients. We treat the efficacy-study component of the study as a pilot study so a formal statistical power calculation will not be performed. The main goal of this efficacy study is to generate some initial data for the clinical outcomes and detect the patterns in the results. Then a formal statistical power calculation can be performed. We believe an additional 10 patients for the efficacy-study component should be sufficient to achieve our needs. All patients in the dose-finding stage will be rolled over and combined with the patients in the extension cohort for the evaluation of

efficacy. With a consideration of about 10% patient drop-out rate throughout the study, a total of about 24 patients will be enrolled.

12.4 Analysis Datasets

Patients to be included for analyses in dose-finding component (MTD Cohort):

1. All patients who complete at least 1 cycle of eribulin+avelumab
2. All patients who get at least one dose of avelumab+ eribulin who experience DLTs. However if a patient permanently discontinued the trial due to non-toxicity reasons related to eribulin or avelumab, then that patient will not be included in the dose-finding component analyses.

Patients to be included for analyses in the efficacy study component (Expansion cohort):

Complete response rate analyses: For the complete response rate, the primary endpoint for the efficacy study component, we will include all patients who complete at least 1 cycle of eribulin+avelumab and whose disease response could be determined. Patients who discontinue the trial due to non-disease related or non-toxicity reasons whose disease response cannot be determined during the course of therapy will be excluded from this part of analyses. We will also include roll over patients from the dose-finding component of the study provided they complete the entire course of treatment per protocol.

PFS and OS analyses: We will follow the intent-to-treat principle and therefore will include all patients who are enrolled and completed at least one dose of the treatment. We will also include roll over patients from the dose-finding component of the study. For PFS and OS time, the survival analysis can handle censoring data for those who drop out early for reasons unrelated to disease or toxicity. For those who may drop out for reasons pertaining to disease or toxicity, they will be followed up for an accurate time of disease progression/survival unless patient withdraws consent.

12.5 Assessment of Safety

Any subject who receives at least one dose of treatment on this protocol should be evaluable for toxicity. We will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4, to record toxicity. Please refer back to the Study Calendar for the schedule of toxicity assessment.

12.6 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of complete response, progression free survival, and overall survival. Please refer to section 9 for more details.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

For the dose-finding component of this trial, the incidence and type of DLTs will be tabulated and reported at the dose level. Other toxicity information will be summarized via frequency tables by type and grade of toxicity.

For the efficacy component of the study, the primary endpoints are the response status (CR + PR) at 12 month. It is a binary variable and the analysis is described below in section 12.7.2.

12.7.2 Analysis Plans for Secondary Objectives

Response rate, the primary end point for the expansion cohort is a binary variable. Another binary outcome variable is the Disease Control status (CR+PR+SD) at 3, 6, 12 months. These binary outcomes will be summarized using point estimate values of the relative frequencies and their 95% confidence intervals. Exact binomial tests will be used to compare the response rate and disease control rate from the study sample to the existing values from historical cohorts.

We also have PFS status and OS status at 12 months as our outcome variables. The PFS and OS will be analyzed using the Kaplan–Meier estimator with particular emphasis for 12-month survival rate. The survival (PFS and OS) time will be graphical displayed by the Kaplan-Meier survival curve. The median survival time and its 95% CI will be reported. Another outcome in the secondary objective is the duration of response, which is a continuous variable. It will be summarized using numerical (point estimate and confidence interval of the mean values) and graphical (histogram/boxplot) methods.
The bivariate relationship between the outcome variables and some key clinical and demographic variables, such as tumor stage, visceral involvement (lungs, liver and bone), ECOG status, smoking status, and gender, etc. will be examined by Fisher's exact test, Log-rank test, and ANOVA models when appropriate. For the factors that show marginally significant relationship (for example, $p<0.1$), their relationship with the outcome variable will be reexamined by using some multiple regression methods, such as multiple logistic regression, multiple Cox proportional hazard regression, and multiple linear regression depending on the type of outcome variable. All analyses will be performed using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA). The statistical significance level to be used is 0.05.

12.7.3 Analysis Plans for Exploratory Objectives

For the exploratory objectives, the expression of PD-L1, PD-1, and some other immune markers in the blood and tumor will be compared between baseline and after treatment. Similarly urine biomarkers will also be compared. The comparisons will be made using nonparametric Wilcoxon Signed-rank test for continuous markers and McNemar's test for markers that can be categorized into high/low values. The correlation PD-L1 expression and response rate will be examined using Fisher's exact test.

12.7.4 Subgroup Analyses

Planned subgroup analysis will be done to compare differences in clinical outcome (response rate and PFS rate, as well as PFS and OS time) with tumor stage (T2, T3, T4), lymph node positivity, ECOG PS (0/1 vs. 2), histology (pure urothelial vs. mixed with predominant urothelial component), visceral involvement (lung or liver or bone vs. lymph node). In addition, we will also compare differences in outcome pre and post platinum based therapy cohorts. Please note that due to the exploratory nature of this study, the subgroup analyses are mainly for pattern detection instead of hypotheses testing.

12.7.5 Other Planned Analyses

Descriptive statistics will be used in the study to analyze patient's characteristics and demographics. In particular, patient age, race, weight, ECOG performance status will be described.

12.8 Interim Analysis/Criteria for Stopping Study

Interim analysis will be performed at the discretion of the Data Safety Monitoring Committee to monitor study progress. Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. The reports contain:
a) Patient accrual rate with a projected accrual completion date,
b) Pretreatment characteristics of accrued patients, and
c) Frequency and severity of toxicities.

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (for example complete response rate, disease control rate, and 1-year PFS rate etc.). The Data and Safety Monitoring Committee will review the accrual to the study and the rate of adverse events on the study at least twice per year until the last subject discontinues study drug.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Penn State Hershey Cancer Center's DSMP.

BTCRC AHQ oversight activities include:
- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP

13.2 Penn State Hershey Cancer Center's Data Safety Monitoring Board

The study will undergo review by the Penn State Hershey Cancer Institute Data Safety Monitoring Board.

BTCRC AHQ will provide the Penn State Hershey Cancer Center DSMB with the following:
- Adverse event summary report
- Audit and monitoring results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Penn State Hershey Cancer Center DSMB will review study data semi-annually, beginning approximately 6 months after first subject enrollment until the last subject discontinues study drug. Documentation of DSMC reviews will be provided to sponsor-investigator and BTCRC AHQ. Issues of immediate concern by the DSMB will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with BTCRC AHQ to address the DSMB's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites will be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by BTCRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Pfizer or Eisai or their designees as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to BTCRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

BTCRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through the web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. BTCRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized

representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until BTCRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, BTCRC AHQ, Pfizer, Eisai, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to BTCRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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