



**An Open-label, Single-arm, Multi-institutional Phase II Trial of Avelumab for Recurrent, Metastatic Nasopharyngeal Carcinoma**

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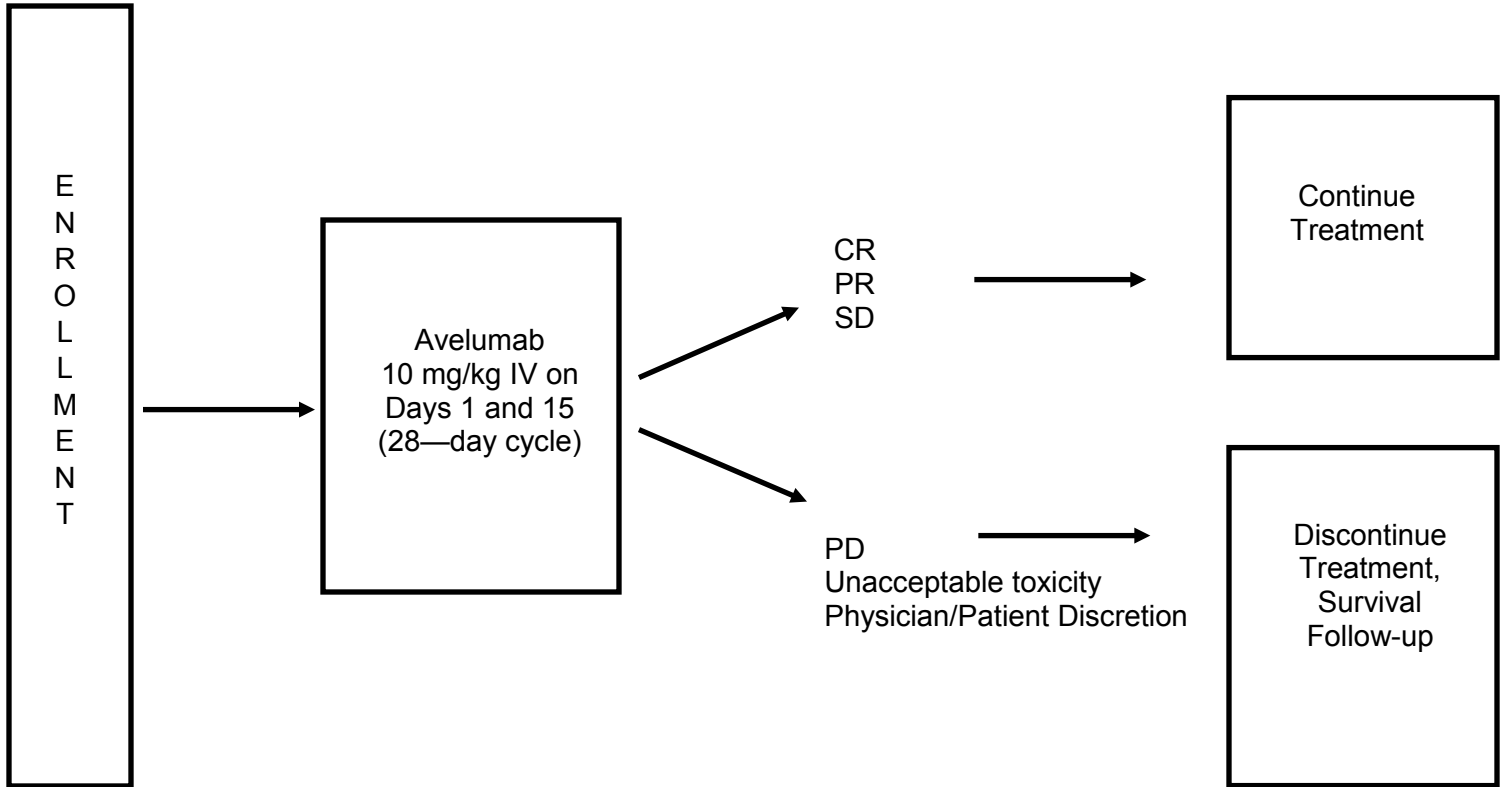
## LIST OF ABBREVIATIONS

AE	Adverse Event
ADCC	Antibody-dependent cell-mediated cytotoxicity
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
HIV	Human Immunodeficiency Virus
HRPP	Human Research Protections Program
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
I.V	Intravenous
LFT	Liver function test
LLN	Lower Limit Normal
MoAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NK	Natural Killer
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1
PET	Positron Emission Tomography
PFS	Progression-free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TSH	Thyroid Stimulating Hormone
UPR	Unanticipated Problems involving Risk to subjects or others
WBC	White Blood Cells



# STUDY SCHEMA



CR complete response  
PR partial response  
SD stable disease  
PD progressive disease

## STUDY SUMMARY

Title	An Open-label, Single-arm, Multi-institutional Phase II Trial of Avelumab for Recurrent, Metastatic Nasopharyngeal Carcinoma
Short Title	Phase II trial of Avelumab for Recurrent/Metastatic Nasopharyngeal Carcinoma
Phase	2
Methodology	Open-label, Single-Arm, Multi-institutional
Study Duration	3 years
Study Center(s)	University of California, San Diego; Stanford Cancer Institute; University of California, Los Angeles; University of California, Irvine; University of Southern California; Providence Portland Medical Center; Dana-Farber Cancer Institute
Objectives	<p><b>Primary Objective</b></p> <ol style="list-style-type: none"> <li>To determine the clinical activity of Avelumab in the management of R/M nasopharyngeal carcinoma.</li> </ol> <p><b>Secondary Objective</b></p> <ol style="list-style-type: none"> <li>To determine duration of response</li> <li>To determine progression-free survival at 6 and 12 months</li> <li>To determine overall survival</li> <li>To assess safety and tolerability of Avelumab</li> <li>To evaluate correlation between molecular markers and disease outcome</li> <li>To determine clinical activity using immune-related RECIST.</li> </ol>
Number of Subjects	39
Diagnosis and Main Inclusion Criteria	<p><b>Diagnosis/Main Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>Histologically/cytologically confirmed, non-keratinizing/undifferentiated, EBV-related nasopharyngeal carcinoma, not amenable to curative intent therapy</li> <li>At least one prior line of chemotherapy</li> <li>Measurable disease per RECIST v1.1</li> <li>Newly obtained tumor specimen for correlative analysis</li> <li>ECOG 0-2</li> <li>Adequate hematologic, renal, hepatic function</li> <li>Willingness to use appropriate contraception</li> </ul> <p><b>Key Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Prior immunotherapy with inhibitors of PD1/PDL1 axis</li> <li>Chemotherapy, RT or major surgery within 4 weeks</li> <li>Active CNS metastases (stable permitted)</li> <li>Uncontrolled HIV, Active Hepatitis B/C</li> <li>Active autoimmune disease</li> <li>Uncontrolled intercurrent illness</li> <li>Chronic use of steroids or other immunosuppressive agents</li> </ul>

	<ul style="list-style-type: none"> <li>Clinically significant cardiac disease</li> </ul>
Study Product(s), Dose, Route, Regimen	Avelumab 10mg/kg on days 1 and 15 of 28-day cycle
Duration of administration	Avelumab will be continued until disease progression, unacceptable toxicity, investigator decision or patient withdrawal.
Reference therapy	None
Statistical Methodology	<p><u>Safety population:</u> all patients who have received at least one dose of Avelumab.</p> <p><u>Intention-to-Treat (ITT) population:</u> all patients who have enrolled to the study.</p> <p><u>Sample Size/Primary Analysis</u> Simon's optimal two-stage design, primary endpoint of overall response (complete and partial responses) at 6 months, based on RECIST.</p> <p>If the overall response rate is <math>\leq 15\%</math>, we will consider the treatment as not meeting the threshold of going further. We will test the null hypothesis <math>H_0: p \leq 15\%</math> against the alternative hypothesis <math>H_1: p &gt; 15\%</math>, where <math>p</math> is the overall response rate after six months of study treatment. The two-stage design proposed below will have an 80% power to reject the null hypothesis and conclude that the true overall response rate is above 15%, if the observed overall response rate is <math>\geq 30\%</math>, at 10% significance level. The study design is described in detail is as follows:</p> <p><u>Stage 1:</u> 19 subjects will be accrued; accrual will be held until the progression results for all the 19 subjects are known for the first six months. The trial will be terminated at Stage 1 if <math>\leq 3</math> of the 19 subjects have any CR/PR by 6 months; otherwise it will continue to Stage 2.</p> <p><u>Stage 2:</u> 20 more patients will be accrued. We will reject the therapy if, among all the 39 (19+20) subjects, the number of patients who have an overall response is <math>\leq 8</math>; if <math>\geq 9</math> patients have a defined response by RECIST, the treatment will be successful. It will be concluded that our study treatment is associated with an overall response in more than 15% of patients.</p> <p>Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 68.4%.</p>

## SCHEDULE OF EVENTS

Procedure	Screen/ Baseline (≤ 21 days, unless otherwise noted)	Treatment Cycles (28-day cycles)					End of Treatment (28 (± 7) days after last dose)	Follow-up (q3 months)
		Cycle 1 (± 3 days)	Cycle 2 (± 3 days)	Cycle 3 (± 3 days)	Cycle 4 (± 3 days)	Each Additional Cycle (± 3 days)		
Informed Consent	<i>Within 28 days</i>							
Eligibility	X							
Medical History	X							
Demographics	X							
Concomitant Medications Assessment	X	X	X	X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X	
Physical Exam <sup>1</sup>	X	X	X	X	X	X	X	
Vital Signs & Height	X	X	X	X	X	X	X	
ECOG	X	X	X	X	X	X	X	
CBC with Diff <sup>2</sup>	<i>Within 7 days</i>	X	X	X	X	X	X	
CMP <sup>3</sup>	<i>Within 7 days</i>	X	X	X	X	X	X	
TSH <sup>4</sup>	<i>Within 7 days</i>		X		X		X	
Pregnancy test <sup>5</sup>	<i>Within 72 hours</i>							
Urinalysis <sup>6</sup> (dipstick)	X				X		X	
HIV (as clinically indicated)	X							
Hepatitis B & C (as clinically indicated)	X							
EBV DNA plasma level <sup>7</sup>	X				X		X	
Tumor tissue collection <sup>8</sup>	<i>Within 42 days</i>						X	
Blood Collection for Correlative studies <sup>9</sup>	X				X			
CT, MRI, or PET/CT <sup>10</sup>	<i>Within 28 days</i>				X			
Avelumab administration		X	X	X	X	X		

Survival contact									X
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Cycles are 28 days in length.

1. Full physical exam at baseline; targeted physical exam at other time points.
2. CBC with Diff: Complete blood count with differential.
3. CMP: Comprehensive metabolic panel (bicarbonate, calcium, chloride, creatinine, glucose, potassium, sodium BUN, albumin, bilirubin total, alkaline phosphatase, total protein, ALT, AST). For patients with known hepatic metastases at time of study entry, liver function tests (including ALT, AST, total bilirubin, and alkaline phosphatase) must be performed once weekly for 7 weeks upon treatment initiation.
4. TSH monitoring will occur at baseline, cycle 2, cycle 4, then every 3 cycles thereafter (ie. Cycle 7, 10 etc.), and at the end of treatment. For patients with asymptomatic TSH elevation, please refer to Section 4.3.1 for further evaluation. Specifically, if TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult.
5. Pregnancy test for females of child-bearing potential only.
6. Urinalysis (dipstick) will be performed at baseline, every 3 cycles following initiation of treatment (ie. Cycle 4, 7 and 10 etc.), and at the end of treatment. Urine microscopic examination should be performed if dipstick is abnormal.
7. EBV DNA plasma levels will be measured at baseline, every 3 cycles following initiation of treatment (ie. Cycle 4, 7, 10 etc.), and at end of treatment.
8. Newly obtained tumor tissue collection is mandatory upon study entry: See Section 5.5 for specifications. The study chair may grant exceptions to the mandatory biopsy should the treating physician deem that a biopsy is not feasible or unsafe for the patient, and archival tissue is available and provided for study purposes. A conversation with the study chair is required to obtain an exception. At time of disease progression, a repeat biopsy is encouraged but optional.
9. Blood for correlative studies should be collected at the same time blood is drawn for CBC and CMP if possible. 30 ml blood to be collected at baseline, at 12 weeks after treatment initiation ( $\pm$  7 days). See Section 5.5.
10. Imaging for radiographic disease assessment will be performed every 12 weeks following treatment initiation ( $\pm$  7 days). The same imaging modality should be used throughout the study when feasible. For patients who are clinically stable, a repeat scan will be required 4 weeks ( $\pm$  7 days) after initial radiographic findings of disease progression as a confirmatory assessment. For CT or MRI, neck and chest should be evaluated; abdomen/pelvis as indicated. If a PET/CT is utilized, CT must be diagnostic quality.

## **1.0 BACKGROUND AND RATIONALE**

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### **1.1 Disease Background**

Nasopharyngeal carcinoma (NPC), with approximately 80,000 cases worldwide, has distinct racial and geographic distributions.<sup>1</sup> While NPC is a leading cancer in endemic areas such as southern China, SE Asia, and Middle East/North Africa, it is much less common in the United States and Western Europe (incidence of 0.5 to 2 per 100,000).<sup>1-2</sup> Epstein-Barr virus (EBV) has been recognized as the primary causative agent in the pathogenesis of nasopharyngeal carcinoma, particularly in cases classified as non-keratinizing carcinomas, which are further subdivided by the World Health Organization (WHO) as differentiated (type II) and undifferentiated (type III). The majority of patients (~70%) present with locally advanced stage III/IV disease, and NPC has a predilection for early systemic dissemination (including lung, liver and bone).<sup>3</sup> For those patients who develop recurrent or metastatic NPC, curative intent therapy is rarely possible and treatment-related morbidity is high with poor survival. While first-line, platinum-based regimens have resulted in response rates as high as 60-70%, these responses are not durable as progression-free survival is still on the order of 5-6 months and median overall survival is typically 19-21 months.<sup>4</sup> Apart from gemcitabine (which has demonstrated clinical activity after platinum-failure in a small series), there is no well-defined paradigm for second line therapies or beyond.<sup>5</sup>

### **1.2 Role of EBV infection on PD-L1 expression**

Enhanced PD-L1 expression has been demonstrated in a variety of EBV-driven processes, including EBV-associated Hodgkin lymphoma, EBV-associated B-cell lymphomas and EBV-associated post-transplant lymphoproliferative disease (PTLD).<sup>6-7</sup>

Based on pre-clinical data, Fang et al have proposed two mechanisms by which EBV results in increased PD-L1 expression in NPC.<sup>8</sup> The innate immune resistance of EBV-induced latent membrane protein 1 (LMP1) correlates with upregulated PD-L1 expression. Secondly, the adaptive immune resistance in response to Interferon-gamma represents a distinct but synergistic mechanism of PD-L1 regulation in EBV-associated NPC. Interestingly, Fang et al were also able to demonstrate in multivariate analysis that PD-L1 expression was an independent poor prognostic factor in EBV-associated NPC; increased PD-L1 expression correlated with significantly shorter disease-free survival.

### **1.3 Rationale for PD-L1 Inhibition with Avelumab**

Because of the known role of programmed death ligand 1 (PD-L1) in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/programmed death 1 (PD-1) interaction presents a highly promising strategy for cancer immunotherapy.

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions.<sup>9-11</sup> PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; PD-L1 expression is greatly up-regulated after activation or interferon treatment.<sup>10</sup> Numerous results from in vitro cellular

assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production.<sup>12-18</sup> In PD-1<sup>-/-</sup> mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies.<sup>19-20</sup> Breaking tolerance through, blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer.<sup>21</sup>

External<sup>20</sup> and internal immunohistochemistry studies have demonstrated that PD-L1 is also expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment. In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue.<sup>14</sup> High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers.<sup>20</sup> Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in combination therapy setting<sup>13, 22-27</sup>.

The antitumor activity of avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor CD8<sup>+</sup> T cell responses.

To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all of the nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores antitumor CD8<sup>+</sup> T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumor immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumor types, but there is recent evidence that PD-L1 tumor expression is a pre-requisite to achieve an objective response upon blockade of the PD-1/PD-L1 axis.<sup>28</sup> The clinical relevance of PD-1/PD-L1 blockade has been demonstrated in Phase I trials performed with antibodies targeting either PD-L1 or PD-1.<sup>28-29</sup>

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

#### **1.4 Non-clinical 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- $\gamma$ ) 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-1+ T cells, CD8+ TEM cells, and antigen-specific T cell responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting.

## 1.5 Clinical Efficacy

Clinical Phase I/II trials with MoAbs targeting either PD-L1 or PD-1 have shown promising hints for clinical efficacy, i.e., objective tumor response in indications such as NSCLC, melanoma, and ovarian cancer.<sup>28-30</sup>

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

1. PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.
2. Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has ADCC potential. Upon binding to PD-L1 on tumor cells and binding with their Fc part to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

The clinical efficacy information 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 13.6% (25 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 19 of 122 subjects (15.6%) 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 to 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% 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).

## **1.6 Clinical Safety**

As of the safety cutoff date of 01 June 2015, 770 subjects have received at least one dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, and were followed for at least 4 weeks. Overall, 717 subjects have received the proposed dose of 10 mg/kg in the expansion cohorts, of which 184 subjects have NSCLC, 120 subjects have gastric cancer, 75 subjects have ovarian cancer and 44 subjects have urothelial carcinoma.

In the dose escalation portion of the Trial EMR 100070-001, 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 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 498 (69.5%) subjects in the pooled expansion cohort. The most frequently observed treatment related TEAE was infusion-related reaction reported in 134 subjects (18.7%), followed by fatigue reported in 130 subjects (18.1%) and nausea reported in 74 subjects (10.3%). Grade  $\geq$  3 treatment-related TEAEs were observed in 77 subjects (10.7%) in the pooled expansion cohort, of which 13.0%, 9.2%, 6.7%, and 4.5% occurred in the NSCLC, gastric cancer, ovarian cancer, and urothelial carcinoma expansion cohorts, respectively. Infusion-related reactions including hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

## **1.7 Clinical Data of PD-1/PD-L1 Axis Inhibition in Recurrent Nasopharyngeal Carcinoma**

Promising interim results from a phase 1b study evaluating the use of a PD-1 inhibitor in solid tumors, including patients with PD-L1 positive, advanced (unresectable and/or metastatic) NPC, was recently presented at the 2015 European Cancer Congress.<sup>31</sup> Twenty-seven patients with NPC were enrolled on study, with 92.5% of patients receiving prior treatment for R/M disease and 33.3% of patients being heavily pre-treated (at least 5 lines of prior therapy). One complete response and 6 partial responses were noted in addition to 14 patients experiencing stable disease. The overall response rate (confirmed and unconfirmed) was 25% (95%CI, 11.1–46.3). This preliminary signal for clinical efficacy in R/M NPC is encouraging, thus meriting further investigation.

## **1.8 Rationale for Study**

Building on the aforementioned findings, we thus propose a prospective phase II open-label trial to evaluate the clinical efficacy of PD-L1 inhibition with Avelumab in patients with R/M nasopharyngeal carcinoma. We hypothesize that PD-L1 inhibition will represent an attractive treatment approach given that EBV upregulates PD-L1 activity, and nasopharyngeal cancer (WHO II, III) is primarily EBV-driven. This therapeutic approach could translate into a clinically meaningful benefit for a patient population with otherwise significantly limited treatment options. Further, demonstration of clinical activity with Avelumab could ultimately lead to registration trials for its use in the management of R/M nasopharyngeal carcinoma.

## **2.0 STUDY OBJECTIVES**

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### **2.1 Primary Objectives**

To determine the clinical activity of Avelumab in the management of R/M nasopharyngeal carcinoma.

### **2.2 Secondary Objectives**

1. To determine duration of response
2. To determine progression-free survival at 6 and 12 months
3. To determine overall survival
4. To assess safety and tolerability of Avelumab
5. To evaluate correlation between molecular markers and disease outcome
6. To determine clinical activity using immune-related RECIST.

### **2.3 Endpoints**

#### Primary Endpoint:

1. Overall response rate (defined as complete or partial response) at 6 months based on RECIST.

#### Secondary Endpoints:

1. Duration of response, defined as time from documentation of tumor response to disease progression
2. Progression-free survival, defined as the time start of Avelumab until disease progression or death
3. Overall survival, defined as the time from start of Avelumab to death from any cause

4. Toxicity (grade 3 or higher), as defined by CTCAE 4.03.
5. Exploratory correlatives:
  - Tissue (new biopsy required upon study entry prior to therapy; repeat biopsy at time of progression will be encouraged but optional):
    - PDL1 expression by immunohistochemistry (ABC technique [Vector labs], using rabbit mAb 1:200 [Cell Signaling])
    - Immunophenotyping by flow cytometry:
      - T cell subsets (CD4, CD8, FOXP3)
      - Macrophages (CD68)
    - Cytokeratin 5/6 (by immunohistochemistry)
  - Peripheral blood (comparison of baseline and 12 week post-treatment samples, unless otherwise denoted)
    - TCR and BCR sequencing
    - T cell subsets (CD3, CD4, CD8, CD25, FOXP3)
    - B cells (CD19, CD20)
    - Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206)
    - Natural killer cell activity (CD56, CD16)
    - EBV DNA plasma levels (will be performed at baseline, every 12 weeks after treatment initiation and at end of treatment)
6. Clinical activity of Avelumab as defined by overall response rate will also be measured utilizing immune-related RECIST.

### **3.0 PATIENT ELIGIBILITY**

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#### **3.1 Inclusion Criteria**

Patients must meet all of the inclusion criteria to participate in this study.

1. Patient has the ability to understand and the willingness to sign a written informed consent.
2. Patient has histologically/cytologically confirmed, non-keratinizing/undifferentiated, EBV-related nasopharyngeal carcinoma, not amenable to curative intent therapy. EBV testing may be completed per institutional standards.
3. Patient must have at least one measurable site of disease as defined by RECIST v1.1, determined by investigator review
4. Patient has received at least one prior line of systemic therapy in the recurrent/metastatic setting.
5. Patient is willing to undergo a fresh tumor biopsy (core or excisional) for correlative analyses (ie. PD-L1 expression). The study chair may grant exceptions to the mandatory biopsy should the treating physician deem that a biopsy is not feasible or unsafe for the patient, and archival tissue is available and provided for study purposes. A conversation with the study chair is required to obtain an exception.
6. Age  $\geq$  18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance status of 0-2.

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

8. Patient has adequate organ and marrow function as defined below:
- Absolute Neutrophil Count  $\geq 1.0 \times 10^9/L$
  - Platelet count  $\geq 75 \times 10^9/L$
  - Hemoglobin  $\geq 8.0$  g/dL
  - Total bilirubin  $\leq 1.5$  x institution's upper limit of normal
  - AST/SGOT and ALT/SPGT  $\leq 2.5$  X institutional upper limit of normal
  - Albumin  $\geq 2.0$  g/dL
  - Serum creatinine  $\leq 1.5$  x institution's ULN, or creatinine clearance  $\geq 60$  ml/min
9. Female patient of childbearing potential has a negative serum or urine pregnancy within 72 hours prior to receiving the first dose of study medication.
10. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 4.6.2).
- Note: Females of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

### 3.2 Exclusion Criteria

Patients meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Patient is currently receiving or has received another investigational agent within 4 weeks prior to Day 1 of study.
2. Patient has received chemotherapy or radiotherapy within 4 weeks prior to Day 1 of study. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been radiated.
3. Patient has received prior immunotherapy with inhibitors of PD-1/PD-L1 axis.

4. Patient has had major surgery or insufficient recovery from surgical-related trauma or wound healing within 14 days of Study Day 1.
5. Patient has had a prior Grade  $\geq 3$  immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE  $>$  Grade 1.
6. Patient has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer.
7. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

Notes:

- Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment within the past 2 years are not excluded.
  - Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Patient has a diagnosis of immunodeficiency, or is receiving systemic steroid therapy ( $>10$ mg prednisone daily, or steroid equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of avelumab.
  10. Patient has a known history of active TB (*Baccillus Tuberculosis*).
  11. Patient has a known history of, or any evidence of active, non-infectious pneumonitis.
  12. Patient has a known history of chronic interstitial lung disease.
  13. Patient has an active infection requiring systemic therapy.
  14. Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
  15. Patient has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.

16. Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial.
17. Patient has known active Hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known Human Immunodeficiency Virus (HIV).
  - Patients with HIV who have a normal CD4 count ( $\geq 200$ ) and an undetectable viral load are not excluded.
18. Patient has received a live vaccine within 30 days of study Day 1.  
*Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

## **4.0 TREATMENT PLAN**

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### **4.1 Study Design**

This is a prospective, multi-center, open-label, single-arm phase II trial to evaluate the efficacy of Avelumab for patients with recurrent/metastatic, EBV-related nasopharyngeal carcinoma. A total of 39 patients will be eligible to enroll. Patients will be enrolled at 7 sites: UC San Diego Moores Cancer Center, Stanford Cancer Institute, UC Los Angeles Jonsson Comprehensive Cancer Center, UC Irvine Chao Cancer Center, University of Southern California Norris Comprehensive Cancer Center, Providence Cancer Center, and Dana-Farber Cancer Institute.

All patients providing informed consent will be screened for eligibility. Baseline assessments will include vital signs, physical exam, ECOG performance status evaluation, blood hematology and chemistries, urinalysis and tumor imaging. Upon study entry, all patients will receive Avelumab 10mg/kg IV on days 1 and 15 of each 28-day cycle. Treatment will be given until disease progression, unacceptable toxicity, investigator decision or patient withdrawal. Dose reductions and/or interruptions may occur per pre-specified criteria for grade 3 or higher toxicity.

History and physical examination, adverse event assessment and routine bloodwork will be performed prior to every cycle. For patients with known hepatic metastases at time of study entry, liver function tests (including ALT, AST, total bilirubin, and alkaline phosphatase) must be performed once weekly for 7 weeks upon treatment initiation. All patients will undergo imaging (CT, MRI, or PET/CT [CT must be diagnostic quality]) within 4 weeks prior to study entry, 12 weeks after treatment initiation (+/- 7 days), and then every 12 weeks thereafter (+/- 7 days). Response will be assessed using RECIST. For patients who are clinically stable, a repeat scan will be required 4 weeks (+/- 7 days) after initial radiographic findings of disease progression as a confirmatory assessment.

A newly obtained tumor specimen will be obtained prior to study entry (unless it is not feasible or deemed unsafe for the patient, archival tissue is available, and study chair has granted an exception) for the purposes of measuring PD-L1 expression, T cell subsets etc. Patients will also provide blood samples at baseline and 12 weeks after treatment initiation for correlative studies, including PBMCs, T and B-cell subsets, frequency and clonality. Peripheral blood will be collected at baseline, and then every 12 weeks after treatment initiation as well as at end of treatment for serial measurement of EBV plasma DNA levels. Additionally, at time of disease

progression, patients will be encouraged but not mandated to undergo a second biopsy for study purposes to permit further correlative studies.

An end of treatment visit for clinical evaluations and safety assessments will be performed approximately 28 days ( $\pm$  7 days) after the last dose of study drug. Patients discontinuing study treatment will be followed every 3 months for disease and survival outcomes.

## **4.2 Treatment Dosage and Administration**

### **4.2.1 Preparation and Administration of Avelumab**

Specific instructions for the preparation infusion fluid and administration of infusion solution are provided in the Pharmacy Manual.

Avelumab is administered on an outpatient basis. Avelumab 10mg/kg body weight, diluted with 0.45% or 0.9% saline solution, will be administered as a 60 minute intravenous (IV) infusion every 2 weeks.

### **4.2.2 Monitoring of Dose Administration**

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Events.

Patients will be monitored for the presence of infusion-related reactions. Dose modification and toxicity management for infusion-related reactions are outlined in the dose modification section (Section 4.3).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

### **4.2.3 Criteria for Starting Subsequent Cycles**

A cycle may be repeated every 28 days if the patient is without ongoing Grade 3 non-hematologic or Grade 4 hematologic toxicities attributable to study treatment.

## **4.3 Toxicities and Dosing Delays/Dose Modifications**

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03.

Adverse events (both non-serious and serious) associated with avelumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Avelumab must be withheld for drug-related toxicities and severe or life-threatening AEs as listed in Sections 4.3.1-4.3.3.

### **4.3.1 Management of Immune-Related Adverse Events**

Gastrointestinal irAEs		
Severity of diarrhea/Colitis (NCI-CTCAE v4)	Management	Follow-up

<b>Grade 1</b> Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	Continue avelumab therapy  Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms  Educate subject to report worsening immediately  If worsens: Treat as Grade 2 or 3/4
<b>Grade 2</b> Diarrhea: 4 to 6 stools per day over Baseline; i.v. fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy  If persists > 5-7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent  When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol.  If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade ¾
<b>Grade 3 to 4</b> Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; i.v. fluids ≥ 24 h; interfering with ADL  Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol  1.0 to 2.0 mg/kg/day methylprednisolone i.v. 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  If persists > 3 to 5 days, or recur after improvement: Add infliximab 5mg/kg (if no contraindication), Note: infliximab should not be used in cases of perforation or sepsis
<b>Dermatologic irAEs</b>		
<b>Grade of Rash</b> (NCI-CTCAE v4)	Management	Follow-up
<b>Grade 1 to 2</b> Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5-1.0 mg/kg/day methylprednisolone i.v. or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy  If worsens: Treat as Grade 3 to 4
<b>Grade 3 to 4</b> Covering > 30% body surface area; Life-threatening consequences	Delay or discontinue avelumab therapy  Consider skin biopsy  Dermatology consult  1.0 to 2.0 mg/kg/day methylprednisolone i.v. or i.v. equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy



<b>Pulmonary irAEs</b>		
<b>Grade of Pneumonitis (NCI-CTCAE v4)</b>	<b>Management</b>	<b>Follow-up</b>
Grade 1 Radiographic changes only	Consider delay of avelumab therapy  Monitor for symptoms every 2 to 3 days  Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks  If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy  Pulmonary and Infectious Disease consults  Monitor symptoms daily; consider hospitalization  1.0 mg/kg/day methyl-prednisolone i.v. or oral equivalent  Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days  If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
<b>Grade 3 to 4</b> Severe new symptoms; New/worsening hypoxia; Life-threatening	Discontinue avelumab therapy  Hospitalize  Pulmonary and Infectious Disease consults  2 to 4 mg/kg/day methylprednisolone i.v. or i.v. equivalent  Add prophylactic antibiotics for opportunistic infections  Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks  If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, i.v. immunoglobulin, or mycophenolate mofetil)
<b>Hepatic irAEs</b>		
<b>Grade of Liver Test Elevation (NCI-CTCAE v4)</b>	<b>Management</b>	<b>Follow-up</b>
<b>Grade 1</b> 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 3-4
<b>Grade 2</b> AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy  Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy  If elevations persist > 5-7 days or worsen : 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume

<b>Grade 3 to 4</b> AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Discontinue avelumab therapy  Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone i.v. or i.v. equivalent  Add prophylactic antibiotics for opportunistic infections  Consult gastroenterologist  Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	<b>avelumab therapy</b> If returns to Grade 2: 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
<b>Endocrine irAEs</b>		
<b>Endocrine Disorder</b>	<b>Management</b>	<b>Follow-up</b>
Asymptomatic TSH abnormality	Continue avelumab therapy  If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function  Consider pituitary scan  Symptomatic with abnormal lab/pituitary scan: Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone i.v. or by mouth equivalent Initiate appropriate hormone therapy  No abnormal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections  Resume avelumab therapy  Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of i.v. steroids with mineralocorticoid activity I.V. fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL: activities of daily living; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computerized tomography; irAE: immune-related adverse event; i.v.: intravenous; LFT: liver function test; LLN: lower limit of normal; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs; T4: free thyroxine; TSH: thyroid-stimulating hormone; ULN: upper limit of normal.

### 4.3.2 Management of Infusion-Related Reactions

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

NCI-CTCAE Grade	Treatment Modification for Avelumab
<b>Grade 1 – mild</b> Mild transient reaction; infusion interruption not indicated; intervention not indicated	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening

	The total infusion time for avelumab should not exceed 120 minutes
<b>Grade 2 – moderate</b> Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤ 24 h	Stop avelumab infusion  Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
<b>Grade 3 or Grade 4 – severe or life-threatening</b> <ul style="list-style-type: none"> <li>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</li> <li>Grade 4: Life-threatening consequences; urgent intervention indicated</li> </ul>	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

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

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from avelumab treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

#### 4.3.3 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at <https://www.resus.org.uk/pages/reaction.pdf>. Subjects should be instructed to report any delayed reactions to the investigator immediately.

##### A. Symptoms

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

##### B. Management

- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert intensive care unit for possible transfer if required

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab i.v. infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the investigator.

#### **4.4 Pre-Medications**

To mitigate infusion-related reactions, premedication with an antihistamine and with acetaminophen, per institutional standards, is mandatory prior to each dose of avelumab.

Management of infusion-related reactions should follow guidelines set forth in Section 4.3.2.

#### **4.5 Permitted concomitant therapy**

Concomitant medication also includes all prescription, over-the-counter (OTC), herbal supplements, blood transfusions, and IV medications. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug.

All concomitant medications received within 7 days before the first dose of trial treatment and 28 days after the last dose of trial treatment should be recorded in the patient's medical record.

#### **4.6 Prohibited concomitant therapy**

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than avelumab.
- Radiation therapy.
  - Note: Radiation therapy to a symptomatic lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the treatment portion of the study. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

#### **4.7 Other Considerations**

##### **4.7.1 Contraception**

Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is  $\geq 45$  years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period as defined above. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

#### **4.7.2 Pregnancy and Lactation**

##### **Pregnancy**

Pregnancy must be excluded before the initiation of and during avelumab therapy, and prevented by the use of reliable contraception during treatment.

If a patient inadvertently becomes pregnant while on treatment with avelumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Study Chair and to Pfizer without delay and within 24 hours to the Study Chair and within 2 working days to Pfizer if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Study Chair. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Study Chair and to Pfizer and followed as described above.

##### **Lactation**

It is unknown if avelumab is secreted in breast milk. Breast-feeding must be discontinued during treatment with avelumab.

#### **4.7.3 Overdose**

##### **Symptoms**

Experience with overdose of avelumab is not available.

##### **Management**

Treatment is directed to symptoms.

#### **4.8 Patient Withdrawal/Discontinuation from Study Treatment**

In the absence of treatment delays due to adverse events, study treatment may continue until:

- Disease progression
- The patient experiences unacceptable adverse event(s) or those events listed in the dose modification guidelines that require discontinuation;
- The patient exhibits an inter-current illness that prevents further administration of study

treatment,

- The patient has a confirmed positive serum pregnancy test;
- The patient or legal representative withdraws consent;
- The patient is noncompliant with trial treatment or procedure requirements;
- The patient is lost to follow-up;
- The patient dies;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator;
- Administrative reasons.

#### **4.9 End of Study Treatment and Follow Up**

After the last dose of study treatment, each patient will be followed for 28 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.1). Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up approximately every 3 months for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent or lost to follow-up.

After documented disease progression, each patient will be followed approximately every 3-6 months by review of medical records, telephone, or review of the Social Security Index for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

#### **4.10 Patient Withdrawal/Discontinuation from Study Criteria**

Patients may be removed from study participation for the following reasons:

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient dies;
- It is the decision of the investigator.

### **5.0 STUDY PROCEDURES**

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Refer to the study Schedule of Events for procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

#### **5.1 Definitions of Study Assessments**

##### **a. Medical history**

A medical history and details regarding the disease for which the patient has enrolled in this study will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Any clinically significant

changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

**b. Demographics**

The patient's demographic profile of date of birth, gender, race, and ethnicity will be obtained unless the patient declines.

**c. Review of eligibility criteria**

Review of eligibility criteria as described in Section 3 to ensure patient qualification for study entry and adjuvant study treatment.

**d. Concomitant Medication**

All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients from seven days prior to the first day of study treatment until 28 days after the last study dose (or until the start of a new treatment, whichever comes first) will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

**e. Physical exam**

The investigator or qualified designee will perform a complete physical examination during screening, which should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, and neurological systems. Subsequent exams may be directed as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

**f. Vital Signs and height**

Vital signs should include temperature, pulse, blood pressure and weight. Height will only be collected at screening.

**g. Performance status**

Performance status is evaluated by the ECOG scale.

**h. Adverse event assessment**

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

**i. Laboratory Assessments**

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5-1.

**Table 5-1. Laboratory tests**

<b>Hematology</b>	<ul style="list-style-type: none"><li>• Complete Blood Count (CBC) with differential<ul style="list-style-type: none"><li>○ hemoglobin,</li></ul></li></ul>
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	<ul style="list-style-type: none"> <li>○ hematocrit,</li> <li>○ platelet count,</li> <li>○ white blood cell count,</li> <li>○ percentage or absolute differential count</li> </ul>
<b>Chemistry</b>	<ul style="list-style-type: none"> <li>● Comprehensive metabolic panel (CMP) <ul style="list-style-type: none"> <li>○ albumin</li> <li>○ alkaline phosphatase</li> <li>○ aspartate aminotransferase (ALT)</li> <li>○ alanine aminotransferase (AST)</li> <li>○ bicarbonate (CO<sub>2</sub>)</li> <li>○ blood urea nitrogen (BUN)</li> <li>○ calcium</li> <li>○ chloride</li> <li>○ creatinine</li> <li>○ glucose</li> <li>○ potassium</li> <li>○ sodium</li> <li>○ total protein</li> <li>○ total bilirubin</li> </ul> </li> <li>● Thyroid stimulating hormone (TSH)</li> </ul>
<b>Pregnancy Test</b>	<ul style="list-style-type: none"> <li>● Urine human chorionic gonadotropin (HCG) or serum βHCG</li> </ul>
<b>Urinalysis</b>	<ul style="list-style-type: none"> <li>○ Blood,</li> <li>○ Glucose,</li> <li>○ Protein,</li> <li>○ Specific gravity</li> <li>○ Microscopic exam (<i>if abnormal</i>)</li> </ul>
<b>If clinically indicated</b>	<ul style="list-style-type: none"> <li>● Hepatitis B: HepB sAg and/ or Hep B DNA</li> <li>● Hepatitis C: Hep C RNA PCR</li> <li>● HIV</li> </ul>

**j. Blood collection for correlative studies**

See Section 5.5 for details.

**k. Tumor assessment**

Radiologic assessment is performed by MRI with gadolinium or CT with contrast (neck and chest; abdomen/pelvis as indicated) or PET/CT. If a PET/CT is performed, the CT must be of diagnostic quality. The same radiographic technique should be used throughout the study. However, a patient who develops a contraindication to undergo an MRI scan during study treatment may remain on study and undergo contrast enhanced CT scans.

**l. Tumor biopsy and tissue collection**

See Section 5.5 for details.

**5.2 Screening/Baseline Procedures**

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 21 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent (*within 28 days*).
- Review of inclusion and exclusion criteria.



- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests (*within 7 days; pregnancy test within 72 hours*).
- Blood collection for EBV DNA plasma levels and correlative studies.
- Documentation of tumor staging (*imaging completed within 28 days*).
- Tumor biopsy tissue collection for correlative studies (*within 42 days*).

### **5.3 Procedures During Treatment**

#### **5.3.1 Cycle 1 Day 1 ( $\pm 3$ days)**

- Focused physical exam, including vital signs, ECOG performance status assessment and weight
- Assess for adverse events
- Update concomitant medications
- Collect blood samples for CBC with differential, CMP
- For patients with known hepatic metastases at time of study entry, liver function tests (including ALT, AST, total bilirubin, and alkaline phosphatase) must be performed once weekly for 7 weeks upon treatment initiation.

#### **5.3.2 Each Additional Cycle, Day 1 ( $\pm 3$ days)**

- Focused physical exam, including vital signs, ECOG performance status assessment and weight
- Assess for adverse events
- Update concomitant medications
- Collect blood samples for CBC with differential, CMP

#### **5.3.3 Thyroid studies and Urinalysis ( $\pm 3$ days)**

- Collect blood sample for TSH at cycle 2, cycle 4, then every 3 cycles thereafter (ie. cycle 7, 10 etc). Obtain urinalysis (dipstick) every 3 cycles following treatment initiation (ie. cycle 4, 7, 10 etc). Urine microscopic examination should be performed if dipstick abnormal.

#### **5.3.4 Additional Blood Collection for Correlative Studies ( $\pm 7$ days)**

- Collect blood sample to measure EBV DNA plasma levels every 3 cycles (ie. cycle 4, 7, 10 etc) and at end of treatment.
- Collect blood sample for additional correlative studies at 12 weeks after treatment initiation (ie. cycle 4).

#### **5.3.5 Imaging (every 12 weeks $\pm 7$ days after treatment initiation)**

- MRI, CT (neck and chest; abdomen/pelvis when indicated) or PET/CT (CT must be diagnostic quality)
- For patients who are clinically stable, a repeat scan will be required 4 weeks ( $\pm 7$  days) after initial radiographic findings of disease progression as a confirmatory assessment.

#### **5.3.6 End of Treatment Visit (*28 days after last dose, $\pm 7$ days*)**

- Focused physical exam, vital signs, ECOG performance status, weight
- Documentation of concomitant medications and adverse events.
- Collect blood samples for CBC with differential, CMP, TSH, EBV DNA plasma level.
- Collect urine sample for urinalysis.
- Optional tumor biopsy for patients who developed disease progression as reason for end of treatment

#### **5.4 Follow-up Procedures**

Patients discontinuing study treatment will be followed every three months after the last dose of study treatment until death with:

- Tumor assessments if they discontinued from study treatment without disease progression- until disease progression or initiation of a new anti-cancer therapy, and
- Survival contacts via medical record review, telephone call, or review of the Social Security Index.

#### **5.5 Correlative Studies**

The goal of the planned laboratory correlative studies is to examine the relationship between presence of EBV infection and PD-L1 expression, to gain a better understanding of the impact of avelumab on the tumor's immunophenotype, and explore potential biomarkers which may correlate with response to avelumab.

##### **5.5.1 Sample Collection Guidelines**

Specimens should be collected as outlined below and ALL samples should be labeled with the following:

- Protocol number
- Institution
- Patient's de-identified study number
- Date of biopsy or surgery

##### **5.5.1.1 Newly obtained tumor tissue**

Newly obtained tumor tissue will be collected, preferably from a diagnostic core biopsy, within 42 days of initiating study treatment.

Samples collected for research will be obtained from only material in excess of that needed for routine clinical care as determined by a staff pathologist.

When possible, 4 core biopsies should be taken for lesions > 1.5 cm, otherwise 2 cores should be taken.

- If 4 cores are obtained, 1 core should be fresh frozen and the rest should be formalin-fixed paraffin embedded (FFPE).
- If < 4 cores are obtained, tissue for research should be FFPE after being divided into the research and diagnostic documentation blocks according to the Pathology staff's specifications.

Ten (10) unstained sections (4-5 micron slices) or one (1) 20 micron roll-ups from FFPE tissue are desired.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

### **5.5.1.2 Peripheral Blood Mononuclear Cells (PBMCs)**

Blood for PBMCs will be collected prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

Blood samples will be collected in two heparin green top tubes (approximately 20 ml).

Additional blood sample collections will be performed at:

- Twelve weeks after treatment initiation (+/- 7 days)

Samples should be processed the day of collection according to the PBMC isolation protocol in the Laboratory Manual.

PBMCs should be stored at -80°C until shipment.

### **5.5.1.3 Buffy Coat**

Blood samples will be collected in one EDTA purple top tube (approximately 10 ml) prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

Additional blood samples will be collected in one EDTA purple top tube (approximately 10 ml) at:

- time of first radiographic disease assessment 12 weeks after treatment initiation, ( $\pm$  7 days)

Samples should be processed the day of collection according to the buffy coat isolation protocol in the Laboratory Manual.

Samples should be stored at -80°C until shipment.

### **5.5.2 Specimen Shipping**

Samples should be batched and shipped overnight for receipt on weekdays only during normal business hours to the Coordinating Site UCSD laboratory at the following address:

Attn: Sharmeela Kaushal  
Moores Cancer Center, 3345/3G, GG  
3855 Health Sciences Drive  
La Jolla, CA 92093-0819  
Phone: 858-822-7661

PBMC and buffy coat samples should be shipped on dry ice. FFPE tumor tissue (archived or newly obtained) can be shipped at room temperature. Please notify the Study Coordinator prior to shipment so it can be expected.

### **5.5.3 Specimen Analyses**

Analyses will be performed at the direction of the study chair, Dr. Sacco.

Tumor specimens will be evaluated by immunohistochemistry (IHC) for such biomarkers as:

- PD-L1 expression
- T cell subsets (CD4, CD8, FOXP3)
- Macrophage (CD68)

- Cytokeratin 5/6

PBMCs will be analyzed by flow cytometry for the following immune cell markers:

- T cell subsets (CD3, CD4, CD8, CD25, FOXP3)
- B cells (CD 19, CD20)
- Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206),
- Natural killer cell activity (CD56, CD16)

Buffy coat samples will be analyzed for T cell receptor (TCR) and B cell receptor (BCR) sequencing.

EBV DNA plasma levels will be evaluated in peripheral blood at baseline, then every 12 weeks after treatment initiation and at end of treatment.

Fresh frozen core biopsies (when available) will undergo whole exome sequencing for neoantigen discovery.

Additional biomarkers may be examined as new information arises.

#### **5.5.4 Specimen Banking**

Patient samples collected for this study will be retained in the UCSD Moores Cancer Center Biorepository for analysis and future cancer research. Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator at each local site will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. This information will be transmitted to and retained by the Coordinating Site UCSD. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

Dissemination of specimens for research is at the discretion of the Study Chair, Dr. Sacco. Potential research collaborators outside of UCSD who approach the Moores Cancer Center for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research, and any specimen left over from research will either be returned to the Cancer Center or destroyed. Any data obtained from the use of clinical specimen will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to the local site principal investigator, who will inform the Study Chair Dr. Sacco. Dr. Sacco will use her best efforts to stop any additional studies and to destroy the specimens. Samples stored in the Biorepository will be destroyed; for samples that have been disseminated outside of the Biorepository, Dr. Sacco will contact the recipient to notify them of the need to halt further research and destroy specimens.

## **6.0 Measurement of Effect**

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### **6.1 Safety/tolerability**

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (<http://ctep.cancer.gov/reporting/ctc.html>) for reporting of adverse events.

### **6.2 Antitumor Effect**

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. See Appendix A.

#### **6.2.1 Best Overall Response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

#### **6.2.2 Progression-Free Survival**

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death.

#### **6.2.3 Time to Progression**

Time to progression is defined as the duration of time from start of treatment until objective tumor progression.

#### **6.2.4 Overall Survival**

Overall survival is defined as the duration of time from start of treatment to death.

## **7.0 ADVERSE EVENTS**

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An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational agent, is also an AE.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

## 7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins at the time of initiating study treatment through **90 days** following the last administration of study treatment or study discontinuation/termination, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to avelumab.

Note: Serious adverse events must be recorded in the case report forms for this 90 day-period; however, non-serious adverse events need only be recorded through 28 days post last study drug administration.

All patients experiencing an adverse event at least possibly related to study treatment will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

## 7.2 Severity

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at <http://ctep.cancer.gov/reporting/ctc.html>

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities; intervention not indicated.

Moderate (grade 2): the event causes discomfort that affects normal daily activities; minimal, local or noninvasive intervention indicated.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status; intervention indicated.

Life-threatening (grade 4): the patient was at risk of death at the time of the event; urgent intervention indicated.

Fatal (grade 5): the event caused death.

### 7.3 Seriousness

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

**1. Results in death.**

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

**2. Is life-threatening.**

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

**3. Requires in-patient hospitalization or prolongation of existing hospitalization.**

Note: Hospitalization (including hospitalization for an elective procedure) for a preexisting condition which has not worsened does not constitute a serious adverse event.

**4. Results in persistent or significant disability or incapacity.** Substantial disruption of one’s ability to conduct normal life functions.

**5. Is a congenital anomaly/birth defect.**

**6. Is an important medical event.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event”.

*For example:* allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

### 7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.

Probable – The AE *is likely related* to the study treatment.

Possible – The AE *may be related* to the study treatment.

Unlikely – The AE *is doubtfully related* to the study treatment.

Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator’s Brochure (or Product Label when applicable).

### 7.6 Reporting Requirements for Adverse Events

#### 7.6.1 Expedited Reporting

Serious adverse events, or a follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time study treatment initiation through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, requires expedited reporting as described below.

### 7.6.2 Expedited Reporting to Site Principal Investigator and Study Chair

The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events (SAEs).

### 7.6.3 Expedited Reporting to Pfizer

Pfizer must be notified within 2 working days of learning of any SAEs or non-serious Events of Clinical Interest:

**Name: TBD**  
**Attn: TBD**  
**FAX: TBD**

The Study Chair will submit a copy of all 15 Day FDA Reports to Pfizer at the time of submission to FDA.

### 7.6.4 Expedited Reporting to Regulatory Authorities

- A.** The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.
- B.** The **UCSD Human Research Protections Program (HRPP) and Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.
- C.** The FDA must be notified by the Study Chair according to the following timelines:
- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
  - within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

### 7.6.5 Routine Reporting Requirements for Adverse events

- A.** The **IRB of each site** must be notified by the site principal investigator according to their local policies.



- B. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- C. The **FDA** must be notified by the Study Chair of all non-serious adverse events annually at the time of the annual report.

## 8.0 AGENT INFORMATION

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### 8.1 Avelumab

Please refer to the Product Label and Investigator's Brochure for more comprehensive information.

**Other names for the drug:** MSB0010718C

**Mechanism of action (or Product description):**

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.

**Availability:** Clinical supplies are provided by Pfizer, and will be affixed with a clinical label in accordance with regulatory requirements.

**Dosage Forms and Strengths:**

Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentrations of 10 mg/mL and 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Each single-use 10 mg/mL vial contains 80 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.5) containing Mannitol, Methionine, and Polysorbate 20 (Tween 20).

Each single-use 20 mg/mL vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

**Preparation:**

Avelumab will be prepared according to the product label unless otherwise directed in the Pharmacy Manual.

Avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques: Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium

chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

For detailed information on the assigned dose levels and the concrete volumes to be replaced to prepare the target doses, please refer to the clinical trial protocol or to the manual of preparation.

**Storage and stability:**

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab.

Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

For application in clinical trials, avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user.

**No other drugs should be added to the solution for infusion containing avelumab.**

**Route of administration for this study:** Intravenous infusion over 1 hour.

**Side effects:**

For the purpose of regulatory reporting requirements during clinical development, the following AEs will be considered as expected and met the threshold of casual association (based on comprehensive evaluation) defined by the Sponsor:

- Infusion-related reactions including hypersensitivity reactions
- Immune-mediated adverse reactions like immune-mediated colitis, immune-mediated hepatitis including autoimmune hepatitis, immune-mediated thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis and autoimmune thyroiditis, immune-mediated pneumonitis, immune-mediated skin reactions including rash, pruritis, rash generalized, rash macula-papular, erythema, pemphigoid, other immune mediated reactions including myocarditis, adrenal insufficiency, uveitis, iritis, myositis.

**8.1.1 Study Drug Accountability and Disposition**

The Study Chair and site Principal Investigators are responsible for ensuring accountability for the investigational agent, including reconciliation of materials and maintenance of drug records.

Dispensing and administration of avelumab will be recorded following institutional practices. An accurate accounting will be available for verification. Accountability records will include:

- Confirmation of delivery to the site

- Inventory at the site
- Dispensing for each patient
- Return or alternative disposition of unused study drug

Upon completion or termination of the study, all unused and/or partially used avelumab will be destroyed at each site per institutional policy. It is the Principal Investigators' responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 9.0 STATISTICAL CONSIDERATIONS

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### 9.1 Study Populations

The Safety population will consist of all patients who have received at least one dose of Avelumab.

The Intention-to-Treat (ITT) population will consist of all patients who have enrolled to the study.

### 9.2 Sample Size and Primary Analysis

A Simon's optimal two-stage design will be used for this cohort. The primary endpoint is overall response (CR or PR) rate at 6 months based on RECIST. If the overall response rate is  $\leq 15\%$ , we will consider the treatment as not meeting the threshold of going further. We will test the null hypothesis  $H_0: p \leq 15\%$  against the alternative hypothesis  $H_1: p > 15\%$ , where  $p$  is the overall response rate after six months of study treatment. The two-stage design proposed below will have an 80% power to reject the null hypothesis and conclude that the true overall response rate is above 15%, if the observed overall response rate is  $\geq 30\%$ , at 10% significance level. The study design is described in detail is as follows:

Stage 1: 19 subjects will be accrued; accrual will be held until the progression results for all the 19 subjects are known for the first six months. The trial will be terminated at Stage 1 if  $\leq 3$  of the 19 subjects have any CR/PR by 6 months; otherwise it will continue to Stage 2.

Stage 2: 20 more patients will be accrued. We will reject the therapy if, among all the 39 (19+20) subjects, the number of patients who have an overall response is  $\leq 8$ ; if  $\geq 9$  patients have a defined response by RECIST, the treatment will be successful. It will be concluded that our study treatment is associated with an overall response in more than 15% of patients.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 68.4%.

The sample size calculation was done using PASS version 8.0.16 (released January 27, 2011).

**Final efficacy analysis** will calculate the UMVUE estimate, p-value and 95% CI for the response rates.<sup>32-33</sup> The calculation will be performed using R *clinfun* package ([www.r-project.org](http://www.r-project.org)).

### **9.3 Accrual**

A minimum of 6 patients with R/M NPC are evaluated monthly across all 7 institutions included in this study. We therefore anticipate this study would require no more than 12 months to accrue.

### **9.4 Secondary Efficacy Analyses**

Secondary analysis will present duration of response, progression-free survival, and overall survival. We will estimate median survival times together with their 95% confidence intervals, and report number of events, as well as Kaplan Meier plots with 95% confidence bands.

### **9.5 Secondary Safety Analyses**

Analyses will be performed for all patients having received at least one dose of study treatment. The proportion of subjects experiencing adverse events, serious adverse events, and treatment delays will be summarized. Tolerability will be assessed based on dosage delays and discontinuation due to adverse events.

All AEs will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown.

### **9.6 Analysis of Biomarkers**

The Chi-Square (or Fisher's Exact test) will be used to assess the association of categorical clinical data with categorical biomarker data. Time-to-event clinical data (PFS, OS) will be correlated with biomarker data using Kaplan-Meier methodology and Cox regression models. Logistic regression models will also be used to predict binary clinical data with baseline biomarker data. Finally, graphical methods and descriptive statistics will be used to summarize the data as well.

## **10.0 STUDY MANAGEMENT**

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### **10.1 Conflict of Interest**

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

### **10.2 Institutional Review Board (IRB) Approval and Consent**

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must

include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

### **10.3 Required Documentation For Multi-site Studies**

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office:

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation. (NOTE: this is required if UCSD holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

### **10.4 Patient Registration**

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to the study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call (858)-xxx-xxx Monday through Friday, 8:00am-4:30pm Pacific Time. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5380).

Patients will be given a unique sequential study number at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration, the patient's study number, and ability to start study treatment.

### **10.5 Subject Data Protection**

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

### **10.6 Data and Safety Monitoring/Auditing**

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon risk-based assessments.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen

toxicities. Data from this study will be reported annually and will include:

- 1) the protocol title, IRB protocol number, and the activation date of the study.
- 2) the number of patients enrolled to date.
- 3) the date and site of patients' enrollment.
- 4) a summary of all adverse events regardless of grade and attribution.
- 5) a response evaluation for evaluable patients when available.
- 6) a summary of any recent literature that may affect the ethics of the study.

## **10.7 Adherence to the Protocol**

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

### **10.7.1 Emergency Modifications**

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

### **10.7.2 Protocol Violations**

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion. For the UCSD IRB:

- A. Major violations** must be reported to the IRB within 10 working days of awareness of the violation.

Major violations include:

- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

- B. Minor violations** may be reported to the IRB at the time of the continuing review.

Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

## **10.8 Amendments to the Protocol**

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRBs at each site and submitted to the FDA by the Study Chair for approval prior to implementation.

## **10.9 Record Retention**

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient

consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

#### **10.10 Obligations of Investigators**

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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## 12.0 APPENDICES

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### Appendix A. Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [Eisenhauer et al. 2009].

#### 1 Measurability of Tumor at Baseline

##### 1.1 Definitions

At baseline, tumor lesions will be categorized as follows:

##### 1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

*Malignant lymph nodes*: to be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in *short* axis when assessed by CT scan. At baseline and in follow-up, only the *short* axis will be measured and followed.

##### 1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

##### 1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

*Bone lesions*:

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

*Cystic lesions*:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable

lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

*Lesions with prior local treatment:*

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

## **1.2 Specifications by methods of measurements**

### **1.2.1 Measurement of lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

### **1.2.2 Method of assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

*Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

*Chest X-ray:* Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

*CT, MRI:* CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

*Ultrasound:* Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

*Endoscopy, laparoscopy:* The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

*Cytology, histology:* These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell

tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

## **2 Tumor Response Evaluation**

### **2.1 Baseline documentation of ‘target’ and ‘non-target’ lesions**

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

*Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

### **2.2 Response criteria**

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

### 2.2.1 Evaluation of target lesions

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

**Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

### 2.2.2 Special notes on the assessment of target lesions

*Lymph nodes.* Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

*Target lesions that become 'too small to measure'.* While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

*Lesions that split or coalesce on treatment.* When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this

instance should be the maximal longest diameter for the 'coalesced lesion'.

### **2.2.3 Evaluation of non-target lesions**

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD):** Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

### **2.2.4 Special notes on assessment of progression of non-target disease**

The concept of progression of non-target disease requires additional explanation as follows:

*When the patient also has measurable disease.* In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

*When the patient has only non-measurable disease.* This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

### **2.2.5 New lesions**

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging

modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

### **2.3 Evaluation of best overall response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’. This is described further below.

#### **2.3.1 Time point response**

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

**Appendix Table 1.** Time point response: patients with target (+/- non-target) disease.

<b>Target Lesions</b>	<b>Non-target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
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CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

**Appendix Table 2.** Time point response: patients with non-target disease only.

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

### 2.3.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

### 2.3.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

*Best response determination in trials where confirmation of complete or partial response IS NOT required:* Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

*Best response determination in trials where confirmation of complete or partial response IS required:* Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

**Appendix Table 3.** Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR



CR	PR	SD, PD OR PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
inevaluable	Inevaluable	Inevaluable

#### 2.3.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to ‘normal’ size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of ‘zero’ on the case report form (CRF).

In trials where confirmation of response is required, repeated ‘NE’ time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define ‘early progression, early death and inevaluability’ are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

## **2.4 Confirmatory measurement/duration of response**

### **2.4.1 Confirmation**

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

### **2.4.2 Duration of overall response**

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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

### **2.4.3 Duration of stable disease**

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.