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Title of Protocol:
A Phase I/II Trial Combining Avelumab and Trabectedin for Advanced Liposarcoma and Leiomyosarcoma

Sponsor- Investigator:		
Seth Pollack, MD	Associate Member, FHCRC, Assistant Professor of Medicine, UW	(206) 667-6629
Biostatistician:		
Chad He	Assistant Member, FHCRC	(206) 667-7004

Fred Hutchinson Cancer Research Center
1100 Fairview Ave
D3-100
Seattle, WA 98109

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PROTOCOL SYNOPSIS

Protocol Title	A Phase I/II Trial Combining Avelumab and Trabectedin for Advanced Liposarcoma and Leiomyosarcoma
Protocol Number	FH9717
Sponsor-Investigator	Seth Pollack
Funding Source & Collaborator	EMD Serono
Trial Phase	Phase I/II
Trial Type	Single-arm, open label
Clinical Indication	Advanced Leiomyosarcoma and Liposarcoma
Study Design	The study will enroll in two phases. The Phase 1 will evaluate safety and tolerability of the combination with the option for dose escalation or de-escalation. If the combination is found to be well tolerated, Phase 2 will expand enrollment to evaluate efficacy.
Primary Endpoints	• Safety as measured by CTCAE v5.0. • Overall Response Rate (PR + CR, best response for each subject) by RECIST v1.1.
Secondary Endpoints	• Adverse event profile (based on National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v5.0) for all subjects, • Time to response, • Duration of response, • Progression-free survival (PFS) at 12 weeks (based on RECIST 1.1), • Clinical benefit rate (CR+PR+SD) at 12 weeks (based on RECIST 1.1), • Overall survival (OS) at 12 months
Type of control	Historical
Investigational Drug	Avelumab
Dose	800 mg q2wk
Route of administration	IV
Regimen	Avelumab 800 mg (q2wk) + Trabectedin 1.5 mg/m^2 (q4wk)
Expected number of trial subjects	22, with possible expansion up to 34 (6 up to 18 in Phase 1, additional 16 in Phase 2)
Estimated duration of trial	2 years
Duration of Participation	1-2 year (estimated)

ABBREVIATIONS

ADL	Activities of Daily living
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APC	Antigen Presenting Cell
APP	Advanced Practice Provider (Nurse practitioners or physician assistants)
BMP	Basic Metabolic Panel
CBC	Complete Blood Count
CMP	Complete Metabolic Panel
CR	Complete Response
CRF	Case Report Forms
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IFN-g	Interferon Gamma
irAE	Immune-related adverse event
IV	Intravenous
LFT	Liver function test
LLN	Lower limit of normal
mAb	Monoclonal Antibody
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NSAID	Non-steroidal anti-inflammatory drug
OS	Overall Survival
OTC	Over the Counter
PD	Progressive Disease
PD-1	Programed Death Receptor 1
PD-L1 & 2	Programed Death Receptor Ligands 1 & 2
PFS	Progression-free Survival
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SBRT	Stereotactic Body Radiation Therapy
STS	Soft Tissue Sarcoma
T4	Free thyroxine

TSH	Thyroid-Stimulating Hormone
Treg	Regulatory T cell
ULN	Upper limit of normal

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1.0 GENERAL INFORMATION

This is a phase I/II trial combining the PD-L1 inhibitory antibody, avelumab, with trabectedin, an FDA approved and commercially available drug for the treatment of leiomyosarcoma and liposarcoma (sometimes called "L-type" sarcomas). Subjects with advanced "L-type" sarcomas typically have survival in the 12-16 month range.Trabectedin has been proven in a phase III trial to improve the progression-free survival (PFS) from 1.5 months with dacarbazine to 4.2 months with trabectedin. This trial seeks to improve on the efficacy of trabectedin through a novel combination.

Trabectedin was discovered through a high through-put screening process and questions remain regarding its primary mechanism of action in sarcoma. Trabectedin binds to the minor groove of the DNA helix and some of its mechanism may be direct activity preventing tumor replication and through cell-cycle specific toxicity in the tumor. However, trabectedin also clearly has potent killing of tumor associated macrophages (TAM) and this may also be related to its efficacy as these macrophages may play a critical role allowing tumor evasion of immune recognition tumor specific T cells.[1-3] We hypothesize that combining the anti-macrophage activity of trabectedin and the T-cell checkpoint inhibition of avelumab will result in synergistic activity because the activated T cells will be unencumbered by inhibitory TAM activity.

An initial 6 subjects (two groups of 3, up to a possible maximum of 18) will be treated in the Phase 1 portion of the study. Should two mor more dose limiting toxicities (DLTs) be observed, there will be a de-escalation, with potential for re-escalation. The primary objective is to assess the safety and tolerability of the study regimen in subjects with advanced L-type sarcomas, with a primary endpoint of safety as measured by CTCAE v5.0. If the combination is determined to have an acceptable toxicity profile, the trial will expand to a Phase 2 and enroll an additional 16 subjects, to determine an endpoint of response rate.

This document is a clinical research protocol and the described study will be conducted in compliance with the IRB approved protocol, associated Federal regulations and all applicable IRB requirements.

1.1 Protocol Title

A Phase I/II Trial Combining Avelumab and Trabectedin for Advanced Liposarcoma and Leiomyosarcoma

1.2 Sponsor-Investigator Information

Seth Pollack
Fred Hutchinson Cancer Research Center
1100 Fairview Ave D3-100
Seattle, WA 98109

Funding Source: EMD Serono

2.0 BACKGROUND AND RATIONALE

2.1 Introduction to "L-type" sarcomas

Leiomyosarcoma (LMS) and Liposarcoma are among the most common soft-tissue sarcoma (STS) subtypes, together with over 4000 new cases diagnosed annually. LMS is a cancer of smooth muscle which arises in the uterus in approximately 1/3 of cases[4]. The other 2/3 of cases frequently originate from the smooth muscles supporting the vascular architecture and can occur in the extremities, retroperitoneum and skin, as well as other anatomic locations. Surgical resection can be curative for localized disease; however, more than half of subjects with large, high-grade tumors will develop metastatic disease. Liposarcomas are cancers of adipocytic origins and are comprised of three subtypes (pleomorphic, myxoid/round cell and well/de-differentiated). They may occur in the extremities or retroperitoneal region and frequently recur regionally.

Currently, the standard front line therapy for advanced sarcoma is single-agent doxorubicin that has an objective response rate (CR+PR) of 15% and results in a median progression free survival (PFS) of approximately 4.6 months[5-7]. The oral tyrosine kinase inhibitor, pazopanib (Votrient), was approved by the FDA for second line treatment of STS based on an improvement in PFS of 3.2 months was observed compared with placebo[8,9]. The drugs Eribulin and Trabectedin have recently been shown to give subjects several additional months of stable disease.

Although no immunotherapies have yet been incorporated into the standard of care for STS, we at the sarcoma group of the Fred Hutchinson Cancer Research Center have built the most comprehensive sarcoma immunotherapy clinical research program in the world, with active clinical trials evaluating checkpoint inhibitors (anti-PD-1/PD-L1), vaccines, intra-tumoral toll-like receptor agonist injection and adoptive transfer of NY-ESO-1-specific autologous $CD8^+$ T cells all for subjects with STS. Unlike some STS subtypes such as synovial sarcoma, LMS has a highly mutated genome[10] suggesting that it has the potential to respond to immunotherapies that stimulate endogenous T cells[11,12].

2.2 Preliminary Data

LMS tumors are infiltrated by immunosuppressive M2 tumor associated macrophages (TAM)

We and others have found that LMS tumors have brisk $CD11b^+$, $CD68^+$ tumor associated macrophage (TAM) populations. Macrophages can be immune activating or inhibitory: M1 macrophages ($HLA\text{-}DR^{high}$) produce IL-12, can lyse tumor and be effective antigen presenting cells. However, LMS tumors are generally infiltrated with immune inhibitory, M2 macrophages ($CD163^+$, $CD206^+$, $CD115^+$) that produce the inhibitory cytokines IL-10 and TGFβ. Furthermore, these cells have the potential to directly promote tumor growth, angiogenesis and metastasis[13]. It has been found that LMS tumors have gene signatures consistent with high levels of M2 TAM infiltration. High TAM numbers correlate with poor prognosis in LMS subjects[14]. Gene expression profiles consistent with M2 phenotypic markers and increased expression of markers associated with M2 have been associated with worse outcomes independent of TAM presence[15]. Preclinical LMS models have demonstrated that elimination of TAM using an anti-CD47 antibody can result in tumor shrinkage and decreased number of metastasis[16]. While an extensive body of literature argues for the role of TAM in LMS immune evasion, our unpublished data demonstrates that liposarcomas, and myxoid/round cell liposarcomas in particular, tend to also have very high levels of infiltrating TAM.

LMS tumors frequently express high levels of PD-L1

We presented data at the 2014 Connective Tissue Oncology Meeting describing the PD-1 and PD-L1 expression in over 80 soft tissue sarcoma samples including tumors from 27 LMS subjects. Expression levels in some STS subtypes, including synovial sarcoma were relatively low. However, positive PD-L1 expression was seen in 58% of LMS tumors tested and expression was high in 32% of the 27 tumors tested, including some subjects with staining in every visible tumor cell. We also saw cells staining for PD-1 in 84% of these tumors with high levels of expression in 63% of tumors tested. While LMS frequently had high numbers of PD-L1 and PD-1 expressing cells, 89% of liposarcoma tumors tested also had detectable PD-1 expressing T cells suggesting there may be a role in this tumor type as well.

Trabectedin is an FDA approved treatment for L-type sarcomas that also kills TAM

Trabectedin (Yondelis, Janssen Pharmaceuticals) was FDA approved on October 23, 2015 for the treatment of LMS and Liposarcoma. This approval was based on an improvement in median progression free survival of 4.2 months versus 1.5 months with dacarbazine.[17] No statistically significant overall survival benefit has yet been reported.

Interestingly, although trabectedin has been in clinical use for over a decade, controversy remains regarding its mechanism of action[18]. The standard explanation for trabectedin's activity is that it binds to the minor groove of DNA and thus interferes with DNA repair machinery. However, trabectedin has also been demonstrated to interfere with TAM and this may be correlated with clinical activity[1-3]. Thus, trabectedin may actually function as an immunotherapy by overcoming TAM-induced immunosuppression in the tumor microenvironment. We believe this activity could lead to potential synergy with a T cell targeted checkpoint inhibitor such as avelumab.

2.3 Clinical Data Using Avelumab in Solid Tumors

Avelumab is a monoclonal antibody targeting PD-L1 currently in clinical development across Phases I, II, and III. The avelumab investigator brochure (IB) includes safety data from the following 4 clinical trials sponsored by the manufacturer, EMD Serono, and their industry collaborators:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma (MCC)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet
- 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. More than 1500 subjects have been enrolled in the EMR 100070-001 trial. The 3 + 3 dose escalation algorithm to determine the MTD is complete and 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. The treatment expansion part of the trial consists of 16 tumor treatment cohorts. As of 05 November 2015 (data cutoff for a pre-planned safety data review by the study Safety Monitoring Committee [SMC]), 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 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for

at least 4 weeks.

The safety summary for the IB summarizes data from 1300 subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Trial EMR 100070-001 (as of 05 November 2015). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Trial EMR 100070-002 and for 88 subjects in the ongoing Phase II Trial EMR 100070-003 (as of 17 December 2015). For Trial EMR 100070-004, an overview of the serious adverse events (SAEs) is provided.

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 have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

Clinical efficacy in diseases other than sarcoma

The clinical efficacy information summarized in the IB includes data from the NSCLC and ovarian cancer expansion cohorts of the ongoing Phase I Trial EMR 100070-001, and for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0 vs 5.9 weeks) and OS (8.9 vs 4.6 months) were both observed in PD-L1 positive compared with PD-L1 negative subjects.

The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% confidence interval (CI): 6.3 to 12.0 weeks).

The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95% CI: 3.2% to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3 weeks).

2.4 Study Agent

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 binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor $CD8^+$ T cells, resulting in the restoration of cytotoxic T cell response.

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-g) 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 crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both 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 (TEM) 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 $CD8^+PD\text{-}1^+$ 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.

Nonclinical pharmacokinetics and metabolism

As expected for a monoclonal antibody (MoAb) binding to a cellular target, avelumab demonstrated pronounced non-linear pharmacokinetic (PK) characteristics in mice and monkeys in single dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Toxicokinetic data from repeated dose toxicity studies in mice, rats, and monkeys indicated that the PK of avelumab was linear within the dose range of 20 to 140 mg/kg, suggesting that the target mediated clearance could be saturated when higher doses than 20 mg/kg are administered. Similar terminal half-lives ($t_{1/2}$) of approximately 60 to 70 hours were observed in toxicity studies in mice and monkeys. A PK/ PD study in C57BL/6 mice was used to correlate receptor occupancy data of avelumab in blood with drug concentrations. A plasma concentration of 58.5 μg/mL was calculated as required for 95% target occupancy (TO) in this model.

Avelumab is immunogenic in mice, rats, and monkeys with a lower incidence of anti-drug antibodies (ADAs) at higher doses. The latter is probably due to interference of free avelumab with the immunogenicity assay (drug interference). In animals, the generated ADAs seem to have the potential to increase the clearance of the avelumab. As the fully human avelumab represents a foreign protein to the immune system of animals, the observed immunogenicity of avelumab in rodents and non-human primates is not deemed predictive for an immune response to avelumab in humans.

Nonclinical toxicology

The toxicological profile of avelumab was evaluated in repeat-dose toxicity studies of 4-week duration with once weekly IV bolus injection/infusion of avelumab in mice, rats, and cynomolgus monkeys. A repeat-dose toxicity study with intermittent once weekly IV infusion of avelumab over 13 weeks followed by an 8-week recovery period in cynomolgus monkeys was also conducted. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) followed by an optimized CRA in phytohemagglutinin (PHA) pre-stimulated PBMCs from 16 human volunteers was completed. Tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues have also been was 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. Due to severe hypersensitivity 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) is applied. In cynomolgus monkeys neither in the pilot 4-week Iv repeat-dose toxicity study nor in the pivotal 13-week study have clinical signs of hypersensitivity 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. 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 PHA pre-stimulated PBMCs.

2.5 Dose Rationale

A dose of 10 mg/kg of avelumab, intravenous (IV) once every 2 weeks, was selected in this trial as well as other on-going trials around the country. This starting dose is based on the preliminary pharmacokinetic (PK), target occupancy, and preliminary clinical safety data collected in the clinical trials. Modeling and simulation in > 1700 patients have been used to provide a rationale for changing the regimen for avelumab from the currently approved 10 mg/kg every 2 weeks to a proposed flat dose of 800 mg every 2 weeks for adults. For patients <18 years of age, the body weight based dosing will still be employed. A flat dose regimen is expected to provide more consistent dosing across body weights, minimize drug wastage, facilitate preparation and administration, and reduce pharmacy errors.

Pharmacokinetics and Target Occupancy

Avelumab plasma levels leading to full programmed death ligand 1 (PD-L1) receptor target occupancy (TO) on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of avelumab to act on its target and to show clinical activity. Preliminary 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 average value was 102 and 120 hours for 10 mg/kg and 20 mg/kg, respectively, with no significant difference between these two dose groups. 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 in vitro target occupancy data further support that a high TO is likely achieved at 10 mg/kg and above:

- Target occupancy was measured ex vivo by flow cytometry on peripheral blood CD3+ T cells from subjects (n=9) treated with avelumab. After the first dose of the initial dose-escalation portion of Trial EMR 100070-001, the observed mean target occupancy reached a plateau of about 90% on Day 15 pre-dose for dose levels of 3 mg/kg and above.
- In addition, in vitro target occupancy was measured using flow cytometry on peripheral blood CD3+ T cells from 8 healthy volunteers after spiking avelumab over a concentration range of 0.003 to 10 µg/mL. A 50% target occupancy was observed at a drug concentration (standard deviation [StD]) of 0.122 (0.042) µg/mL, and a concentration of 1 µg/mL avelumab was required for > 95% target occupancy. Based on these data and the trough serum levels observed in EMR 100070-001, target occupancy was projected to reach or exceed > 95% throughout the entire dosing interval for 10/13 subjects at 3 mg/kg, and for all (15/15) subjects at 10 mg/kg group from dose escalation group in EMR 1000700-001. Based on the ex vivo peripheral blood CD3+ T cell and in vitro target occupancy results, the dose of 10 mg/kg every 2 weeks is expected to achieve target saturation during the entire dosing interval in the majority of subjects. Clinical Safety Data Related to Dose As of the safety cutoff date of 05 November 2015, 1353 subjects have received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10 mg/kg (15 in the dose escalation part of the study and 1300 subjects in the pooled expansion cohort).

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. Treatment-related treatment-emergent adverse events (TEAEs) were observed in 813 (62.5%) subjects in the

pooled expansion cohort. The most frequently observed treatment related TEAEs (incidence > 5%) were fatigue (212 subjects, 16.3%), infusion-related reaction (209 subjects, 16.1%), nausea (108 subjects, 8.3%), chills (102 subjects, 7.8%), diarrhea (79 subjects, 6.1%), and pyrexia (72 subjects, 5.5%). Grade ≥ 3 treatment-related TEAEs were observed in 124 subjects (9.5%) in the pooled expansion cohort. The most frequently reported Grade ≥ 3 treatment- related TEAEs were gamma-glutamyl transferase increased (GGT) and infusion-related reaction (each occurred in 9 subjects; 0.7%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies. Preliminary data from EMR 100070-001 showed that avelumab at doses up to 20mg/kg Iv every 2 weeks was well tolerated, and the dose of 10 mg/kg Iv every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

In conclusion, based on the PK results and the receptor occupancy data, sufficient trough concentrations appear to be achieved for full TO in the blood in the majority of subjects receiving the 10 mg/kg dose. Within the dose range of 1 mg/kg to 20 mg/kg, avelumab was well tolerated and is deemed to have an acceptable safety profile. 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.

2.6 Trabectedin - Commercially Sourced

Trabectedin is an FDA approved synthetic, marine-derived alkylating agent discovered in a high through-put screen of compounds from the Caribbean tunicate, Ecteinascidia turbinate[20]. With limited systemic therapy options available for sarcomas as a whole, trabectedin has the opportunity to be significantly beneficial for subjects with metastatic disease. Evidence shows that disruption of DNA by trabectedin ultimately causes apoptosis and sensitization of cell lines to Fas-mediated cell death [21].

Multiple studies, including specific experiments in soft tissue sarcomas, have also validated that trabectedin works at the level of the tumor microenvironment with selective activity against monocytes and tumor-associated macrophages [22,23]. The inhibition of these immune factors allows for the prevention of angiogenesis and further disease progression [24,25]. Deprivation of inflammatory-mediated support in the tumor microenvironment may be one of the most important aspects of trabectedin's mechanism of action, making the drug efficacious as a cancer treatment. Other mechanisms for the chemotherapeutic actions of trabectedin may include modulation of the cell cycle and interaction with transcription factors [26,27].

Phase I Trials

A number of Phase I trials have assessed differential dosing and infusion schedules for the administration of trabectedin [28-34]. Results from these studies have established the optimal regimen of administration to be a 1.5 mg/m^2 infusion over 24 hours every 3 weeks [35]. Notably, Taamma and colleagues performed a Phase I trial of trabectedin in 52 subjects with treatment refractory tumors that recommended the current optimal dosing schedule of 1.5 mg/m^2 for a 24-hour continuous infusion [31]. The most prevalent dose limiting toxicities in the study were hematological in nature. At the recommended dose, severe neutropenia was reported in 33% of cycles, severe thrombocytopenia in 10% of cycles and reversible, but severe, elevations in transaminase levels in 38% of cycles.

Combination therapies of trabectedin with other chemotherapeutic agents including gemcitabine, doxorubicin, doxil, and cisplatin have also been assessed in Phase I trials [36-41]. The most promising results from these studies in sarcoma subjects have been from the trials administering trabectedin in combination with doxorubicin. One of the trials showed a response rate (RR) of 18% and stable disease in 56% of soft tissue sarcoma subjects (n=29) [40]. None have seen significant safety concerns.

Based on these studies, the US, standard starting dose is 1.5mg/m^2 – this is noted in the trabectedin package insert, however around the world standard dosing varies. In Japan, the standard starting dose is 1.2 mg/m^2 as this was the MTD they found on a phase I trial they performed.[19] The DLTs observed on the Japanese phase I at the 1.5 mg/m^2 dosing were LFT abnormalities.

Phase II Trials

Two Phase II trials in 2004 provided the initial analysis of trabectedin in soft tissue sarcomas. The first of these studies was run on 54 pretreated soft tissue sarcoma subjects, and reported a low response rate of 4%, but a high disease control rate at 6 months of 24% [42]. Trabectedin was administered at a dose of 1.5 mg/m^2, over 24 hours every 3 weeks. Approximately half of

the subjects in the study eventually developed grade 3/4 AST and ALT levels. Another common adverse event was fatigue, being grade 3/4 in 15% of subjects. In this trial, 4 subjects (7.4%) discontinued trabectedin due to adverse events. In addition, there were two treatment-related deaths, both were subjects who developed acute renal failure.

The second Phase II trial, published in 2004, again reported a low response rate of 8% and a one year overall survival rate of 53% in 36 previously treated sarcoma subjects [43]. This study also utilized the same dosing schedule of trabectedin (1.5 mg/m^2, over 24 hours every 3 weeks). The toxicity profile of the drug was similar to previous trials with subjects experiencing elevations in transaminases, fatigue and hematological toxicity. Growth factors such as, G-CSF, can be administered to help prevent hematological toxicity, however a recent retrospective study showed that G-CSF administration has only been used in about 10% of Phase II trials of trabectedin in solid tumors [44].

Early promising results in these Phase II studies led the European Organization for the Research and Treatment of Cancer (EORTC) to initiate a Phase II trial of trabectedin in 104 subjects treated in the second and third-line setting [45]. This trial also reported a low response rate of 8%. The 6-month PFS was 29% and the median overall survival (OS) was reported as 9.2 months. Subsequently, a further Phase II trial in 36 subjects was run to evaluate the activity of trabectedin in the first-line setting. The overall response rate was reported as 17%, and the 1-year PFS and OS rates were 21% and 72%, respectively [46]. This study also importantly concluded that trabectedin has similar ranges of objective responses and overall survival rates in the first-line setting to the two most active drugs in soft tissue sarcomas: doxorubicin and ifosfamide.

Demetri and colleagues performed a Phase II trial randomizing 270 subjects with leiomyosarcoma and liposarcoma to receive either 1.5mg/m^2 of trabectedin over 24 hours every 3 weeks, or 0.58 mg/m^2 over 3 hours every week for 3 out of 4 weeks [47]. Subjects were required to have experienced documented disease progression while on doxorubicin and ifosfamide prior to trial entry. The 24-hour infusion schedule showed a significantly longer median time to progression (TTP) (3.7 vs. 2.3 months) and PFS at 6 months (3.3 vs. 2.3 months) as compared to the 3-hour infusion schedule. No significant difference in overall survival was observed between the two arms of the trial, however, there was a strong trend favoring the 24-hour infusion schedule (13.9 months vs. 11.8 months). Trabectedin was generally well tolerated in this study, with the most frequently reported grade 3/4 adverse events being neutropenia and elevated transaminases. Febrile neutropenia occurred in 1% of subjects, and the majority of adverse events were mild to moderate. There was also no documentation of cumulative toxicities. Another Phase II trial recommended the use of trabectedin as a neoadjuvant therapy for subjects with advanced myxoid liposarcoma [48].

The results of these Phase II trials led to licensing approval of trabectedin by the European Union for advanced soft tissue sarcoma in 2007, and the drug is now approved in over 70 countries.

Phase III and FDA Approval

The Phase III trial of trabectedin vs. dacarbazine resulted in FDA approval of trabectedin based on a PFS improvement of 2.7 months over single agent dacarbazine[17]. FDA approved trabectedin under the trade name Yondelis® on October 23, 2015 for the treatment of LMS and Liposarcoma.

2.7 Risks/Benefits

Trabectedin as a single agent represents a clear advance in the standard of care for subjects with leiomyosarcoma however with PFS in the 3-5 months range and the OS on the trial used for the approval of trabectedin was 12.4 months, there is clearly a desperate need for improved treatments. Given that immunomodulation clearly occurs as a result of trabectedin, including the elimination of TAM in LMS, there is the potential for synergy with a highly active checkpoint inhibitor such as avelumab.

3.0 STUDY OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objectives

- To assess the safety and tolerability of the combination of trabectedin and avelumab in subjects with advanced leiomyosarcoma and liposarcoma
- To assess the objective response rate of advanced L-type sarcoma subjects receiving the combination regimen of avelumab and trabectedin

3.1.2 Primary Endpoints

- Safety as measured by CTCAE v5.0.
- Overall Response Rate (PR + CR, best response for each subject) by RECIST v1.1.

3.1.3 Secondary Objectives

- To further explore the clinical activity and safety profile of avelumab and trabectedin as a combination therapy

3.1.4 Secondary Endpoints

- Adverse event profile (based on National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v5.0) for all subjects
- Time to response
- Duration of response
- Progression-free survival (PFS) at 12 weeks, based on RECIST 1.1
- Clinical benefit rate (CR+PR+SD) at 12 weeks, based on RECIST 1.1
- Median overall survival (OS) at 12 months

4.0 TRIAL OVERVIEW

4.1 Study Design

4.1.1 Introduction

This is a Phase I/II, non-randomized, open-label, interventional study of avelumab combined with trabectedin for subjects with advanced L-type sarcoma.

The Phase I stage will evaluate trabectedin (1.5 mg/m^2) combined with avelumab (800 mg flat dose). Dose reduction for the trabectedin therapy is permitted after the first cycle. Events which would required a dose reduction of trabectedin are outlined in Section 10, however additional dose reductions may be made at the discretion of the treating clinician down to a lowest possible dose of 1 mg/m^2. There will be no dose escalation or re-escalation of trabectedin.

4.1.2 Definition of dose limiting toxicity (DLT):

During the phase I portion of the protocol, a DLT will be defined as any grade 3 or higher adverse events, at least possibly-related to protocol therapy, which occur during the first 6 weeks of treatment, with the following specifications and limitations:

- Lab abnormalities that have no clinical sequalae (e.g. febrile neutropenia from low ANC, bleeding from thrombocytopenias etc.) and resolve to grade 1 or better within 7 days will not be considered a DLT.
- Any elevation in total bilirubin > 2x institutional ULN will be considered a DLT.
- Any elevation in AST and ALT over 8x institutional ULN will be considered a DLT.
- ANC <500/µL lasting 5 days or more will be considered a DLT.
- Platelets < 25,000/ µL (grade 4 toxicity) lasting 5 days or more will be considered a DLT.
- Hemoglobin < 7.0 lasting 5 days or more will be considered a DLT.

Additionally, should any grade 5 toxicity (death) occur that is at least possibly-related to treatment (e.g. not easily otherwise explained; for example: a car accident), this will be considered a DLT. In the event of any grade 5 toxicity, enrollment will immediately be put on hold and a data safety monitoring board (DSMB) meeting will be requested immediately.

All clinically significant grade 3 or higher toxicities will be recorded and presented to the DSMB at scheduled meetings. Expected toxicities are those outlined in **Section 10**. The DSMB will be specifically instructed to consider whether there are increased frequency of known toxicities and to make recommendations accordingly if appropriate. Section 10 summarizes criteria for required dose adjustments.

Enrollment during the first cohort of the Phase 1 portion of the trial will be staggered. The first subject must have received their second dose of both avelumab and trabectedin prior to treatment of the second subject, and the second subject must have received their second dose of both avelumab and trabectedin prior to treating the third subject. In cases where the first subject's second doses of avelumab and/or trabectedin is delayed beyond week 4, either due to trabectedin toxicity or DLT, or is withdrawn or discontinued from the study, the second subject will be allowed to enroll and start therapy. However, the second subject must complete their second dose of trabectedin and avelumab prior to the start of the third subject.

Should 2 or more DLTs be observed in the first 6 subjects, the starting trabectedin dose will be reduced to 1 mg/m^2 and the Phase 1 will expand to enroll an additional 6 subjects at the new starting dose. Should two or more DLTs be observed in the 6 subjects enrolled at 1 mg/m^2 the study will go on hold and a DSMB will meet to discuss if there are modifications that could allow the protocol to safely be re-opened. If <2 DLTs are observed in the 6 subjects on the 1.0 mg/m^2 cohort, enrollment will expand to a third cohort, enrolling an additional 6 subjects at 1.2 mg/m^2 of trabectedin. If 2 or more DLTs are observed at 1.2 mg/m^2, then 1.0mg/m^2 will be determined to be the recommended Phase 2 dose (RP2D). The highest dose with <2 DLTs will be selected for Phase 2 dosing. If one of the first six subjects does not complete the DLT period for a reason unrelated to toxicity (for example withdrawal of consent or tumor progression) that subject may be replaced.

In Phase 2, the study will go on hold and a DSMB meeting will be triggered if more than 30% of subjects have unexpected, probably related SAE's grade 3 or higher that do not resolve to grade 2 within 2 weeks.

In any subsequent Phase 1 cohorts (1.0 mg/m^2 dosing and 1.2 mg/m^2 dosing of trabectedin) subjects may be treated concurrently without delay. Prior to beginning Phase 2, each subject on the phase 1 portion must have received their second dose of both avelumab and trabectedin or completed their treatment (e.g. come off study for symptomatic progression).

4.1.3 Dosing Administration and Schedule

A treatment schedule is provided in Appendix C. Avelumab will be administered via IV infusion over 60 minutes (+/- 10 minutes). Trabectedin is given as an outpatient 24-hour infusion by pump. During week 1, subjects will receive both drugs: avelumab followed by the standard 24-hour infusion of trabectedin. Following avelumab infusions, subjects must be observed for 60 minutes ± 10 minutes (Cycle 1) or 30 minutes ± 5 minutes (Cycle 2+) post-infusion, prior to beginning trabectedin, for potential infusion-related reactions.

Avelumab will be administered every 2 weeks. Trabectedin will be administered every 3 weeks for the first two doses (Week 1 and Week 4), and then every four weeks (Week 7, Week 11,…) moving forward. After Cycle 2 of trabectedin, dosing may extend to every 5 weeks at investigator discretion, for management of trabectedin-associated toxicity only. Delays of trabectedin beyond 5 weeks may be allowed but require written approval from the Sponsor-Investigator.

It should be noted that trabectedin has significant single agent toxicity. Treatment schedule and evaluation of toxicity are discussed in **Section 7.0**.

4.1.4 Assessment of Response and duration of therapy

Subjects will have their first post-treatment scan during week 12 and every 12 weeks after that. Additional scans may be ordered at the discretion of the treating physician, if clinically indicated. If any non-protocol scans are collected, a RECIST 1.1 read should be obtained. Response assessment will be based on RECIST 1.1. Subjects who are demonstrating CR must be treated for at least 12 weeks after CR was confirmed (2nd scan with CR). Subjects confirmed to have a CR who have been taken off treatment will continue to be followed on study and monitored radiographically every 12 weeks for up to 2 years. Upon relapse they may be re-treated with trabectedin and avelumab.

It is possible that a subject may become surgically resectable during the course of treatment. Subjects who are rendered no evidence of disease via a surgical intervention after successful combination therapy should be treated just as if they had a CR in response to the medication. These subjects will receive an additional 12 weeks of protocol therapy post-surgery, and will be followed on study and monitored radiographically every 12 weeks for up to 2 years. Upon relapse, they may be re-treated with trabectedin and avelumab.

Subjects with an unconfirmed or equivocal progression of disease may continue trial treatment until progression is confirmed by repeat CT/MRI, 6 weeks later. Subjects may continue protocol therapy until a confirmation scan is obtained, or until symptomatic progression or clinical decline. Subjects may only continue to receive study treatment while waiting for confirmation of PD if the following criteria are met:

- No significant decline in ECOG performance status in the opinion of the treating investigator
- Absence of rapid progression of disease in the opinion of the treating investigator
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

4.2 Estimated Accrual

- **Phase 1:** 6 subjects, may expand up to 18
- **Phase 2:** 16 subjects

A minimum of 22, and up to a possible total of 34 subjects are anticipated to receive treatment.

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion criteria:

1. Subjects, ≥ 18 years old, must have a histologically confirmed diagnosis of advanced (metastatic or unresectable) soft tissue sarcoma with one of the following subtypes:
    a. Leiomyosarcoma
    b. Liposarcoma
2. Subject must be clinically indicated to receive trabectedin therapy as part of routine care. Subjects may be first line, or have received any number of prior systemic therapies.
3. Subjects must have adequate organ function and blood chemistry and blood count parameters as defined below. Transfusion is permitted as clinically indicated.
    a. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) mg/dL
    b. AST ≤2.5 x ULN and ALT ≤2.5x ULN
    c. Alkaline Phosphatase < 2.5x ULN
    d. Serum creatinine ≤1.5 x ULN
    e. Calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault formula may be included)
    f. Creatinine phosphokinase (CPK) ≤2.5 × ULN
    g. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
    h. Platelet count ≥100,000/mm^3 (100 × 10^9/L);
    i. Hemoglobin ≥9 g/dL
4. Subjects must demonstrate a left ventricle ejection fraction (LVEF) of > 45% by ECHO or MUGA.
5. Male or non-pregnant and non-breast feeding female:
    a. Females of child-bearing potential must agree to use highly effective contraception without interruption from initiation of therapy and while on study medication and have a negative serum pregnancy test (β - hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and at the end of study treatment. A highly effective method of contraception is defined as one that results in a low failure rate (that is, <1% per year), when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner (Appendix C).
    b. Male subjects must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study (Appendix C).
6. All ongoing toxicities related to prior therapies must be resolved to Grade 1 or better (except alopecia).
7. Subjects must have an ECOG performance status ≤ 1 or Karnofsky performance scale ≥ 70 (see Appendix A and B).
8. Subjects must have one or more measureable lesions, as determined by RECIST v1.1 assessed by CT or MRI.
9. Subjects must have a life expectancy of ≥ 6 months, as determined by the treating physician.
10. Ability to understand and sign informed consent document.
11. Willingness and ability to comply with the scheduled visits, laboratory tests, and other study procedures.

5.2 Exclusion criteria:

Subjects are not eligible for the trial if they fulfill any of the following exclusion criteria:

1. Known active, uncontrolled, or symptomatic central nervous system (CNS) metastases. A subject with controlled and asymptomatic CNS metastases may participate in this study. As such, the subject must have completed any prior treatment for CNS metastases ≥ 28 days (including radiotherapy and/or surgery) prior to the start of treatment in this study and should not be receiving chronic corticosteroid therapy in excess of 10 mg daily prednisone (or equivalent) for CNS metastases. Subjects with known CNS metastases must be confirmed radiographically stable by at least one imaging study, at least 28 days from last treatment.

2. Receipt of any type of cytotoxic, biologic, or other systemic anticancer therapy (including investigational) within 2 weeks of enrollment.
3. Prior organ transplantation, including allogeneic stem-cell transplantation.
4. Prior treatment with trabectedin.
5. Significant acute or severe chronic infections including, among others:
    - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
    - Known active infection with Hepatitis B or Hepatitis C.
6. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
    a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
    b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day
    c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, introocular, or inhalation) are acceptable
7. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 5.0), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)
8. Pregnant or lactating females.
9. Known, active alcohol or drug abuse.
10. All other significant diseases (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment.
11. Any vaccination within 4 weeks of the first dose of avelumab, with the following exceptions:
    a. Administration of inactivated vaccines, including inactivated flu vaccines, are allowable. However, they should not be given within 2 weeks prior to starting study treatment.
12. Clinically significant cardiovascular disease including cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), congestive heart failure with NYHA class II or greater or serious cardiac arrhythmia requiring medication.
13. Severe (requiring active treatment) acute or chronic medical conditions including: colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.
14. Recent (within the past year) or active suicidal ideation or behavior.

6.0 SUBJECT REGISTRATION

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related procedures are performed. The subject identification number will be assigned. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the electronic case report form (eCRF).

7.0 TREATMENT PLAN

7.1 Treatment Plan

Trabectedin is given every three or four weeks (Cycle 1 and Cycle 2 Q3W, and then Q4W for Cycle 3+) and avelumab is given every two weeks. During week 1, subjects will receive avelumab followed by a 24 hour infusion of trabectedin afterwards. Trabectedin should be administered on a Q3W schedule for Cycle 1 and Cycle 2. Starting at Cycle 3, trabectedin will be administered on a Q4W schedule, to coincide with avelumab dosing. For toxicity management after Cycle 2, trabectedin administration may delay to Q5W, as clinically indicated for toxicity management only. Delays of trabectedin beyond 5 weeks may be allowed but require written

approval from the Sponsor-Investigator. On days where both drugs are scheduled to be administered, avelumab will be administered first.

Avelumab is administered as a 60 minute IV infusion at a flat dose of 800 mg, diluted with either a 0.9% or 0.45% saline solution. In order to mitifate infusion-related reactions, subjects should be premdicated with an antihistamine and paracetamol (e.g., 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent)) within 30-60 minutes prior to the first four (4) doses of avelumab. Premedication may be discontinued for Cycle 5 and beyond of avelumab, at the investigator's discretion. If any infusion-related reaction occurs, the premedication should immediately be reinstated for all cycles of avelumab.

For Cycle 1, avelumab will be given first over 60 minutes (+/- 10 minutes), followed by a 60 minute observation period (+/- 10 minutes). For Cycle 2 and beyond, the post-avelumab observation period will be 30 minutes (+/- 5 minutes). Following completion of the avelumab infusion and observation period, the trabectedin pump will be connected and started. Trabectedin should start within 3 hours (+15 minutes) after the end of the avelumab infusion, but not prior to the end of the observation period post-avelumab dose. Subjects will return to clinic 24 hours later to have the pump disconnected.

Trabectedin is administered by a pump which is callibrated to provide the full, correct dose and rate regardless of whether the pump is actually disconnected at 24 hours or after 24 hours. Every attempt should be made to disconnect the trabectedin as close to 24 hours after starting the infusion as possible, however delays in disconnection will not constitute a protocol deviation. Avelumab infusion will occur over 1 hour, with a +/- 10 minute window.

Trabectedin is a moderately emetogenic chemotherapy and anti-emetics should be given according to standard of care.

Dexamethasone 20 mg IV is recommended as per the trabectedin package insert and should be given 20-30 minutes before trabectedin. Dexamethasone premedication should not be administered until after the 60 minute observation period in Cycle 1, and not until the avelumab infusion has been completed for Cycle 2+ on days where both avelumab and trabectedin are to be administered. Alterations to the dexamethasone are strongly discouraged as dexamethone does not only function as an anti-emetic, it also may prevent serious toxicities of trabectedin including liver toxicity. Alterations could be considered for extenuating circumstances with Sponsor-Investigator approval. Outside of this pre-medication recommended in the trabectedin package insert, corticosteroids use is discouraged when not absolutely necessary and is not allowed for the treatment of trabectedin associated nausea and vomiting unless the subject has tried and failed to control their nausea with 2 prior anti-emetic regimens.

7.2 Administration of agents

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Avelumab	800 mg flat dose	Q2 Weeks	60 minute (+/- 10 min) IV infusion	Every 2 weeks, regardless of trabectedin dosing	Experimental
Trabectedin	1.5 mg/m^2, 1.2 mg/m^2, or 1.0 mg/m^2	Q3 Weeks (Cycle 1 and 2) Q4 Weeks (Cycle 3+)	24 hour IV infusion	Day 1 of each cycle*	Standard

*Cycles may be adjusted to q5 weeks, or greater with Sponsor-Investigator approval. No schedule adjustments are permitted until after Cycle 2 of trabectedin is administered.

7.3 Drug Product Information

Avelumab will be provided by EMD Serono. 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. Vigorous 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 is used immediately.

A pharmacy manual will contain details regarding administration and preparation of avelumab.

Trabectedin will be stored, prepared, and administered per institutional and FDA-approved product labeling guidelines. Trabectedin will be obtained commercially as this is an FDA approved product.

7.4 Schedule of Treatment Visits

Avelumab will be administered every two weeks starting at Week 1. Dosing may be delayed in response to certain toxicities, as described under Section 10.

Trabectedin will be given every three weeks for Cycle 1 (Week 1) and Cycle 2 (Week 4), and then will be given every 4 weeks (Week 7, Week 11,…). For toxicity management after Cycle 2 (Week 4) Day 1, trabectedin administration may delay to Q5W, as clinically indicated for toxicity management. Delays of trabectedin beyond 5 weeks may be allowed but require written approval from the Sponsor-Investigator.

Administration of either study drug may vary ±3 days from planned date.

The administration of study drugs during the first 12 weeks (first response assessment timepoint), assuming no dose delays or modifications due to toxicity, is shown below.

The study calendar will be managed in Weeks, with each dose of each drug being noted by a Cycle. For example, assuming there are no deviations from the planned schedule events, Week 1 will have Cycle 1 of avelumab and trabectedin. Week 3 will have Cycle 2 of avelumab, Week 4 will have Cycle 2 of trabectedin, Week 5 will have Cycle 3 of avelumab, Week 7 will have Cycle 4 of avelumab and Cycle 3 of trabectedin, etc. This may change based on dose delays or modifications. Weeks should be counted sequentially regardless of what number the dose of each agent is.

	Week											
Drug	1	2	3	4	5	6	7	8	9	10	11	12*
Avelumab	●		●		●		●		●		●	
Trabectedin	●			●			●				●	

*Response assessment.

8.0 SUBJECT EVALUATION

8.1 Screening Evaluations

This study will be conducted at the Fred Hutchinson Cancer Research Center, Seattle, USA. Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related procedures are performed. The subject identification number will be assigned. This number will be used to identify the subject throughout the clincal study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Before subjects may be entered into the study, the site must obtain written IRB/IEC approval for the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable. A signed and dated Institutional review Board (IRB) approved informed consent form (latest approved version) must be obtained from each subject prior to performing any study-specific procedures. All subjects or legally authorized representatives must personally sign and date the consent form

before commencement of study-specific procedures. Adverse events are to be collected for a subject once they have signed informed consent through 90 days after the End of Treatment visit.

Screening evaluations will be performed for all subjects to determine eligibility. These evaluations must be obtained ≤ 28 days prior to C1D1. Efforts should be made to complete screening procedures as close to initiation of protocol therapy as possible. Standard of care evaluations done prior to signing of consent may be used if they fall within the specified window prior to starting treatment.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and upon completion of an eligibility review packet. The investigator is to document this decision and date, in the subject's medical record and/or in/on the electronic case report form (eCRF). Subjects should initiate treatment within 7 days of being enrolled to the study, and within the 14 day screening window from time of informed consent.

The following procedures are to be completed during the screening period, after signed informed consent has been obtained, designated in the Schedule of Assessments found in **Appendix C**.

- Informed Consent
- Demographics and Medical History
- Complete Physical Exam and ECOG performance status evaluation
- Vitals Signs, including height and weight
- Electrocardiogram (ECG) (Phase 1 Portion Only)
- Serum Pregnancy Test – For Women of Childbearing Potential only (WCBP)
- Hematology:
    - White blood cell (WBC) count with differential, absolute neutrophil count (ANC), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, PT/PTT, and INR
- Clinical chemistry and liver function:
    - Sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, albumin, amylase, lipase
- Creatine Kinase (CK)
- Thyroid panel:
    - Total T3, Free T4, and thyroid stimulating hormone.
- Urinalysis:
    - Protein, glucose, blood, leukocytes, nitrites, urobilinogen, bilirubin, pH, specific gravity, and ketones.
- Tumor imaging, by CT or MRI
- Echocardiogram or MUGA
- Archival Tissue Collection (if available, this does not have to be obtained prior to C1D1)

8.2 On-Study Clinical Evaluations

A subject is considered on treatment on study day 1 when protocol defined therapy is first administered. Day 1 Avelumab is to be administered after all other protocol-specified pre-dose assessments have been performed during each visit that is required. Subjects will continue therapy until the completion of planned course of treatment, disease progression, or unacceptable AEs. Subjects should be instructed to immediately inform the treating investigator of an AEs. Clinical evaluations take place according to the Study Calendar (**Appendix C**).

Subjects on the Phase I portion of the trial should be evaluated as described below every week for the first 6 weeks and then on all weeks the subject is receiving treatment. Subjects on the Phase II portion of the study are evaluated as described below on weeks that they have treatment, prior to treatment. Every effort should be made to keep the schedule within ± 3 days from the exact date the subject should be scheduled.

The study calendar will be managed in Weeks, with each dose of each drug being noted by a Cycle. For example, assuming there are no deviations from the planned schedule events, Week 1 will have Cycle 1 of avelumab and trabectedin. Week 3 will have Cycle 2 of avelumab, Week 4 will have Cycle 2 of trabectedin, Week 5 will have Cycle 3 of avelumab, Week 7 will have Cycle 4 of avelumab and Cycle 3 of trabectedin, etc. This may change based on dose delays or modifications. Weeks should be counted sequentially regardless of what number the dose of each agent is.

The following assessments will be performed on each treatment visit, unless otherwise specified:

- Tumor and Symptom-Directed Physical Exam and ECOG performance status evaluation
- Vitals Signs, including weight
- Urine or Serum Pregnancy Test – For Women of Childbearing Potential only (Only on days where avelumab is given as treatment, either alone or in combination with trabectedin. Screening pregnancy test must be serum pregnancy.)
- Hematology:
    - White blood cell (WBC) count with differential, absolute neutrophil count (ANC), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count
- Clinical chemistry and liver function:
    - Sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, albumin
- Creatine Kinase (to be drawn on days of trabectedin infusion and as clinically indicated)
    - If trabectedin dosing schedule is modified to every 5 weeks or more at the discretion of the investigator, then the creatine kinase draw will be modified to follow the same schedule.
- Thyroid panel:
    - Total T3, Free T4, and thyroid stimulating hormone (on weeks 1, 7, and every 6 weeks thereafter on a treatment day [+/- 7 days], and at discontinuation)
- Correlative Studies Blood Collection (See **Section 19.3** for schedule)
- Tumor imaging (every 12 weeks).
    - Subjects will have their first post-treatment scan during week 12 and every 12 weeks after that. Additional imaging may be ordered if clinically indicated. All routine care scans ordered for clinical indication should be reviewed via RECIST 1.1.
- Echocardiogram or MUGA (Week 6, then every 12 weeks while receiving trabectedin, beginning with week 18)
- Adverse Event and Concomitant Medication collection and review
- Correlative Studies Blood Collection

8.3 End of Treatment (EOT) Procedures

Procedures to be performed during the EOT Visit are listed in the Appendix. Briefly, these include:

- Directed Physical Exam and ECOG performance status evaluation
- Vitals Signs, including weight
- Electrocardiogram (ECG) (Phase 1 Portion)
- Pregnancy Test – For Women of Childbearing Potential only (WCBP)
    - Either serum or urine pregnancy tests are sufficient
- Hematology:
    - white blood cell (WBC) count with differential, absolute neutrophil count (ANC), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count
- Clinical chemistry and liver function:
    - sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, albumin
- Creatine Kinase

- Thyroid panel:
    - Total T3, Free T4, and thyroid stimulating hormone
- Tumor imaging (if not done within 4 weeks of last study visit)
- Adverse event and concomitant medication collection and review
- Correlative studies blood collection

8.4 Short Term Follow-Up / 30 Day Safety Assessment

The 30 Day Safety Assessment Visit is a safety follow-up visit that is to be performed 30 days after the End of Treatment Visit Date (+/- 7) days). All efforts should be made to conduct this visit. If it is not possible to conduct the 30 Day Safety Assessment Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the 30 Day Visit as designated in the Schedule of Assessments:

- Physical examination and ECOG performance status evaluation
- Vital signs, including weight
- Electrocardiogram (ECG) (Phase 1 Portion)
- Pregnancy Test – For Women of Childbearing Potential only (WCBP)
    - Either serum or urine pregnancy tests are sufficient
- Hematology:
    - white blood cell (WBC) count with differential, absolute neutrophil count (ANC), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count
- Clinical chemistry and liver function:
    - sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, albumin
- Creatine Kinase
- Thyroid panel:
    - Total T3, Free T4, and thyroid stimulating hormone
- Adverse Event and Concomitant Medication collection and review
- Survival status/post-study anticancer therapy status

8.5 Long Term Follow-Up / 90 Day Safety Assessment

AEs will be monitored and recorded in the subject's medical chart and research shadow chart from the time of first exposure to the investigational product avelumab, through 90 days (+/- 7 days) following last dose of a study drug. AEs with an onset date prior to the first exposure to an investigational product will not be followed, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame. Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration. The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

8.6 Long-Term Follow-Up for Survival

Disease status and any subsequent anticancer therapy information status will continue to be monitored. Subjects will be followed for survival status via chart review or telephone contact every 12 weeks (+/- 2 weeks) from baseline for up to 2 years, or until disease recurrence, death, withdrawal of consent, or the study closes – whichever is earliest. Subjects will then be followed every 6 months (+/- 3 months) for survival status, until death or the study closes. Subjects who have a CR and discontinue therapy (section 4.1.4) should continue to return to clinic for assessment and scans every 12 weeks for two years. Extended follow-up will be performed as mentioned in **Section 9.7.1**

8.7 Imaging Assessments

Disease status will be assessed by CT or MRI scan of the chest, abdomen, and pelvis (CAP), in addition to any additional known disease sites (per institutional guidelines); image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) must be used at screening and throughout the study. For subjects with stable disease or better per RECIST v1.1 criteria, scans will continue to be performed while receiving study treatment. Scans will follow this schedule even if a subject has a dosing delay that causes the beginning of a treatment cycle to be delayed.

CT/MRI scans to be performed at the following frequency:

- ≤28 days prior to C1D1
- Followed by every 12 weeks (± 1 week) from baseline, regardless of missed or delayed doses, until disease progression, withdrawal of consent, end of study, completion of protocol participation, or death – whichever occurs first.

An unscheduled scan for suspected disease recurrence/progression may be performed at any time at investigator discretion. RECIST reads via RECIST 1.1 should be performed on any imaging obtained for suspected disease recurrence/progression during the course of the trial.

8.8 .Analyte Listing

Table 1 - Analyte Listing

Chemistry	Hematology	Urinalysis	Other Labs
Sodium	WBC	Specific gravity	Pregnancy test
Potassium	RBC	pH	PT/INR
Bicarbonate	Hemoglobin	Blood	PTT
Chloride	Hematocrit	Protein	Amylase
Total protein	MCV	Glucose	Lipase
Albumin	MCH	Ketones	Creatinine Kinase (CK)
Calcium	MCHC	Microscopic	
Glucose	RDW		
BUN	Platelets		
Creatinine	Differential:		
Total bilirubin	-Neutrophils		
Alkaline phosphatase	-Lymphocytes		
AST (SGOT)	-Monocytes		
ALT (SGPT)	-Eosinophils		
Lactate Dehydrogenase	-Basophils		

8.9 Correlative Studies

8.9.1 Tumor Specimens

Subjects with paraffin embedded tumor available should have 10 slides collected for immunohistochemical staining with PD-1, PD-L1, and immune infiltrates. When possible, up to 2 additional curls, 1 mm thick should be obtained for nanostring analysis and TCR sequencing. This archival tissue does not need to be collected prior to initiating therapy on Week 1.

8.9.2 Research Blood Specimens

Research blood will be processed and frozen by the Digel Lab. This will include 30 mL for PBMC (green top or any heparinized tube) and 10 mL for serum in red top.

A schedule for collection of research labs is included in **Appendix C**.

9.0 SAFETY

Monitoring for both acute and chronic toxicities will be evaluated at all study related visits and will be assessed by the Sponsor-Investigator. Toxicity information will be recorded and periodically reported to the the DSMB and EMD Serono. The Investigator will follow the guidelines below for treatment for toxicity. If a subject experiences toxicity, lab value abnormality, or other adverse event that is not described below, it will be up to the discretion of the treating Investigator if they want to delay study treatment and duration.

All adverse events and toxicity will be evaluated using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as described in **Section 9.5**.

9.1 Adverse Event

According to ICH guidelines for Good Clinical Practice; 21 CFR 312.32, IND Safety Reports; and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

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

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Medical conditions present at screening (i.e., before the study treatment is administered) should be captured as baseline in the subject's research shadow chart. Medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.

9.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth	An adverse outcome in a child or fetus of a subject exposed to the molecule

defect:	or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

Classification of an event as serious or non-serious determines the reporting procedures to be followed.

9.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

9.4 Monitoring and Recordings Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the subject's research shadow chart. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

9.5 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

9.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely or probably related; unrelated if it is assessed as possibly, unlikely related or unrelated.

9.7 Adverse Event Recording Period

AEs will be monitored and recorded in the subject's medical chart and research shadow chart from the time of first exposure to the investigational product avelumab, through 90 days following last dose of a study drug. AEs with an onset date prior to the first exposure to an investigational product will not be followed, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

9.7.1 Extended safety follow-up

- Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.
- The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

9.8 Adverse Event Reporting Requirements

9.8.1 Reporting to Product Manufacturer (EMD Serono)

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided.

- Serious Adverse Events
- 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): These events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914
OR
E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:

- PROTOCOL Number
- SUBJECT Number
- SITE Number/Sponsor-Investigator Name

9.8.2 SAE/ONSET DATE Reporting to IRB

The investigator or designee must report events to the FHCRC IRB in accordance with the policies of the IRB.

9.8.3 FDA Reporting Requirements

The Sponsor-Investigator assumes responsibility for IND safety reporting to the FDA, in accordance with regulations under 21 CFR 312.32.

Each SAE report will be evaluated by the Sponsor-Investigator to assess the seriousness of the event, the expectedness of the event, and the relationship to participation in the study. For regulatory reporting purposes, the Sponsor-Investigator will determine expectedness relating to avelumab and trabectedin using safety information specified in the avelumab investigator brochure and trabectedin FDA-approved package insert. An event will be classified as related if the Sponsor-Investigator determines that the event may be related to the study drug.

For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition described in 21 CRF 312.32 as an AE for which there is a reasonable possibility that the drug caused the adverse event

where “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are serious, related, and unexpected will be reported to the FDA as an IND safety report, in accordance with regulations under 21 CFR 312.32.

The Sponsor-Investigator will provide written notification of safety report to the FHCRC IRB per IRB policies.

All SAEs must be reported to EMD Serono from the time of study drug administration through completion of the study. SAEs that occur after the study-specific informed consent is signed but prior to the first dose of the investigational agent will be collected only if they are considered by the investigator to be causally related to the study required procedures. Probably related SAE will be reported to EMD Serono within 2 business days or 3 calendar days (whichever comes first) of investigator becoming aware.

10.0 MANAGEMENT OF TOXICITY AND COMPLICATIONS

10.1 Adverse Drug Reactions (ADRs) Related to Avelumab

Adverse Drug Reactions Requiring Avelumab Discontinuation or Modifications

The following ADR/AEs require permanent treatment discontinuation of avelumab if they are not expected toxicities of trabectedin and their management is not specifically outlined below:

Any Grade 4 ADR/AEs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve or return to baseline within 7 days with adequate medical management

Any Grade 3 ADR/AEs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Laboratory values out of normal range that may be related to trabectedin.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration). Subjects may continue on study with ECOG PS ≤ 2.

Any Grade 2 ADR/AE should be managed as follows:

- If a Grade 2 ADR/AE resolves to Grade ≤ 1 by the last day of the current week, treatment may continue.
- If a Grade 2 ADR/AE does not resolve to Grade ≤ 1 by the last day of the current week, infusions should not be given on the following week. If at the end of the following week the event has not resolved to Grade 1, the subject should permanently discontinue treatment with a avelumab ADR/AE (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

10.2 Avelumab-Specific Adverse Events or Adverse Drug Reactions

10.2.1 Symptoms of Infusion-Related Reactions

Symptoms of infusion-related reactions include:

- Fever
- Chills
- Rigors
- Dyspnoea, wheezing
- Diaphoresis
- Headache

10.2.2 Management of Infusion-Related Reactions

10.2.2.1 Table 1: Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Study Drug
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 study drug 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 $\leq$ 24 h.	Temporarily discontinue 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 have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion 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 at the subsequent infusions based on treating investigator's medical judgment. If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.

10.2.2.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

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, as indicated per standard institutional practice. Alternative treatments for fever (for example, acetaminophen) may be given to subjects at the discretion of the Investigator.

10.2.2.3 Tumor Lysis Syndrome

In addition, avelumab can induce antibody-dependent cell-mediated cytotoxicity and can therefore theoretically cause tumor lysis syndrome. Should this occur, subjects should be treated per standard of care and the management algorithm listed in the appendix (Howard 2011). Because tumor lysis is almost never seen in soft tissue sarcoma subjects with the exception of several case reports, all subjects should be treated as having a low risk for tumor lysis syndrome.

10.2.2.4 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Table 2 Management of Immune-mediated Adverse Reactions: Guidance in this table is relevant to toxicities probably related to Avelumab. For toxicity attributed to trabectedin, treat according to the protocol or standard of care if treatment is not otherwise specified.

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4)	**Management**	**Follow-up**
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, 3 or 4.
Grade 2 **Diarrhea:** 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL **Colitis:** abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	**If improves to Grade ≤ 1:** Resume 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 for Grade 3. Permanently discontinue avelumab 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 steroids 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.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	**If persists > 1 to 2 weeks or recurs:** Withhold avelumab therapy. Consider skin biopsy. 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 steroids 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).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy. 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 opportunistic infections. Consider bronchoscopy, lung biopsy .	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 steroids taper**.** **If not improving after 2 weeks or worsening or for recurrent Grade 2:** 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 therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 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 1 month **If not improving after 48 hours or worsening:** Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
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 (this is common for trabectedin)	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days.	**If returns to Grade ≤ 1 or Baseline:** Resume routine monitoring; resume avelumab therapy. **If elevation persists > 5 to 7 days or worsens:** Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy. 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 or baseline:** 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.

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
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 hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). 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.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**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 or baseline:** Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. **If worsens:** Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy. 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.	**If returns to Grade ≤1 or baseline:** Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
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		

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**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 or baseline:** Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy. Up to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	**If improves to Grade ≤ 1 or baseline**: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy. Up 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 or baseline:** 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 hepatic toxicity is common with trabectedin and grade 3 can happen occasionally. While it is necessary to include these treatment guidelines for safety, in reality it is more likely that hepatic toxicity will be related to trabectedin.

10.3 Toxicity of Trabectedin

Trabectedin is given as standard of care and does have notable toxicities. The following are to be considered expected toxicities of trabectedin:

- Leukopenia (with neutropenia as the predominant component)
- Malaise
- Infection/sepsis
- Transaminase Elevation
- CK elevation
- Bilirubin or Alkaline phosphatase elevation
- Fatigue
- Nausea/vomiting
- Renal toxicity

Rhabdomyolysis is an unusual but well-described toxicity of trabectedin. If rhabdomyolysis is observed in a single case, this should not be considered a DLT but if multiple cases are seen, this must be reviewed by the DSMB.

10.4 Dose Modification of Trabectedin

Trabectedin is to be started at 1.5 mg/m^2. After the first week, the dose may be reduced if clinically indicated for toxicity management. Dose reductions will be noted in the subject's clinical record or research shadow chart.

As per standard practice, the subjects first dose reduction will be to 1.2 mg/m^2 and the second dose reduction will be to 1 mg/m^2. Dose reductions beyond 1 mg/m^2 are not permitted. If a subject is unable to tolerate a dose of 1mg/m^2, they must come off study. Trabectedin may be spaced out initially to 4 weeks and then to 5 weeks, as needed for toxicity management. If, in the opinion of the treating investigator, trabectedin needs to be spaced out greater than 5 weeks, Sponsor-Investigator approval is required.

Trabectedin dose reduction is required for the following adverse reactions:

- ANC < 1000/µL with fever and infection
- ANC <500/µL lasting > 5 days
- Platelets < 25,000/ µL
- Grade 3 or higher nausea and vomiting that persists despite a full anti-emetic regimen
- Grade 3 transaminitis not recovering to <2.5 x ULN or subject's baseline by 3 weeks post infusion
- Grade 3 Alk Phos Elevation not recovering to <2.5 x ULN or subject's baseline by 3 weeks post-infusion
- Total Bilirubin > 2.5 x ULN (direct bilirubin can be used if there is suspicion for Gilbert's syndrome)
- CK > 2.5 x ULN
- EF <45%

Subjects receiving the 1mg/m^2 dose of trabectedin with liver involvement from their cancer or baseline liver dysfunction, who are otherwise tolerating treatment well and appear to be benefiting from treatment on the study, may continue at the 1mg/m^2 after recovery from their liver dysfunction to grade 2, with Sponsor-Investigator approval.

11.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study medications.

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Documentation in the medical record

or source should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

An explanation for discontinuing treatment is recorded for each subject discontinuing treatment In the subject's medical record or research shadow chart. The Sponsor-Investigator must be notified immediately if a subject discontinues treatment. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor-Investigator decides to stop the study;
- at Investigator's discretion;
- at the subject's request;
- if the subject enrolls in a trial of another investigational agent;
- Grade 4 or life-threatening toxicity (See Section 9, Adverse Events) attributable to study agent, unless otherwise addressed;
- progression;
- pregnancy.

A subject that enters hospice care will be considered withdrawn from the study. Adverse events will no longer be monitored or recorded. If the subject experiences a serious adverse event related to study treatment prior to withdrawal, this event will be followed to resolution or recovered with sequelae. Subjects and their families will no longer be contacted, however survival status may be obtained via electronic medical record or public database.

12.0 CONCOMITANT MEDICATIONS

All medications taken at the start of the study will be documented/recorded in in the subject's medical record or research shadow chart.

12.1 Pre-Medication Treatment with Trabectedin and Avelumab

Pre-medication: Subjects will receive avelumab by IV infusion following pretreatment with H1 blockers and acetaminophen once every 2 weeks. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) 30 to 60 minutes prior to the first four (4) doses of avelumab. Premedication may be discontinued for Cycle 5 and beyond of avelumab, at the investigator's discretion. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Likewise, trabectedin is a moderately emetogenic chemotherapy and anti-emetics should be given according to standard of care including 20 mg dexamethasone IV given at 20-30 minutes before trabectedin. Alterations to the dexamethasone route of administration may be allowed with Sponsor-Investigator approval. Outside of this pre-medication recommended in the trabectedin package insert, corticosteroids use is discouraged when not absolutely necessary and is not allowed for the treatment of trabectedin associated nausea and vomiting unless the subject has tried and failed to control their nausea with 2 prior anti-emetic regimens. Additional information regarding premedication and administration schedule is noted in Section 7.0.

12.2 CYP3A4 Inhibitors and Inducers with Trabectedin

It is notable that trabectedin is metabolized through CYP3A4. All inhibitors or inducers of cytochrome CYP3A4 (see below) should be noted prior to study entry.

Inhibitors of CYP3A4 include but are not limited to:

- aprepitant
- clarithromycin
- clotrimazole

- diltiazem
- erythromycin
- fluconazole
- grapefruit juice
- indinavir
- itraconazole
- ketoconazole
- nefazodone
- nelfinavir
- ritonavir
- saquinavir
- telithromycin
- troleandomycin
- verapamil

Inducers of CYP3A4 include but are not limited to:

- barbiturates
- phenytoin
- carbamazepine
- rifabutin
- rifampin
- St. John's Wort

Should a subject start on any of these drugs, dose modifications of trabectedin may be considered in consultation with the pharmacy and at the discretion of the subjects treating physician.

Inactivated vaccines, including inactivated flu vaccines, are allowed on study. All other vaccinations that include live-virus components are prohibited for subjects on while on study.

13.0 CONTRACEPTION

Avelumab may have adverse effects on a fetus in utero. Furthermore, it is not known if avelumab has transient adverse effects on the composition of sperm.

Contraception guidance and definitions are provided in Appendix E.

14.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety

information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

15.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

15.1 Data Quality Assurance

Accurate and reliable data collection will be ensured by verification and crosscheck of the eCRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator.

15.2 Data Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy; and the laboratories, as well as copies of CRFs or CD-ROM.

15.3 Data Management

Data will be collected and entered into the eCRF. These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (in Appendix B, the investigator can search publicly available records (where permitted) to ascertain survival status.

This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

16.0 STATISTICAL CONSIDERATIONS

16.1 Study Design

The first six subjects (may expand up to 18) treated with avelumab combined with trabectedin will constitute the Phase 1 portion of the trial. If the combination is safe, the trial will be expanded to treat an additional 16 subjects. If a dose reduction is required based on 2 out of 6 subjects in the first phase having DLT, a dose reduction will be made, first to 1.0 mg/m^2 and if <2 subjects have DLTs at that dose, re-escalated to 1.2 mg/m^2. An additional 16 Phase 2 subjects will accrue using the highest dose tolerated with <2 DLTs.

A data and safety monitoring board will review any dose limiting toxicities that should arise on the Phase I portion of the trial. The DSMB will also review any DLTs in the extension portion of the trial at meetings described in the DSMB Charter. Should more than 30% of subjects have DLTs, accrual will halt until the DSMB can meet to advise on whether the trial may resume, with or without modification. Subjects on the Phase I portion of the study will also be included in the efficacy analysis.

16.2 Phase I Design

The primary objective of the Phase I component of this study is to evaluate the safety of avelumab given in combination with trabectedin among subjects with advanced L-type sarcomas. The phase I component of this study will treat 6 subjects (modified 3+3 design) to demonstrate safety of the combination. Dose-limiting toxicities will be defined as unexpected, probably-related toxicities of grade 3 or higher.

The study design is as follows:

6 subjects will be treated initially.

- If 2 or more subjects experience a DLT at any point during the Phase 1 portion, a new cohort will be added, enrolling an additional 6 subjects at a reduced dose of 1 mg/m^2 trabectedin.
- Should 2 or more of these next 6 subjects at the reduced dose have a DLT, stop and convene DSMB meeting to recommend changes to the protocol.
- If at any time in the study (including those above) 30% of subjects have a DLT, have a DSMB meeting to review specific toxicities. We will re-calculate the percent of subjects who have had a DLT each time there is a new DLT.

If <2 subjects have DLTs on the 1 mg/m^2 dose level, another Phase I cohort of 6 subjects implemented, re-escalating to 1.2 mg/m^2 dosing of trabectedin. If <2 DLTs are seen there, that will be the recommended Phase II dose. If 2 or greater DLTs are seen there, the Phase 2 will move forward at the 1.0 mg/m^2 dose level, after discussion with the DSMB.

Safety analysis will continue through the entire trial, if at any point during the trial 30% of subjects experience a DLT, the trial should halt and convene a meeting of the DSMB.

A total of up to 18 subjects may enroll on Phase 1, and an additional 16 on Phase 2.

16.3 Phase II Design

The primary objective of the Phase II portion is to compare the objective response rate (ORR) with historical rates for single agent trabectedin. Subjects from the Phase I portion of the trial who are treated at the dose ultimately used in the expansion will be included in the efficacy analysis. Our null hypothesis estimates the overall response rate of single agent trabectedin at 9.9%. We believe an increase in the response rate to 35% would be highly compelling. A total subject number of 22 gives us an 85% power to detect this increased response rate assuming a two-sided alpha of 0.05. 6 or more subjects with responses would suggest clinical activity of this regimen over single agent trabectedin.

16.4 Data and Safety Monitoring Board (DSMB)

A DSMB will make recommendations to the Sponsor-Investigator should significant toxicity be observed. The DSMB will meet if 2 of the first 6 subjects have a DLT or at any point after that if more than 30% of subjects have a DLT at the 1.5, 1.2 or 1 mg/m^2 dose. The DSMB will otherwise meet every 6 months while the study is actively enrolling and has active subjects on trial. If the trial is closed to enrollment and all subjects on study are in follow-up, the DSMB will meet once a year.

16.5 Additional Efficacy Hypotheses

The study is not powered to detect specific hypotheses with regards to correlative endpoints, rather this data and analysis will help better identify subjects having the potential to benefit from this therapy and aid in designing larger Phase III studies.

Summary statistics will be used to for describing changes across time. In addition, the time course of biomarker outcomes will be investigated graphically by summary plots or individual subject plots. Peripheral blood will be analyzed to examine the impact of T cell subpopulations and investigational work using formalin fixed tumor samples for immunohistochemistry and molecular analysis; this work will be exploratory. Categorical data analysis and logistic regression will be used to evaluate the associations between correlative measures and clinical outcome (eg, response, clinical benefit, time to progression, progression-free survival, and survival). If there is suggestion of meaningful trend, methods such as linear mixed models may be used to

characterize the pattern of change over time. Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.

16.6 Ethnic and Gender Distribution Chart

Projected Target Accrual

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	4	4	8
Not Hispanic or Latino	13	13	26
Ethnic Category Total of All Subjects*	**17**	**17**	**34**
Racial Categories			
American Indian / Alaska Native	1	1	2
Asian	3	3	6
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	2	2	4
White	8	8	16
More Than One Race	2	2	4
Racial Categories: Total of All Subjects*	**17**	**17**	**34**

17.0 INVESTIGATOR OBLIGATIONS

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the evaluation of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures.

18.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

18.1 Study Site Training

The Sponsor-Investigator is responsible for ensuring that all staff involved in the study are well acquainted with the protocol, study procedures, record keeping and administrative requirements, AE reporting, Good Clinical Practice guidelines, CRF/eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF/eCRF completion will be provided.

18.2 Documentation

The documentation of clinical data must be stored by the Sponsor-Investigator according to legal requirements. The Sponsor-Investigator and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor-Investigator, the FDA, and/or other applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all

amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, site, and Sponsor-Investigator); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

18.3 Data Collection

Electronic case report forms must be completed and submitted for each subject enrolled in the study. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the Sponsor-Investigator. All data fields in the CRF/eCRF must be completed to avoid queries.

18.4 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the Sponsor-Investigator and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC approval. The Sponsor-Investigator is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments) and other regulatory agencies according to national, state or local requirements. The Sponsor-Investigator, or its designee, is always available to answer protocol- or subject-related questions.

18.5 Study Monitoring and Data Collection

A study monitor may be used to ensure adherence to the protocol, applicable FDA regulations and/or other regulatory agencies national, state or local requirements, and the maintenance of adequate and accurate clinical records. Electronic case report forms are reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol, using the REDcap database platform. The monitor will be permitted to access subject medical records, laboratory data and other source documentation as needed to appropriately monitor the trial. Please reference Section 15 for additional information regarding data management and confidentiality.

18.6 Disclosure of Data/Publication

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, the Sponsor-Investigator and by the IRB/EC. Public presentation of data in any form will be thoroughly de-identified to ensure confidentiality.

18.7 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

18.8 Informed Consent

The Sponsor-Investigator assumes the responsibility of obtaining written Informed Consent from each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, their right to withdraw consent at any time, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the

original signed Consent Form will be filed with the subject's medical and/or research records, and copy maintained with the subject's study records. The date of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

18.9 Institutional Review Board/Ethics Committee

The Sponsor-Investigator will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the Sponsor-Investigator or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval.

The Sponsor-Investigator or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The Sponsor-Investigator or designee must notify the IRB of SAEs occurring at the site and of safety reports (e.g., IND Safety Reports) received from EMD Serono, in accordance with the IRB's policies.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

18.10 Subject Privacy

The Sponsor-Investigator affirms and will uphold the principle of the subject's right to privacy. The Sponsor-Investigator shall comply with applicable national and local privacy laws.

19.0 APPENDICES

19.1 APPENDIX A: ECOG Performance Status Scale

ECOG Performance Status Scale

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

19.2 APPENDIX B: Karnofsky Performance Status Scale

KARNOFSKY PERFORMANCE STATUS SCALE

General	Index	Specific Criteria
Able to carry on normal activity; no special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed	70	Care for self, unable to carry on normal activity or to do work
	60	Requires occasional assistance from others but able to care for most needs
	50	Requires considerable assistance from others and frequent medical care
Unable to care for self, requires institutional or hospital care or equivalent; disease may be rapidly progressing	40	Disabled; requires special care and assistance
	30	Severely disabled, hospitalization indicated, death not imminent
	20	Very sick, hospitalization necessary, active supportive treatment necessary
	10	Moribund
	0	Dead

19.3 APPENDIX C: Study Calendar

Study Flow Chart (for phase I portion)

Please note phase I and phase II schedules differ in that subjects on the phase I portion are required to be evaluated weekly up to week 7. Subjects on the phase II portion of the study and subjects on the phase I portion following week 7 are not required to be evaluated during weeks when they are not receiving therapy.

The study calendar will be managed in Weeks, with each dose of each drug being noted by a Cycle. For example, assuming there are no deviations from the planned schedule events, Week 1 will have Cycle 1 of avelumab and trabectedin. Week 3 will have Cycle 2 of avelumab, Week 4 will have Cycle 2 of trabectedin, Week 5 will have Cycle 3 of avelumab, Week 7 will have Cycle 4 of avelumab and Cycle 3 of trabectedin, etc. This may change based on dose delays or modifications. Weeks should be counted sequentially regardless of what number the dose of each agent is.

Treatment Week	Screening	1	2[13]	3	4	5	6[13]	7+[10]	EOT	30D Post EOT	90 Day Post EOT[12]	LTFU[12]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	Q12W
Drug Administration[1]	None	A+T	None	A	T	A	None	A+T	None	None	None	
Echo/MUGA[2]	X						X[2]					
Informed Consent, IC/EC Review, Demographnics and Med History	X											
Prior and Con-Med Review	X	X	X	X	X	X	X	X	X	X	X	
Post-study anticancer therapy status										X	X	X
Survival Status									X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	
Full Physical Examination (to include vitals, weight, ECOG)	X											
Directed Physical Examination (to include vitals, weight, ECOG)		X	X	X	X	X	X	X	X	X		
ECG (Phase 1 only)	X								X	X		
Pregnancy Test – Serum (WCBP Only)[3]	X	X		X		X		X[3]	X	X		
PT/INR and aPTT	X											
CBC with Differential, Blood Chemistry[5]	X[5]	X	X	X	X	X	X	X	X	X		
Urinalysis	X											
CK	X	X			X			X[6]	X	X		
T3, FT4 and TSH[7]	X							X[7]	X	X		
Tumor Imaging[8]	X							X[8]	X[8]			
Archival Tissue Collection (slides)[11]	X											
Correlative Studies Blood Collection[9]		X		X		X		X[9]	X			

[1]A= Avelumab, T = Trabectedin. Avelumab is administered every 2 weeks. Trabectedin is administered every 3 weeks for Cycle 1 and 2 (Week 1 and Week 4), and every 4 weeks after that (Week 7, Week 11, Week 15,…). Trabectedin may be given every 5 weeks if required due to toxicity (see section 9). Please reference Section 7 for additional details.

[2]ECHO or MUGA to be completed at baseline, week 6, and every 12 weeks while on trabectedin, beginning with week 18.

[3]Serum pregnancy test to be performed at baseline, and every 2 weeks (or every visit where avelumab is to be administered). Serum pregnancy will also be collected at end of treatment and 30 day follow-up visit. Women of childbearing potential only.

[5]Amylase and Lipase are only to be collected at baseline. Chemistry and LFT panel should include sodium, chloride, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, total protein, and albumin. Reference Table 1 for a full analyte listing.

[6]CK to be performed at all visits where trabectedin is administered. If trabectedin dosing schedule is modified at discretion of investigator to q4weeks or q5weeks or more, the creatine kinase draw should also be modified to follow that schedule.

[7]Thyroid studies should be checked at baseline, week 1, and every 6 weeks (+/- 7 days) (Week 1, Week 7, Week 13…)

[8]Can be done up to 28 days prior to Week 1. While on treatment, tumor imaging should be performed every 12 weeks. Subjects will have their first post-treatment scan during week 12 and every 12 weeks thereafter at the provider's discretion. Imaging schedule will continue every 12 weeks regardless of dose delays or schedule modifications. Tumor imaging will only be performed at EOT visit if not done within 4 weeks of the study visit.

[9]On treatment days, correlative blood should be drawn before study related treatment is administered. Correlative blood will be collected at week 7, and then starting at week 12 every 6 weeks on a treatment day (+/- 7 days). (Week 12, Week 18, Week 24…).

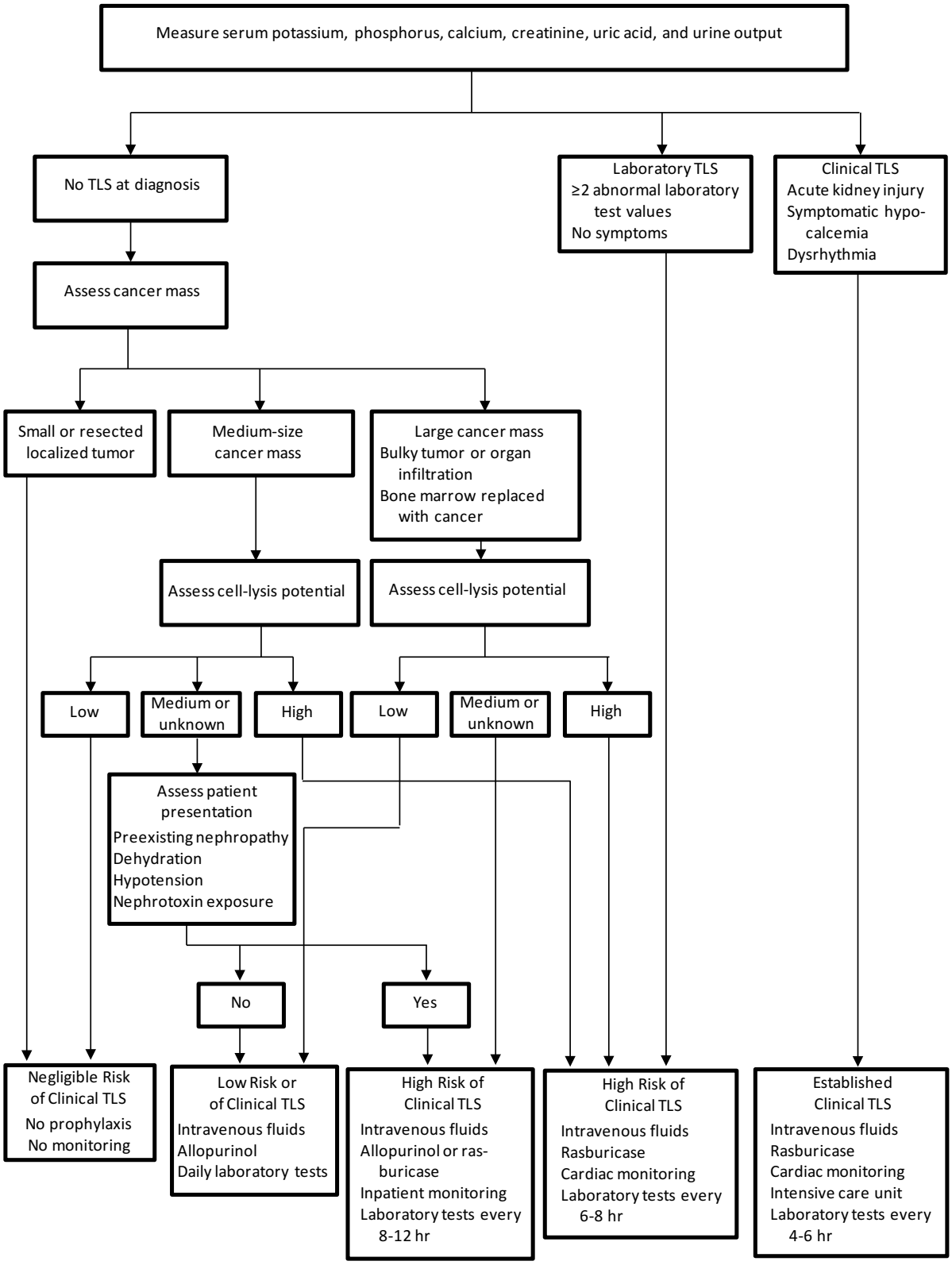
[10]Additional treatment days where avelumab is administered as a single agent should follow the schedule for Week 3, unless otherwise noted. Additional treatment days where trabected is administered and connected/disconnected as a single agent should follow the schedule for Week 4, unless otherwise noted. Additional treatment days where both avelumab and trabectedin are administered should follow the schedule for Week 1, unless otherwise indicated.

[11]Archival tissue collection does not need to be completed prior to beginning protocol therapy, but every effort should be made to ensure these samples are collected.

[12]The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

[13]Subjects enrolled to Phase 1 must complete weekly visits through Week 7. Subjects on the Phase II portion of the study and subjects on the Phase I portion after week 7 are not required to be evaluated during weeks when they are not receiving any therapy.

19.4 APPENDIX D: Assessment and Initial Management of Tumor Lysis Syndrome



19.5 APPENDIX E: Women and Men of Childbearing Potential Definitions and Methods of Contraception

19.5.1 Definitions

19.5.1.1 Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
      Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

19.5.1.2 Male of Childbearing Potential (WOCBP)

- For this trial, male subjects will be considered to be of non-reproductive potential if they have azospermia (whether due to having had a vasectomy or due to an underlying medical condition).

19.5.2 Contraception Guidance for Females of Childbearing Potential

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 3 months after last treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
- Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in related to the duration of the study and the preferred and usual lifestyle of the participant.
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - WOCBP participants who choose complete abstinence must continue to have pregnancy tests as specified in study calendar.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

Highly Effective Methods That are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of Ovulation

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Less Than Highly Effective Contraceptive Methods That are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

19.5.3 Contraception Guidance for Males of Childbearing Potential

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 5 months after last systemic dose.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 5 months after last systemic dose.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 5 months after last systemic dose.

- Refrain from donating sperm for the duration of the study treatment and for5 months after last systemic dose.

- Male participants may experience testicular side effects, such as reduced sperm production rates, reduced sperm concentrations, decreased epidydimal weights, atrophy and degeneration of the testes with aspermia (no sperm production), hypospermia (low or reduced sperm production), and cellular changes in the epididymis (a tube within the testes that transports sperm).

19.6 APPENDIX F: References

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