UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

NCT03312114

Title: Phase II trial of Concurrent Anti—PD-L1 and SAbR for Patients with Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (with safety lead-in)

Document Date: 10/17/18

UTSouthwestern Harold C. Simmons Comprehensive Cancer Center | NCI Designated Comprehensive Cancer Center

STU 032017-078 Phase II trial of Concurrent Anti—PD-L1 and SAbR for Patients with Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (with safety lead-in)

Principal Investigator: Kevin Albuquerque, MD
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd, Dallas, TX 75390
Telephone: (214) 645-7296; Fax: (214) 645-9233
Email: kevin.albuquerque@utsouthwestern.edu

Co-Principal Investigator Jayanthi Lea, MD
Division of Gynecologic Oncology
University of Texas Southwestern Medical Center
Dallas, TX 75390
Telephone: (214) 648-3111
Email: jayanthi.lea@utsouthwestern.edu

Co-Investigator(s): Raquibul Hannan, MD
David Miller, MD
Matthew Carlson, MD

Biostatistician: Hong Zhu, Ph.D.
Email: hong.zhu@utsouthwestern.edu

Study Drug/Treatment: **MSB0010718C:** Avelumab

IND/IDE Number: 135852

IND/IDE Holder Name: Kevin Albuquerque, MD
University of Texas Southwestern Medical Center

Funding Source: Individual Investigator Grant from Pfizer (trial and drug funding)

Version:

Version	Date
Initial	**3/31/2017**
v2	**09/19/2017**
v3	**10/27/2017**
v4	**12/11/2017**
v5	**08/22/2018**

UT Southwestern Medical Center (UTSW)
Radiation Oncology
Attn: Clinical Research Office
2280 Inwood Rd

Dallas, Texas 75235

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

TABLE OF CONTENTS

List of Abbreviations

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio

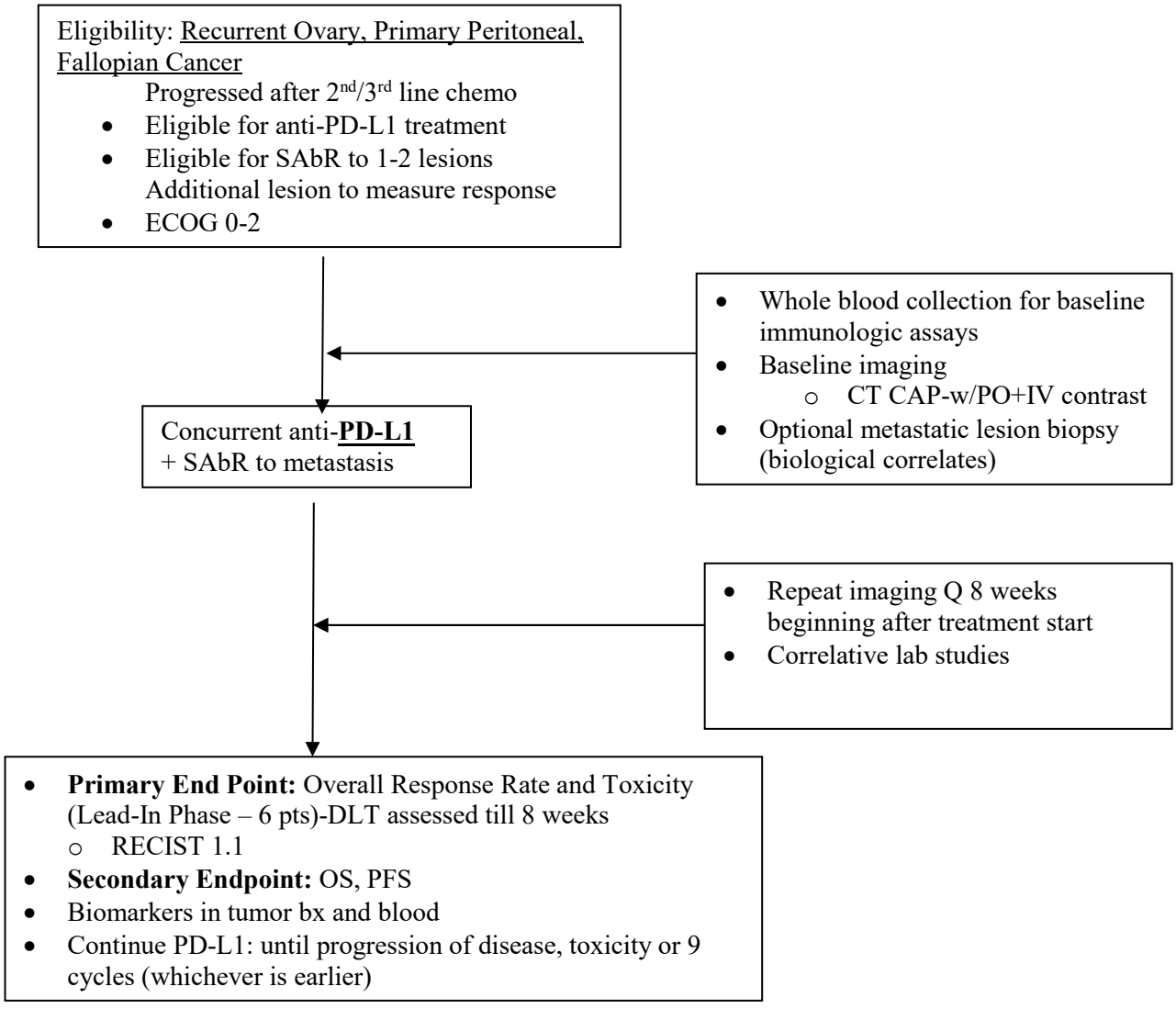
Abbreviation or special term	Explanation
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
SBRT	Stereotactic body radiotherapy
IMRT	Intensity modulated radiotherapy
UTSW:	University of Texas-Southwestern
SABR:	Stereotactic Ablative Radiotherapy

STUDY SCHEMA

SCHEMA:

(Diagram):



STUDY SUMMARY

Title	Phase II trial of Concurrent Anti—PD-L1 and SAbR for Patients with Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (with safety lead-in)
Short Title	Avelumab and SABR for Recurrent Ovarian cancer
Protocol Number	STU 032017-078
Phase	Phase II
Methodology	Open label, one-arm, bi-modality, single center trial
Study Duration	3 years
Study Center(s)	Single-center
Objectives	Trial of combined Avelumab (MSB0010718C) anti-PD-L1checkpoint blockade with SAbR for Recurrent Ovarian and peritoneal, fallopian tube cancer (ROPT) to assess overall clinical response rates per-RECIST, with prior safety lead-in
Number of Subjects	29
Diagnosis and Main Inclusion Criteria	**Recurrent Ovarian, peritoneal and fallopian tube cancer (ROPT)**
Study Product(s), Dose, Route, Regimen	Concurrent Anti—PD-L1 (Avelumab) and SAbR. Avelumab will be dosed intravenously (IV) over 60 minutes (±10 min) at 10 mg/kg every 2 weeks (± 2 days) of each treatment cycle until disease progression or 9 cycles. SABR will be administered to 1-2 sites of metastatic disease within 15 days after commencing the immunotherapy with 3 fractions to a total dose of 24-36 Gy (8-12 Gy per fraction x 3 fractions) targeted to the largest easily accessible metastases based on normal tissue tolerances.
Duration of administration	Up to 9 cycles
Reference therapy	Avelumab alone
Statistical Methodology	Exact binomial method will be used to estimate the Overall Response and toxicity rate in patients receiving SAbR+avelumab along with corresponding 95% confidence interval. Correlation analysis will be performed with tumor immune cell PD-L1 and serial serum cytokine estimation.

1.0 Background and Rationale

1.1 Disease Background

Epithelial Ovarian cancer (EOC) is the leading cause of gynecologic cancer deaths, and the fifth most common cause of cancer deaths in women in the United States. An estimated 14,346 women will die of ovarian cancer in the United States in 2015[1]. Although about 75% of patients with epithelial ovarian cancer will respond to first-line chemotherapy with platinum and paclitaxel, most patients with advanced stage epithelial ovarian cancer will recur. While there are several active cytotoxic agents for the treatment of recurrent epithelial ovarian cancer, median survival after recurrence is about 2 years [2]. Like recurrent ovarian, most recurrent epithelial cancers of fallopian tube and primary peritoneal origin are genetically unstable, aggressive neoplasms accounting for the majority of gynecologic cancer deaths. About 25% of patients are platinum resistant (defined as recurring within 6 months of completing platinum-based chemotherapy) at the time of first recurrence, and essentially all women with recurrent ovarian cancer eventually become platinum-resistant. In a recent trial, chemotherapy alone (weekly paclitaxel, liposomal doxorubicin, or topotecan), resulted in a median progression-free survival of 3.4 months. While this improved to 6.7 months with the addition of bevacizumab, there was no improvement in median overall survival [3] Therefore, there is a need for developing and testing novel agents in this population.

Some other drugs have single agent activity in refractory cases, but the response rates are low (10–20%) and without a clear survival. For example, in a GOG study looking at Gemcitabine , the Overall response rate (CR+PR) was 16% and Time to progression was 5.4 months [4]

A more recent study was conducted The Gynecologic Oncology Group (GOG) to evaluate the impact of the histone deacetylase inhibitor, belinostat, in combination with carboplatin in women with platinum-resistant ovarian cancer. An ORR of 7.4% with TTP of 3.3 months was obtained highlighting the very poor prognosis for these patients.

1.2 Immunotherapy (IT) and Recurrent Ovarian Cancer (ROPT)

Studies have demonstrated that ovarian cancers are immunogenic and elicit spontaneous antitumor immune responses from immunotherapy.[5, 6] Preclinical studies have shown that ovarian cancer mouse models develop immunosuppressive phenotypes which enable them to evade the immune system, whereas combined immune checkpoint blockade reverses this phenotype. Expression of PD-L1 by tumors has been associated with decreased intraepithelial TILs and poor overall survival in EOC. In an immune-competent murine model of EOC, PD-1 and PD-L1 blockade has led to eradication of tumors through the expected reprogramming of the tumor microenvironment, which suggests potential benefit from PD-1/PD-L1 inhibition for patients with EOC .The presence and the number of tumor-infiltrating lymphocytes in recurrent ovarian cancer has shown to be a significant prognostic factor[7, 8] Programmed death-1 receptor ligand (PD-L1) the ligand for PD-1 is a key therapeutic target in the reactivation of the immune response against multiple cancers [9]. Pharmacologic inhibitors of PD-1 have also demonstrated significant anti-tumor activity and are currently under active clinical exploration[10]. FDA approval has been granted to biologic agents Nivolumab (BMS936558) and Pembrolizumab (Pembro, MK-3475) for treatment of advanced (metastatic) squamous non-small cell lung cancer (NSCLC) and melanoma, respectively. PD-L1 expression levels have been correlated with poor clinical prognosis in renal, gastric, ovarian, breast and esophageal cancers [11-15]. Avelumab* (MSB0010718C; anti-PD-L1 is a fully human anti-PD-L1 IgG1 antibody that has shown promising efficacy and an acceptable safety profile in multiple tumor types[16]. There are now published data showing the activity of avelumab in treatment of patients with Merckel cell carcinoma (Kaufman HL et al, 2016, Lancet Oncology) and the drug has received accelerated FDA approval for second line treatment of metastatic bladder cancer.

Role of Radiation in Recurrent Ovarian Cancer The role of radiation in ovarian cancer is controversial in the adjuvant setting though ovarian cancer is known to be radio-sensitive[17] . However, there is the

emerging data that focal radiation is effective in selected patients with Localized Recurrent ovarian cancer.[18-21].We have previously shown a benefit for loco-regional control of selected localized ROC with involved field radiation therapy (IFRT)[21] In a comparison cohort we demonstrated a 50% improvement in OS for radiation compared to chemotherapy in a limited recurrent setting.

Radiation therapy (RT) is one of the mainstream treatments of cancer therapy along with surgery and chemotherapy, yet RT is the only treatment that does not leave the patients immunocompromised (unlike chemotherapy) and keeps the dying tumor / antigen depot within the host (unlike surgery), providing an opportunity for antigen presentation. Therefore, RT is a rational choice to combine with immunotherapy for cancer treatment.

1.3 Study Agent(s) Background and Associated Known Toxicities

1.3.1 Immunotherapy (IT) Avelumab* (MSB0010718C; anti-PD-L1 is a fully human anti-PD- L1 IgG1 antibody that has shown promising efficacy and an acceptable safety profile in multiple tumor types.[5]. Because of the known role of programmed death ligand 1 (PD-L1) in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/programmed death 1 (PD-1) interaction presents a highly promising strategy for cancer immunotherapy. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. The non-clinical and clinical experience is fully described in the current version of the Avelumab Investigator's Brochure (IB Version 7.0). The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143,832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1.

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-□□ 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.

1.3.1.1 Non-clinical studies and Toxicity

The toxicological profile of avelumab was investigated in vivo in mice, rats, and cynomolgus monkeys. In addition, in vitro cytokine release assays in human and cynomolgus monkey whole blood and PBMCs as well as tissue cross reactivity studies in normal human and cynomolgus monkey tissues were performed. Additionally, data on the UV absorption of avelumab were generated.

On the basis of the binding affinity data, the cynomolgus monkey was selected as relevant species for the nonclinical safety testing of avelumab. Signs of hypersensitivity or avelumab-related infusion reactions were not observed in cynomolgus monkeys after repeated treatment with avelumab at dose levels of 20, 60 and 140 mg/kg. Avelumab was well tolerated systemically and accordingly, the NOAEL was established at the high dose of 140 mg/kg in both, the 4-week and the pivotal 13-week, repeat-dose monkey studies.

1.3.1.2 Clinical studies –summary of efficacy and safety

Several clinical studies have been initiated as detailed in the IB. However, none have been reported except in abstract form. Data from 1629 subjects from ongoing Studies EMR100070 001 (20 November 2015 cut-off date), EMR100070 002 (20 November 2015 cut-off date), and EMR100070

003 (03 March 2016 cut-off date) were used to estimate PK parameters and to evaluate the PK interindividual variability. Safety data is also available from this same dataset.

Some preliminary individual trial results are as follows:

The second-line NSCLC expansion cohort in the ongoing Phase I Trial EMR100070-001 had a cutoff date of 15 January 2015, 6 months after the start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). This group of subjects with NSCLC presented with a median age of 65.0 years, and all of whom had Stage IIIB or IV NSCLC that had progressed after at least 1 line of platinum-containing doublet chemotherapy for metastatic or locally advanced disease. As of 15 January 2015, 41 of 184 subjects (22.3%) remained on study treatment, and 143 subjects (77.7%) discontinued study treatment at the time of the data cutoff. The major reason for treatment discontinuation was disease progression (93 subjects, 50.5%) followed by AE (18 subjects, 9.8%). Of 184 patients, 22 had a confirmed objective response, including one complete response and 21partial responses, resulting in a confirmed objective response rate of 12.0% (95% CI: 7.6, 17.5).

The unconfirmed objective response rate was 14.1% (95% CI: 9.4, 20.0), including one complete response and 25 partial responses. Based on confirmed or unconfirmed responses, 10 of 26 responding patients (39%) had responded by the first assessment at 6 weeks, and 19 of 26 (73%)had responded by 12 weeks; median duration of response was not reached, with response durations ranging from 0.1 to ongoing at 54.1 weeks. Among 22 patients with a confirmed response, response was maintained for 24 weeks or longer in 83% of cases (95% CI: 54, 94) by Kaplan-Meier estimates. Median PFS was 11.6 weeks (95% CI: 8.4, 13.7), and PFS rates at 24 weeks and 48 weeks were 26% (95% CI: 20, 33) and 18% (95% CI: 12, 26), respectively. At the time of analysis, 139 of184 patients (76%) had a PFS event (progressive disease (116 [63%]) or death (23 [13%]). Based on immune-related response criteria, median PFS was 17.6 weeks (95% CI: 12.1, 22.9), and rates at 24 and 48 weeks were 39% (95% CI: 31, 46) and 33% (95% CI: 25, 42), respectively.

1.3.1.3 Ovarian Cancer: Recently the first experience with Avelumab in ovarian cancer;

The JAVELIN Solid Tumor phase IB trial [6] specifically reported safety and clinical activity of avelumab in a large series of patients with recurrent/refractory ovarian cancer (OC; NCT01772004). Patients received avelumab 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 wks. (RECIST 1.1). As of Oct 23, 2015, 124 pts were treated with avelumab (median 12 wks. [range 2-54]) and followed for a median of 54 wks. (range 11-101). Median number of prior therapies was 4 (range 1-13). Treatment-related (TR) AEs occurred in 82 pts (66.1%); most common (≥10%) were fatigue (13.7%), infusion-related reaction (12.1%), and diarrhea (11.3%), all of grade 1/2. Grade 3/4 TRAEs were reported in 8 pts (6.5%); of these, only increased lipase occurred in > 1 pt (n = 2). There were no treatment-related deaths. ORR was 9.7% Stable disease was observed in 55 pts (44.4%); disease control rate was 54.0%.The first published phase 2 study by Hamanishi et al [7] from Japan using the PD-1 checkpoint inhibitors Nivolumab for (with platinum-resistant, recurrent, or advanced ovarian cancer to evaluate the safety and antitumor efficacy of nivolumab have been reported show the best ORR of 15%.

1.3.1.4 Urothelial cancer:

Trial EMR100070-001 enrolled 2 cohorts of subjects with locally advanced or metastatic UC who were either cisplatin ineligible or had PD after at least 1 line of platinum-based therapy (Table 16). As of 19 March 2016, a combined 241 subjects had been treated in the 2 UC cohorts, of whom 153 had at least 6 months of follow-up (all 44 subjects in the secondary UC cohort and 109 of the 197 subjects in the efficacy UC cohort). Of the 241 subjects, 87 (36.1%) were still on treatment at the time of data cut-off.

In the pooled group of 153 subjects with at least 6 months of follow-up, the confirmed ORR was 17.6% (95% CI: 12.0, 24.6), consisting of 9 subjects (5.9%) with CR and 18 subjects (11.8%) with

PR. Onset of response was documented at the first or second tumor assessment for 21 of the 27 confirmed responses (77.8%), with a median time to response of 11.43 weeks (range: 5.6 to 48 weeks). Median duration of response was not yet reached (95% CI: 42.14 weeks, not estimable [NE]); the Kaplan-Meier estimate of 24-week durability of response was 92.0% (95% CI: 71.6, 97.9). Of the 27 confirmed responses, 24 (88.9%) were ongoing at the time of data cutoff, with duration of response ranging from 4.7 to 65.7 weeks.

1.3.1.5 Pregnancy:

Based on its mechanism of action, avelumab can cause foetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to foetal tissue. Human IgG1 immunoglobulins are known to cross the placenta. Therefore, avelumab has the potential to be transmitted from the mother to the developing foetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. Therefore, potential risks of administering avelumab during pregnancy include increased rates of abortion or stillbirth.

Reported toxicity Treatment-related TEAEs and Grade ≥ 3 treatment-related TEAEs

The most frequently reported (incidence at least 5 subjects, 0.3%) treatment-related TEAEs (any grade) in the pooled safety dataset are summarized in Table 19 of IB v7.0 . The most frequently reported Grade ≥ 3 treatment-related TEAEs in the pooled safety dataset (occurring in at least 3 subjects, 0.2%) are presented in Table below.

Treatment-related TEAEs were observed in 1164 (67.0%) subjects in the pooled safety dataset. Treatment-related TEAEs with an incidence of ≥0.3% of any grade were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

Grade ≥ 3 treatment-related TEAEs were observed in 177 subjects (10.2%) in the pooled safety dataset. As shown in table, the most frequently reported (at least 3 subjects, 0.2%) Grade ≥ 3 treatment-related TEAEs were fatigue, lipase increased (17 subjects each; 1.0%), GGT increased, infusion related reaction (10 subjects; 0.6%), AST increased (8 subjects; 0.5%), pneumonitis (7 subjects; 0.4%), anaemia, blood CPK increased (6 subjects each; 0.3%), diarrhea, asthenia (5 subjects each; 0.3%), autoimmune hepatitis, ALT increased, amylase increased, hyponatraemia, hypophosphataemia (4 subjects each; 0.2%). Other Grade ≥ 3 treatment-related TEAEs that were observed in 3 subjects (0.2%) included lymphopenia, adrenal insufficiency, hypothyroidism, colitis, vomiting, autoimmune disorders, lymphocyte count decreased, transaminase increased, decreased appetite and hypokalaemia.

1.3.2 Most Frequently Reported (at Least 3 Subjects [0.2%]) Grade ≥ 3 Treatment Related TEAEs by SOC and PT in the Pooled Safety Dataset

The table below contains toxicity data from a pooled dataset of patients on several Avelumab studies. The 1738 subjects comprising the pooled safety dataset includes subjects from 16 tumor expansion cohorts from Study EMR100070-001 as well as from MCC subjects from Part A of Study EMR100070-003.the data refers to Grade ≥ 3 treatment emergent adverse effects reported. Overall, the severe significant toxicity appears to be low.

Table 20 **Most Frequently Reported (at Least 3 Subjects [0.2%]) Grade ≥ 3 Treatment-Related TEAEs by SOC and PT in the Pooled Safety Dataset**

Body System or Organ Class Preferred term	Pooled Safety Dataset (N=1738) N (%)
Number of Subjects With At Least One Event	177 (10.2)
Blood and lymphatic system disorders	13 (0.7)
Anaemia	6 (0.3)
Lymphopenia	3 (0.2)
Endocrine disorders	7 (0.4)
Adrenal insufficiency	3 (0.2)
Hypothyroidism	3 (0.2)
Gastrointestinal disorders	16 (0.9)
Diarrhea	5 (0.3)
Colitis	3 (0.2)
Vomiting	3 (0.2)
General disorders and administration site conditions	28 (1.6)
Fatigue	17 (1.0)
Asthenia	5 (0.3)

Body System or Organ Class Preferred term	Pooled Safety Dataset (N=1738) N (%)
Hepatobiliary disorders	8 (0.5)
Autoimmune hepatitis	4 (0.2)
Immune system disorders	4 (0.2)
Autoimmune disorder	3 (0.2)
Injury, poisoning and procedural complications	12 (0.7)
Infusion related reaction[a]	10 (0.6)
Investigations	58 (3.3)
Lipase increased	17 (1.0)
Gamma-glutamyltransferase increased	10 (0.6)
Aspartate aminotransferase increased	8 (0.5)
Blood creatine phosphokinase increased[b]	6 (0.3)
Alanine aminotransferase increased	4 (0.2)
Amylase increased	4 (0.2)
Lymphocyte count decreased	3 (0.2)
Transaminases increased	3 (0.2)
Metabolism and nutrition disorders	20 (1.2)
Hyponatraemia	4 (0.2)
Hypophosphataemia	4 (0.2)
Decreased appetite	3 (0.2)
Hypokalaemia	3 (0.2)
Respiratory, thoracic and mediastinal disorders	18 (1.0)
Pneumonitis	7 (0.4)

[a] Numbers (percentages) refer to the preferred term (PT) of infusion related reaction only, and differ from the numbers (percentages) for the composite of PTs reported elsewhere in this document.

1.3.3 SAbR: Stereotactic ablative body radiation (SAbR) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body" [22] . Potential indications for SAbR include a broad spectrum of tumor types and locations. The safety and efficacy of SAbR to multiple sites is excellent as documented in multiple studies [23-25]. Recently, SAbBR was shown to have multiple immunogenic properties including induction of an immunogenic tumor cell death and initiation of tumor antigen presentation [13, 14]. Since SAbBR is a highly focused therapy, it does not inherently immunocompromise the host. It also spares the surrounding lymph nodes which are vital for an effective immune response. Furthermore, since SBRT causes local inflammation, dendritic cells (DCs) are attracted into the tumor. The antigen- presenting properties and the induction of immunogenic cell death by SBRT via the release of danger-associated molecules (DAMPS) such as HMGB1, HSP and Calreticulin are well documented [15-17].

A recent comprehensive literature review [26] of SAbR for gynecological tumors between 1993-2013 identified 12 case series and one phase 2 trial [27]. This phase 2 II clinical trial evaluated the safety and efficacy of SAbR in 50 patients with recurrent cervical, endometrial, ovarian, and vulvar cancer. SRS was used to deliver 24 Gy in 3 fractions to a clinical target volume (CTV) that included the gross tumor volume (GTV) as well as surrounding fluorodeoxyglucose (FDG)-avid

areas. Sixty-two percent of patients showed clinical benefit at 6 months. Most toxicity was mild, though one patient did experience grade 4 hyperbilirubinemia and another developed an enterovaginal fistula. SAbR was considered safe for recurrent gynecological tumors by the authors.

1.4 Rationale

Programmed death receptor 1 (PD-1) is a transmembrane protein of the immunoglobulin CD-28 family and is expressed on activated immune cells including macrophages, dendritic cells, activated B and T cells [28]. Two ligands specific for PD-1 have been identified: PD-L1 and PD-L2. PD-L1 is a member of the B7 family costimulatory molecules. Except for some immune cell lineages, human cells do not normally express PD-L1. In addition, while not commonly expressed in tumor cell lines in vitro, PD-L1 is widely expressed in various in vivo tumor tissues. Multiple studies have shown that interferon-gamma (IFN-γ) produced by activated T-cells induce the over expression of PD-L1 on tumor cells [29]. Tumor cells, induced by IFN-γ, can express high levels of PD-L1, which interacts with PD-1 on immune cells, and through PI3K/Akt inhibition, suppresses their immune response by inducing T cell apoptosis, anergy, exhaustion, dendritic cell suppression, IL-10 production and Treg induction. PD-L1 and PD-1 interaction also protect tumor cells from lysis by cytotoxic T lymphocytes [30]. Given the expression of PD-L1 on host immune cells, anti-body mediated PD-L1 inhibition should work in both PD-L1 positive tumors.

As discussed above, Avelumab* (MSB0010718C; anti-PD-L1) is a fully human anti-PD-L1 IgG1 antibody that has shown promising efficacy and an acceptable safety profile in multiple tumor types. Avelumab blocks the interaction between PD-1 and PD-L1, and thus activates the immune system in a non-specific manner. SABR should be able to provide a specific direction to the immune response by promoting antigen presentation. Recruited and activated by the DAMPs and other changes brought onto the tumor microenvironment by radiation therapy, the APCs migrate to the lymph node for antigen presentation and T-cell activation. RT also increases tumor infiltrating lymphocyte (TIL) trafficking within irradiated tumors [31, 32]. Typically, TILs produce IFN-γ which promotes antigen presentation but at the same time induces PD-L1 expression which is meant to prevent the propagation of the inflammatory response and limit tissue damage. In the presence of PD-1 inhibitors, INF-γ will enhance antigen presentation and stimulate the immune response without the down-stream effects of PD-1/PD-L1 interaction [33]. Nonetheless, not all PD-L1 expression on tumor cells is IFN-γ-dependent. Certain tumors intrinsically express PD-L1 and certain cancer mutations can also upregulate PD-L1 expression [34, 35].

NK cells are part of the immune system's innate defense against cancer and were first discovered because of their anti-tumor activity [36]. In fact, *ex vivo* expansion and re-infusion of autologous NK cells has shown to induce long-term remission in cancer patients [37]. Specific destruction of cancer stem cells has been demonstrated by NK cells [38]. Radiation therapy increases expression of retinoic acid early inducible-1 (RAE-1) in carcinoma cells, which binds to the NKG2D receptor present in NK cells and CTLs and leads to their activation [32, 39]. Interestingly, NK cells also express PD-1 and it has been shown that PD-1 inhibition enhances NK cell response against multiple myeloma [40]. This suggests another possible synergistic interaction of Avelumab and SABR in producing an anti-tumor effect mediated by NK cell activation.

1.5 Correlative Studies

The goal of laboratory correlative studies will be to identify immune-biomarkers to better identify patient populations that are more responsive to this regimen.

Metastatic Tumor Profile. Archival tissue of metastatic site or retrospective primary tumor biopsy slides can be used if present. These tissues will be studied to perform immunologic assays for PD-1, PDL1 and TIL levels. Tumor PD-L1 membrane expression and immune cell PD-L1 expression (≥1% vs. <1% and ≥5% vs. <5%, ≥10% vs. <10%,) using SP263 IHC will be quantified in sections which have at least 100 tumor cells as assessed with immunohistochemical staining. It has been shown previously that tumors with higher PD-L1 expression have worse outcomes but it remains to be shown whether these tumors respond better to anti-PD-L1 therapy in the setting of ovarian cancer and Avelumab treatment. It would be very interesting to examine the correlation between PD-L1 expression and tumor response to Avelumab therapy [41]. Specific TIL receptor studies will also be performed if feasible.

Serum Immune Markers Whole blood will be collected pre-treatment and at specific intervals during treatment (prior to cycle 1, cycle 3, cycle 5, cycle 7,and two weeks post last cycle*) to perform immunologic assays evaluating induction of a tumor-specific adaptive as well as humoral immune response. These blood draws will be performed in sync with the routine lab draws for patient care scheduled prior to each cycle so not to inconvenience the patient. Cytokines are hormonal messengers responsible for most of the effects in the immune system such as activation of innate versus adaptive immune response, cellular versus humoral immune response [42, 43]. Serum cytokines from this clinical trial before and after SAbR and at time-points of Avelumab administration as described above will be measured using an extensive array of cytokines to explore the specific immune pathways that are initiated/inhibited by our treatments.

The planned array will measure levels of the different cytokines and correlate with immune response with clinical outcomes.

In addition, live white blood cells will be stored in DMSO to measure tumor-specific immune response and its amplification following treatment, pending availability of additional funding.

2.0 Study Objectives

Specific hypotheses (SAbR-IT)

Anti-PD L1 checkpoint inhibition Immunotherapy(IT) combined with Stereotactic Ablative Radiation Therapy (SAbR –IT) in Recurrent Ovarian and peritoneal ,fallopian tube Cancer(ROPT) will be well tolerated and have increased response rates compared to current second-line treatment options and to Anti-PDL1 alone.

2.1 Primary Objectives

The primary objective of this phase II(with safety lead-in) trial of combined Avelumab (MSB0010718C) anti-PD-L1checkpoint blockade with SAbR for Recurrent Ovarian and peritoneal ,fallopian tube cancer (ROPT) is to assess overall clinical response rates per RECIST criteria . This will be after the safety lead-in is completed without DLT at 8 weeks from start of Avelumab, to evaluate the safety of Avelumab and SABR to an acceptable dose of the site radiated.

2.2 Secondary Objectives

2.2.1 To evaluate the overall survival (OS), which is defined as the time between date of first cycle and the date of death due to any cause,

2.2.2 To evaluate and compare progression free survival (PFS), which defined as the time between date of first cycle and the first date of documented disease progression or date of death due to any cause.

2.2.3 To evaluate and compare complete response rate, which is defined as the percentage of patients who show complete response as per RECIST criteria

2.2.4 To evaluate and compare time to progression (TTP), which is defined as time between date of first cycle and date of documented progression.

2.2.5 To evaluate and compare median response duration, which is defined as the time between the date a response (CR or PR) was first seen until date of progression.

2.3 Exploratory Objectives

Biological correlates including Tumor Immune profile, serum cytokines and additional correlates as described in section 1.5

*2 weeks post treatment collection optional

2.4 Endpoints

2.4.1 Dose limiting Toxicities as assessed via NCI's CTCAE v4.1 toxicity criteria. Only those Grade 3-4 AEs which interfere with drug and therapy administration will be considered as detailed below.

Additional details regarding toxicities are listed in section 7.

Dose Limiting toxicity will be defined as follows if detected within 8 weeks after initiating Avelumab

a) Any immune related Grade 4 AE (except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management)

b) Grade 3 hepatitis, pneumonitis colitis for >3 days despite adequate medical management. Also any other Grade 3 AEs persisting >5 days despite adequate medical therapy

c) Any other Grade ≥3 AEs (persisting >5 days despite adequate medical therapy) to be considered a DLT; there should not be a reasonable alternative explanation for the AE (e.g. disease progression)

d) Any Immune –related Myocarditis

e) Hematologic AE:

Hematologic:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 or <0.5 x 10^9/L) lasting >7 days;
- Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (>101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour;
- Neutropenic infection (ANC <1,000/mm^3 or <1.0 x 10^9/L, and Grade >3 infection);
- Grade ≥ 3 thrombocytopenia (platelet count <50,000 - 25,000/mm^3 or <50.0 – 25.0 × 10^9/L) with bleeding;
- Grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0 x 10^9/L);
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated).

– The following exclusions listed below will not be considered DLT
  - Grade 3 fatigue for ≤ 7days
  - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
  - Concurrent vitiligo or alopecia of any AE grade
  - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
  - Grade 3 Neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
  - Grade 3 or 4 lymphopenia
  - Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days

- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

2.4.2 ORR (objective response rate) will be measured by RECIST v1.1 at weeks 8, 16, and 24. New developing lesions and progression of target and non-target lesions will be assessed by iRECIST guidelines before labelling as progressive disease[44]

2.4.3 Tumor cell and tumor immune cell PD-L1 level, and (optional) tumor CD8+ and CD8+granzyme B+ T lymphocyte density and FoxP3+ Treg density.(TIL markers) also to look at cytokines such as TNF-alpha, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12,

3.0 Subject Eligibility

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

1. Female subjects aged ≥ 18 years.

2. Performance ECOG status of 0-2

3. Patient is able and willing to comply with protocol and study procedures for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up visits.

4. Adequate Physiologic function:

   - Hematologic: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)
   - Hepatic: Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver).
   - Renal: Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

5. Pregnancy and contraception:

   Pregnancy test: Negative serum or urine pregnancy test at screening for women of childbearing potential.

   Contraception: Highly effective contraception for female subjects and their male partners throughout the study and for at least 30 days after last avelumab treatment administration if the risk of conception exists.

6. Histologic diagnosis of recurrent epithelial ovarian, fallopian, peritoneal cancer

7. Patients with platinum sensitive ovarian cancer must have progressed within 6 months of their last platinum-containing regimen, consistent with definition of platinum resistant disease.

8. Patients with platinum resistant ovarian cancer must have progressed through at least one prior chemotherapy regimen for recurrent ovarian cancer.

9. Eligible patients with germline or somatic BRCA mutations must have disease progression after treatment with a PARP inhibitor. For patients with unknown BRCA status, it is recommended patients undergo the test unless patient refuses. However, non-mutation patients will also be eligible for study

10. Patients must have received at least one prior chemotherapy regimen and up to any number of prior systemic regimens including chemotherapy and molecular targeted therapy other than PD1/ PDL1/ PDL2 inhibitors.

11. Metastatic/Recurrent disease of at least two Non-CNS sites (including the index lesion to be treated) measurable by RECIST criteria with at least one site outside of the radiation field and evaluable by RECIST criteria for evaluation of response.

12. Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

1. **IMMUNOSUPRESSANTS:** "Current use of immunosuppressive medication, EXCEPT for the following: a. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)."

2. **AUTOIMMUNE DISEASE:** "Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible."

3. **ORGAN TRANSPLANTATION:** "Prior organ transplantation including allogenic stem-cell transplantation."

4. **HIV/AIDS:** "Known history of testing positive for HIV or known acquired immunodeficiency syndrome."

5. **HEPATITIS:** "Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)"

6. **VACCINATION:** "Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines"

7. **HYPERSENSITIIVTY TO STUDY DRUG:** "Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)"

8. **CARDIOVASCULAR DISEASE:** "Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication."

9. **OTHER PERSISTING TOXICITIES:** "Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 2); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable."

10. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease,

pneumonitis, pulmonary fibrosis ,Severe COPD requiring > 3 hospitalizations in the past year

11. Or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

12. Concomitant therapy with any of the following: IL2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; or other investigational therapies; all such therapies must have been discontinued >4weeks prior to registration.

13. Active TB.

14. Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

16. Patients must not be pregnant or nursing.

17. No history of prior treatment with inhibitor of PD-1 or PD-L1 or PDL2.

18. Major surgery within 2 weeks prior to registration or first dose of drug.

19. Subjects who have had radiation therapy within 2 weeks prior to first dose of drug.

20. Uncontrolled adrenal insufficiency or active chronic liver disease.

21. Any history of CNS metastases not adequately treated (surgery or radiation) >14 days prior to registration.

22. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses up to 10 mg daily prednisone equivalent are permitted (although not encouraged) in the absence of active autoimmune disease.

3.3 Subject Recruitment and screening

Subjects will be identified by their treating gynecologic oncologist within PMH and UTSW. The target population of participants will include all patients with a known diagnosis of recurrent metastatic ovarian, fallopian, peritoneal cancer outlined in Inclusion Criteria.

3.3.1 Withdrawal of Subjects

Patients may be withdrawn at any time at the discretion of the investigator/sponsor for safety, behavioral, or administrative reasons, or may withdraw from the trial at any time at their own request. If a patient does not return for a scheduled visit, every effort should be made to contact the patient and arrange for a scheduled visit to assess for assessment of adverse events. Every effort should be made to document patient outcome. The investigator should request the patient to return for a final visit and follow-up regarding any unresolved adverse events. If the patient withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no

additional data should be collected. The investigator-sponsor may retain and continue to use any data collected before such withdrawal of consent.

3.3.2 Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

3.4 When and How to Withdraw Subjects from Study Treatment

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

- Withdrawal of consent from the study and or further treatment with investigational product.
- Lost to follow-up
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Pregnancy or intent to become pregnant
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g. refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy (excluding surgery), including another investigational agent.
- Dose-limiting toxicity (see definition of DLT)
- Grade ≥ 3 infusion reaction anaphylaxis, severe dyspnea (see DLT definition)
- Confirmation of progressive disease (unless there is evidence of clinical benefit per physician per section 4.6.2)
- Treatment delayed > 6 weeks (except in cases where the delay is due to the need for a prolonged steroid taper to manage drug-related adverse events or the delay is not drug related).

3.5 Replacement of Subjects

Subjects in the safety phase may be replaced if for reasons other than toxicity, they do not receive the second infusion of Avelumab and continue on study for safety evaluation. Subjects in the second phase that fail to initiate any treatment may be replaced.

3.6 Total Number of Subjects and Sites

Recruitment will end when approximately 29 patients are enrolled.

4.0 Treatment Plan

4.1 Treatment Dosage and Administration

4.1.1 In this phase II study (with safety lead-in) we will begin with a 6 patient cohort of PD-L1 blockade combined with 3 fractions SABR to an acceptable dose of the site radiated to determine the safety and feasibility of this regimen. We will enroll 3 patients at a time, evaluating DLT at week 8 from start for the first 3 patients before enrolling an additional 3 patients if 0 or 1/3 patients have a DLT. If ≤ 2/6 patients develops a DLT we will open up to an expansion cohort evaluating PDL-1 inhibition + SABR to assess response rates, PFS, OS and collect further toxicity data. We propose treating up to two lesions in different metastatic sites and the largest lesion when appropriate since there is tumor microenvironment heterogeneity between metastatic sites and this may further augment T-cell mediated responses.

4.1.2 Arms/Regimens

1. The immunotherapy(IT) infusion regimen will be delivered as follows:

   Concurrent Anti—PD-L1 (Avelumab) and SAbR. Avelumab will be dosed intravenously (IV) over 60 minutes (±10 min) at 10 mg/kg every 2 weeks (± 2 days) of each treatment cycle until disease progression or 9 cycles. The main purpose is studying synergistic effect of radiation with the drug and RT is administered in the early part of the treatment –we have included only 9 cycles (as per available funding) or progression (whichever is earlier)

2. SABR will be administered up to 1-2 sites of metastatic disease within 15 days after commencing the immunotherapy, given in treatments every other day, completed within 12 workdays. SAbR will be given in 3 fractions to a total dose of 24-36 Gy (8-12 Gy per fraction x 3 fractions) targeted to the largest easily accessible metastases based on normal tissue tolerances. Patients must have at least one untreated metastatic lesion which is completely outside of the radiation treatment field and can be followed by RECIST criteria. If treating two metastatic sites patients must have 3 sites of metastatic disease.

4.2 SAbR Dose and Techniques

Patients should have at least 2 measurable non-CNS lesions. Lesions receiving SAbR will be called "radiated" lesions. "Target" lesions will be selected from non-treated lesions. In any case, there should be at least one non-CNS measurable lesion for effect measurement. Prior irradiated lesions--outside of the trial will be excluded from target lesions. SABR will be administered to 1-2 sites of metastatic disease within 15 days after commencing the immunotherapy with 3 fractions to a total dose of 24-36 Gy (8-12 Gy per fraction x 3 fractions) targeted to the largest easily accessible metastasesbased on normal tissue tolerances. The sites of larger, bulky disease and the sites of symptomatic disease will be prioritized for treatment.

Due to normal organ toxicity and limits of dose constraints, a three fraction treatment is recommended, the treatment course should be completed within 10-15 days (preferably 12 business days). Radiation dose-(immune) response studies have shown a linear increase in immune response with increased dose per fraction of radiation without demonstration of a plateau [31, 44-46]. Two studies comparing 15Gy x 1 vs 5Gy x3, and 20Gy x1 vs 5Gy x4 have shown a superior immune response generated by the single fraction radiation [31, 44]. Clinical experience with oligometastatic patients treated at 1-5 sites of disease has also showed an increase in progression free survival with the increasing radiation dose per fraction [47]. A dose of less than 7.5 Gy per fraction has demonstrated lower induction of systemic IFN-γ producing cells [46], and a previous phase II study of mRCC patients treated with HD IL-2 and singe fraction of 8Gy irradiation to a single lesion did not show an overall improvement in response rate [48]. Therefore 8Gy per fraction is the lowest permitted dose for this study and can be used only when administering the three fraction regimen as described in the prescription dose table below.

The SABR prescription dose will be delivered to the periphery of the planning target volume (PTV, see below for definitions). Treating physician will have further discretion in selecting the number and location of sites to treat if multiple sites of disease are present (up to 2 sites total). Physicians will be REQUIRED to leave at least one site of disease for the purpose of measuring a radiographic response (see section 6) at a non-treated site, as this is part of the primary endpoint. If left untreated, this site can be treated once patient

meets the definition of progressive disease (PD) (see section 6). To clarify the definition of "site", each site is an area or organ with active extracranial disease (</=3 in the liver = one site and </=3 in the lung= one site) identified by CT scan, or PET/CT, within6 weeks prior to initiation of SABR (up to 2 contiguous vertebral metastasis will be considered a single site of disease). For example: a patient with 4 right axillary lymph nodes, L1-L2 bone metastasis, 3 right lung lesions, 1 left lung lesion, 2 liver lesions, and T2-T3 bone metastasis would be defined as having 6 sites of disease. Preference should be given to the largest feasible disease site, symptomatic sites and sites where palliative and preventative (i.e. to prevent a pathologic fracture in weight bearing bone, impending cord compression, impending SVC compression etc.) indications are applicable. The gross target/tumor volume (GTV) should be at least 2 cm^3 in size, corresponding to roughly a 1.5 cm diameter tumor. This is to ensure that adequate tumor volume and therefore adequate tumor cells (roughly 108 -109 cells/cm3 [49]) are killed for antigen presentation. Treating physicians should choose their dose based on established planning guidelines at their center including their ability to respect normal tissue tolerance listed below. It is not required that all targets be treated with the same dose fractionation. A dose from the following table should be used:

Table 4.1.1 Prescription Dose

	Total Cumulative Dose Encompassing 95% of Planning Target Volume (Gy)	
Number of Fractions	Protocol Compliant	Deviation
3	24-36 Gy**	<24 Gy or >36 G

** Based on normal tissue tolerances

Dose tolerance limits should be adhered to for all treatments. Protocol compliant dose should be used in all cases, if possible. When treating tumors abutting the spinal cord, tolerance limits should not be exceeded. To facilitate this requirement, minor deviation dose ranges listed above in the table will be considered fully compliant for tumors abutting the spinal cord.

4.2.1 SAbR Planning Constraints and Concerns

The tolerance dose of SABR to the gastrointestinal tract is not established, and patients with metastatic disease involving the esophagus, stomach, intestines, or mesenteric lymph nodes will be eligible only if no other sites of lesions are present that can be safely targeted, and the treating radiation oncologist feels that a sufficiently conservative dose constraints to these organs can be met. Patients with renal or adrenal metastases are potentially eligible if normal tissue constraints are otherwise met.

It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy [45]. However, in this protocol the goal is not just to relieve pain within an osseous metastasis but also to debulk the tumor present and induce in immune response, and the higher dose is more likely to accomplish this goal given a higher biological potency [46]. Long term survival after bone metastasectomy has been reported [47]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity weight-bearing bones should undergo surgical stabilization if there is plain film evidence of cortical erosion.

4.2.2 SABR Treatment Technique

Simulation, beam arrangements, tumor prescription dose

Treatment to skeletal lesions and paraspinous lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT) technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

At the time of simulation for patients who will receive SABR to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

With the patient is immobilized in a vacuum-type or equivalent body mold, a planning CT scan with 2-5 mm slices is performed. Intravenous contrast is recommended for lesions near mediastinal structures and lesions within the liver. The form of respiratory control to be used during treatment should also be used during the simulation. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe.

The planning target volume (PTV) is constructed to account for the positional uncertainty of the GTV during treatment. The PTV for each contoured GTV should be at least 5mm larger than the GTV in the axial plane and 1.0 cm larger than the GTV in the cranio-caudal plane. Larger margins may be used in cases where greater motion of the hemi-diaphragm is observed in simulation despite standard maneuvers to diminish motion. For lung SABR the same principles apply; the entire lung volumes are contoured, as are each individual GTV within the lung.

The prescription dose for each lesion is listed in Table 4.1.1(see section 4.2), prescribed to the periphery of the PTV. There is no restriction on the dose "hotspot" except that it must be located within the PTV. A Linear Accelerator with effective photon energies of $\geq$ 6 MV is required. The use of a multi-leaf collimator (MLC) or custom blocks are acceptable. A stereotactic relocalization system that relies upon stereoscopic radiographs, implanted fiducials, or near real-time CT based verification will be used. The PTV may be treated with any combination of coplanar or non-coplanar three-dimensional conformal fields, shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by the planning system to produce the optimal conformal plan in accordance with volume definitions.

Normal Tissue Dose Constraints

In accordance with prior Phase I studies [48], certain normal tissue dose constraints must be respected. The possibility that SABR-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered [49]. An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences. In such a case, the treating radiation oncologist should discuss any proposed dose modifications with the PI to decide whether a regimen of similar biological potency can be safely given.

The same special condition applies in the setting of a patient whose primary disease has been irradiated previously and is present as a site of disease. Since re-irradiation toxicity is a concern, these patients will be considered by the PI on a case-by-case basis and SABR to a site previously irradiated with conventional fractionation within two years is not recommended. Re-irradiation to a

site that has received previous SABR is not allowed. Deviations from the intended dose regimen will be documented, with calculations of the BED of the applied regimen included in the patient's research chart along with documentation of the discussions pertaining to the idiosyncrasies of the case.

The following table lists the specific organ and dose fractionation constraints on normal tissues and also the toxicities.

Three Fractions **Timmerman**

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****	**Endpoint (≥Grade 3)**
Optic Pathway	<0.2 cc	15.3 Gy	17.4 Gy	Neuritis
Cochlea			14.4 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	15.9 Gy	23.1 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc	15.9 Gy	22.5 Gy	Myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	Neuritis
Sacral Plexus	<5 cc	22.5 Gy	25.5 Gy	neuropathy
Esophagus*	<5 cc	27.9 Gy	32.4 Gy	esophagitis
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	39 Gy	43 Gy	impairment of pulmonary toilet
Bronchus- smaller airways	<0.5 cc	25.8 Gy	30 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc	22.5 Gy	30 Gy	ulceration
Jejunum/Ileum*	<30 cc	20.7 Gy	28.5 Gy	enteritis/obstruction
Colon*	<20 cc	28.8 Gy	45 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	43 Gy 30.3 Gy	47 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc for males and 950cc for females***	10.8 Gy		Basic Lung Function
Lung (Right & Left)			V-11.4Gy<37%	Pneumonitis
Liver	700 cc***	17.7 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc***	14.7 Gy		Basic renal function

***Avoid circumferential irradiation**
**** "point" defined as 0.035cc or less**
*****or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater**

Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation.
Exceeding these dose tolerances by more than 5% constitutes a major protocol violation

4.3 Avelumab: Treatment Dosage and Administration

The standard and current guidelines for Avelumab administration will be used for this protocol. It will be dosed intravenously (IV) over 60 minutes (±10 min) at 10 mg/kg on day 1 (+2 days) of each treatment cycle until disease progression or 9 cycles , unacceptable toxicity or other reasons specified in the protocol. Each cycle length is 2 weeks (14 days (+2 days)).

All doses should be rounded to the nearest milligram. Dosing calculations will be based on the screening body weight. If body weight at a given cycle is changed more than 10% from baseline, the dose will be recalculated. If Avelumab dosing is delayed for a drug-related adverse event, treatment may resume when the event has resolved to Grade 1 or baseline. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except in cases where the delay is due to the need for a prolonged steroid taper to manage drug-related adverse events or the delay is not drug related. See details AE and indication for modifying Avelumab dose.

Special Precautions for Administration:

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

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

Observation period: Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions with vitals done on discharge.

Toxicities and Dosing Delays/Dose Modifications

Each subject will stay on the avelumab assigned dose of 10 mg/kg unless treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in the tables below. There will be no dose reductions.

Table 2. Adverse Drug Reactions requiring avelumab discontinuation or modification

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

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 ADR should be managed as follows:

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

Table 3. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
-If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction isobserved in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. .- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical	

practice.

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

Table 4. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.

	for opportunistic infections Consider bronchoscopy, lung biopsy	
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: 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.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).

	low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month.

	Specialty consult as appropriate	
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

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

4.4 Other Modalities or Procedures

SABR- see section 4.2.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for **9** cycles or until:

- Disease progression (unless the investigator assesses clinical benefit to additional cycles)
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Subjects will be followed for up to **2 years** after removal from treatment..

4.6.1 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 3.4 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was

removed in the Case Report Form. The subject should be followed-up per protocol. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event if extending beyond the follow up period.

4.6.2 Continued Treatment Beyond Progression of Disease

As indicated above, we will use the RECIST criteria for tumor measurement and RR determination.

In addition, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease. For this reason, subjects will be permitted to continue study therapy beyond initial investigator-assessed RECIST progression as long as they meet the 2 criteria listed below at the discretion of the treating medical oncologist and NO more than 9 cycles

- Investigator-assessed clinical benefit,

and

- Subject is tolerating study drug.

Subjects should discontinue study therapy upon evidence of further progression at the discretion of the treating medical oncologist, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm). For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

5.0 Study Procedures

5.1 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 28 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

Complete medical and surgical history, history of infections

5.1.3 Demographics

Age, gender, race, ethnicity

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 Performance status

Performance status evaluated prior to study

5.1.8 Adverse event assessment

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.9 Hematology CBC and diff (within 2 weeks of registration)

5.1.10 T 4 levels, TSH and CMP as below (within 2 weeks of registration)

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.11 Hep B and Hep C testing – (within 4 weeks of registration)

5.1.12 Pregnancy test (for females of child bearing potential)

(within 2 weeks of registration)

See section 3.1.5 for definition.

5.1.13 Tumor assessment (within 6 weeks of registration)

Baseline imaging by CT scan of chest, abdomen, and pelvis.

5.2 Procedures During Treatment

5.2.1 Prior to Each Treatment Cycle

- Physical exam, PS, vital signs, medication review, AE assessment
- Hematology
- Serum chemistries

5.2.2 Every 8 weeks after start till end of treatment

- Serum TSH
- Pregnancy test
- CT chest abdomen and pelvis

5.2.3 Additional Immune coorelate lab testing: Prior to cycle 1, cycle 3, cycle 5, cycle 7 and optionally 2 weeks post last cycle. (See section 9)

5.3 Follow-up Procedures

5.3.1

- For patients who completed 9 cycles of Avelumab:
  Subject will be followed every eight weeks (+/- 4 weeks) starting from the final cycle of treatment for the first year, then every 12 weeks (+/- 2 weeks) till 2 years after last dose of drug. This follow-up will be performed by Gynecologic Oncologist per patient's routine accepted followup for cancer. The following procedures will be performed at each follow up:
  - Physical exam, PS, vital signs, medication review
  - AE assessment (for 8, 16 and 24 week follow up)
  - Blood collection per time table and for labs
  - Radiographic imaging: Tumor assessments will be completed by the investigator using the RECIST criteria as above.
  - CT chest, abdomen and pelvis with IV contrast(if indicated per time table), if allowable by renal function
  - After that, survival information will be collected through record review every 6 months until patient death.

5.3.2

- For patients who discontinue Avelumab early (prior to 9 cycles):
  Subjects will be followed within eight weeks (+/- 4 weeks) from discontinuation of treatment by the treating gynecologic oncologist

  The following procedures will be performed at that visit:
  - Physical exam, PS, vital signs, medication review, AE assessment
  - Subsequent anti-cancer treatment/s
  - For first visit only, or may repeat if study drug related toxicity persists: CBC w/ differential, LFTs, BUN, creatinine, fasting glucose, and TSH

After that, survival information will be collected through record review every 6 months until patient death. Patients may be followed up as per standard routine by their gynecologic oncologist for at least one year after the last dose of avelumab. At subsequent routine follow ups survival information must be collected every six months until patient death.

5.2 Time and Events Table

Event	Pre-Study (Day-28 – Day 0)	Prior to every cycle(cycle length=2weeks)	Follow up Post therapy per 5.3.1 (subjects who completed 9 cycles of Avelumab)	Follow up Post therapy per 5.3.2 within 8 weeks (subjects who discontinue Avelumab)
Informed Consent	X			
History[a]	X		X	
Physical[a] & ECOG/PS[a]	X	X	X	X
Vitals Signs[b] + Weight	X	X	X	X
Height[c]	X			
Concomitant Medication Review	X	X	X	X
CBC + Diff	X[d]	X	X	X
CMPL +	X[d]	X	X	X[m]
Hep B & Hep C	X[k]			
Free T4,TSH	X[d]	X[i, l]		X[i]
Pregnancy Test	X[e]	X[l]		
Concomitant Medications	X			
Toxicity Evaluations		X	X[n]	X
CT chest, abdomen, pelvis	X[j]	X[l]	X	

Event	**Pre-Study (Day-28 – Day 0)**	**Prior to every cycle(cycle length=2weeks)**	**Follow up Post therapy every 8 weeks (+/- 4 weeks) (subjects who completed 9 cycles of Avelumab)**	
SAbR		X[h] See 4.2		
Avelumab Therapy		X		
Correlative Labs[g]		X		

[a]Performed by physician or advanced practice provider (NP/PA);
[b]Include blood pressure, heart rate, temperature, and respiratory rate before treatment , and 2 hours after end of infusion;
[c]Obtain Height at Baseline only;
[d] within 2 weeks of registration
[e]Urine or Serum Pregnancy Test for women of childbearing potential as described Section 3.1.5;
[f]Toxicity Assessments will be performed from the first dose of study drug until removal from study,. Use CTCAEv4.0 as described Section 7; DLT evaluation will be performed at initial follow up (wk 8).
[g]For correlative studies prior to Cycles 1, 3, 5, 7 (see Section 1.5)
[h]SABR commenced after first dose of Avelumab as per protocol
[i]TSH only
[j]within 6 weeks of registration
[k]within 4 weeks of registration
[l]every 8 weeks from first Avelumab infusion to end of treatment
[m] LFTs, BUN, creatinine, fasting glucose only
[n] toxicity follow up per section 7.2.1

5.4 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.4.2 Subject withdraws consent (termination of treatment and follow-up);

5.4.3 Subject is unable to comply with protocol requirements;

5.4.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.4.5 Subject experiences toxicity (DLT) that makes continuation in the protocol unsafe;

5.4.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.4.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.4.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.4.9 An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing

5.4.10 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

6.1.1 Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Additional criteria for bone lesions and clinical endpoints of pathologic fracture and cord compression are added to this study (see Section 6.1.4). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria outlined in http://www.recist.com/Definitions.

Before labelling as progressive disease, as indicated above in study endpoints, we will use the iRECIST criteria for tumor measurement and RR determination. Accordingly, an initial progression on the first set of scans would be labelled as iUPD should be verified by a second set of scans before considering it as disease progression and before the decision to discontinue treatment is made.) Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm .If progression is confirmed on the second set of scans, the first date will be used in evaluations of PFS.

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral (Helical) CT scan (CT/MRI scan slice thickness should be no greater than 5 mm). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). For malignant lymph nodes to beconsidered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. 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.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan) and lymph nodes <15 mm, are considered non-measurable disease. Leptomeningeal disease (patients excluded), ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable. Blastic bone lesions are non-measurable. Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Note: Lesions receiving SABR will be called "radiated lesion" which should not be confused with "target lesions" defined here for the for the purpose of radiographic measurement. Radiated lesions and target lesions are mutually exclusive lesions. Therefore, radiated lesions will not be used as target lesions for evaluating response. At least 2 non-CNS measurable lesions are required for enrollment.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements will be done digitally on the PACs system. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Whenever possible, 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 using appropriate radiologic imaging.

CT scan of Chest, abdomen and pelvis with IV contrast (whenever possible) will be performed at baseline. Lesions found on bone scan must be verified with a CT. Bone scans will not be used for measuring lesion size.

Spiral CT and MRI. All CT scans will be Spiral CT and should be performed using a 5 mm contiguous reconstruction algorithm.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesion, verified by a second scan > 6 weeks apart. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4.2 Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD@	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

@ iRECIST criteria will apply to determine progression-and the initial label will be iUPD

Appearance of new lesions or increase in size of target /non-target lesions Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same

Note: Subjects 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 the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

Evaluation of Bone Lesions:

Bone lesions will be evaluated by CT if seen initially on bone scan. Since the size of the lesion is difficult to measure in a bone scan, particularly if it is not well visible in CT, the following guideline will be used. Any ambiguity will require MRI for resolution:

Progression of bone lesions will be defined as follows:

Appearance of 1 or more new bone lesion in Bone scan, confirmed by a repeat bone scan in ≥6 weeks.

Response of bone lesions in bone scan will be defined by either a complete resolution (CR) at the metastatic sites or partial resolution (PR) of radiotracer uptake by a radiologist.

Evaluation of Pathologic Fracture:

Any clinical suspicion of pathologic fracture will prompt radiologic evaluation with plain film, CT or MRI as appropriate and if confirmed by a radiologist, will constitute progression, unless it is at a treated site, in which case a treatment-related toxicity will be considered. In that case, patients will be referred for orthopedics specialist evaluation.

Evaluation of spinal cord Compression or Cauda Equina compression:

Any clinical suspicion of cord or cauda equina compression will prompt radiologic evaluation with MRI (CT myelography if patient is not eligible for MRI) as appropriate and if confirmed

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or 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 since the treatment started).

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (**http://ctep.cancer.gov/reporting/ctc.html**) and modified criteria for hematologic adverse events per section 2.4.1.

7.0 Adverse Events

7.1 SAbR

The contraindications and adverse events for SAbR are mostly related to the treatment site and its radiation dose tolerance, as discussed in detail in section 4.2.

Contraindications:

Treatment of patients who have received conventional radiation therapy at same site of new metastasis is at the discretion of the radiation oncologist. Treatment of patients who have received SAbR at same site of new metastasis is contra-indicated. Treatment of patients with scleroderma or active Lupus is at the discretion of the radiation oncologist.

Special Warnings and Precautions for Use: N/A

Interaction with other medications: None

Adverse Reactions: Site-specific. Please see Table 4.

Experimental Therapy

Avelumab Therapy

For the most recent safety update, please refer to the current investigator brochure.

Contraindications

See exclusion criteria

Special Warnings and Precautions for Use

See section 4.3

Interaction with other medications

No formal pharmacokinetic drug-drug interaction studies have been conducted.

7.2 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 subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

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

7.2.1 Definition

Acute Adverse Events

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or imaging finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Adverse events occurring in the time period (Defined as occurring from the time of signing informed consent, through 8 weeks post treatment) will be considered acute adverse events. All acute adverse events will be assessed and reported as per below.

Late Adverse Events

Adverse effects occurring in the time period from the end of acute monitoring, through week 24 post treatment, will be defined as late adverse events. These events will include all adverse events reported directly to a member of the study team and will be captured, assessed, graded and reported as appropriate.
In addition, the study team will review encounters in a select specialty category relevant to study endpoints: Medical Oncology; Radiation Oncology; any hospital admissions or Emergency Department visits.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely or probably related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 Reporting

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

7.2.3.1 UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. (See Appendix IV of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

All serious adverse events which occur on research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

The following instructions section may be modified as needed to ensure clear guidance for institutions participating in the trial who will not report directly to the UTSW Institutional Review Board. If needed, this reporting may be facilitated by the UTSW study team for example.

Telephone reports to: (Investigator/study team: Insert names and phone numbers for required notifications) Kevin Albuquerque, MD c/o Clinical Research Manager 214-648-1892
Written reports to: (Investigator/study team: Insert names, fax numbers, an addresses for required notifications) Kevin Albuquerque, MD c/o Clinical Research Manager

2280 Inwood Road Dallas, TX 75235 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

   Serious adverse events (SAEs) for studies where the SCCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

   Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction).

   Local UPIRSOs (non-serious events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness of the event.

   External UPIRSOs including those that occur as non-local events require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

   For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories 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.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

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 Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

The following reportable events must be submitted to Pfizer within 24 hours (or immediately for death or life-threatening events) using the provided *Investigator-Initiated Research Serious Adverse Event Form (IIR SAE)* with *the Pfizer Reportable Events Fax Cover Sheet* with each SAE submission.

Serious Adverse Events

Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)

Occupational exposure (even if not associated with an adverse event)

Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Detailed guidance on the safety reporting is provided in the *Safety Reporting Reference Manual.*

Contact information for submission of reportable events to Pfizer:

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

or

E-mail: USA.AEReporting@pfizer.com, specifying:

- PROTOCOL:
- SUBJECT:
- SITE/PI:
- SAE/ONSET:

Stopping Rules: The study will be stopped if the combination treatment of SABR and Avelumab resulted in >50% of increased Grade 3-5 toxicity as compared to those reported in the literature for patients receiving Avelumab alone in the first 6 patients, or if the regimen is deemed to be unsafe by the Data Safety Monitoring Committee.

8.0 Drug/Treatment Information

Avelumab (MSB0010718C)

Mode of action: Avelumab (company code: MSB0010718C) 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.

Storage and stability:

General Information: The active pharmaceutical ingredient in avelumab drug product is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1.

8.1 General Properties of Drug Substance

The calculated molecular weight of the molecule is 143,832 Dalton. The antibody is produced by mammalian cell culture in a serum-free growth medium. The antibody is purified by affinity, ion-exchange, and mix-mode chromatography. The process also includes specific viral inactivation and removal steps. The antibody is then transferred into formulation buffer and brought to the desired concentration.

Pharmaceutical Formulation

- Introduction

  Avelumab drug product is a sterile solution intended for IV infusion.

- Pharmaceutical Properties

  Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentration of 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® seal closure.

- Description of the Formulations

  Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).
  For avelumab drug product, only excipients that conform to the current Ph. Eur. and/or the current USP are used.

- Instructions for Storage

  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 administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. 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, for purposes of this protocol, diluted solution should be used within 4 hours if stored at room temperature and used within 24 hours if stored under refrigeration at 2-8C..
  No other drugs should be added to the solution for infusion containing avelumab.

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

- Preparation: Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia provided labelled by the sponsor
- Route of administration for this study: intravenous
- Incompatibilities: NA
- Administer the diluted solution over 60 minutes through and intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron.)
- Availability: provided by sponsor Pfizer
- Side effects (see section on toxicity)

- Nursing implications: As dictated by clinical course

9.0 Correlatives/Special Studies

The goal of laboratory correlative studies will be to identify immune-biomarkers to better identify patient populations that are more responsive to this regimen.

9.1 Metastatic Tumor Profile

Archival tissue of metastatic site or retrospective primary tumor biopsy slides will be studied to perform immunologic assays for PD-1,PDL1 and TIL levels(i.e. CD4, CD8, CD68, CD1a, FoxP3).. If a recent tumor /metastatic site biopsy is available or has been obtained prior to study entry that tissue can be used for immune analysis .Tumor PD-L1 membrane expression and immune cell PD-L1 expression (≥1% vs. <1% and ≥5% vs. <5%, ≥10% vs. <10%,) using SP263 IHC will be quantified in sections which have at least 100 tumor cells as assessed with immunohistochemical staining. It has been shown previously that tumors with higher PD-L1 expression have worse outcomes but it remains to be shown whether these tumors respond better to anti-PD-L1 therapy. It would be very interesting to examine the correlation between PD-L1 expression and tumor response to Avelumab therapy[41]. Specific TIL receptor studies will also be performed if feasible.

9.2 Serum Immune Markers

Whole blood will be collected pre-treatment and at specific intervals during treatment (prior to cycle 1, cycle 3, cycle 5, cycle 7, and two weeks post last cycle*) to perform immunologic assays evaluating induction of a tumor-specific adaptive as well as humoral immune response. These blood draws will be performed in sync with the routine lab draws for patient care scheduled prior to each cycle so not to inconvenience the patient. Cytokines are hormonal messengers responsible for most of the effects in the immune system such as activation of innate versus adaptive immune response, cellular versus humoral immune response [42, 43]. Serum cytokines from this clinical trial before and after SAbR and at time-points of Avelumab administration as described above will be measured using an array of cytokines to explore the specific immune pathways that are initiated/inhibited by our treatments. The planned array will measure levels of the cytokines (Th1 vs Th2, pro- vs anti-inflammatory) and correlate immune response with clinical outcomes. to correlate immune response with clinical outcomes.

In addition, live white blood cells will be stored in DMSO to measure tumor-specific immune response (i.e. ELISpot) and its amplification following treatment, pending availability of additional funding

*2 week post treatment correlative lab will be optional

9.3 Sample Processing Guidelines

Samples will be labeled with the subject's de-identified study number and collection date and delivered for analysis during regular business hours to: NC7: 208; Attn Dr. Raquibul Hannan/pathology lab

Whole blood sample: Patient's whole blood will be collected in EDTA (Lavender top) tubes for ~ 40-50 ml. In addition, ~10 ml will be collected in anti-coagulant-free tubes (Red top) for the collection of sera. The blood will immediately be processed (within 2 hours) by centrifugation (1000 g, 15 min, 4°C), collecting the supernatant and freezing at -80°C in 5 aliquots for future experiments. The pellet will be re-suspended in PBS and PBMC will be isolated using standard protocol. Briefly, the cell suspension will be carefully placed on 10ml polystyrene tube containing 1ml ficoll and centrifuged (400g, 30min, RT). PBMC region will be collected from the ficoll and washed 3x with PBS. Cells will be counted and frozen in 5 aliquots with 10% DMSO, 90% FBS at -80°C

9.3.1 Assay Methodology

a) Specimen Immunohistochemical staining (IHC): Standard immunohistochemistry staining procedure for will be performed using the Benchmark XT automated stainer (Ventana) for both antibodies. Briefly, formalin-fixed, paraffin-embedded tissue sections will be cut at 3-4 micron and air-dried overnight. The sections will be deparaffinized, rehydrated, and subjected to heat-induced epitope retrieval. Sections will then be incubated with appropriate primary antibody. For signal detection, ultraView universal detection system (Ventana) will be used. The slides will be developed using 3-3'-diaminobenzidine chromogen and counterstained with hematoxylin. Appropriate positive and negative controls will be utilized for each run of immunostains. The evaluation of the immunostaining will be carried out by a gynecologic pathologist without knowledge of any clinicopathologic data. Only nuclear reactivity will be considered positive. Tumor PD-L1 membrane expression and immune cell PD-L1 expression (≥1% vs. <1% and ≥5% vs. <5%, ≥10% vs. <10%,) using SP263 IHC will be quantified in sections which have at least 100 tumor cells as assessed with immunohistochemical staining. An H score will be assigned as the product of average intensity of staining (0 for negative, 1 for weakly positive, 2 for moderately positive, and 3 for strongly positive) and extent of immunoexpression (0-100% percentage of cells staining). In addition, Dual-antibody ISH will be performed to identify and analyze(if possible) TILs, CTL (CD3+,CD8+), Tregs (CD4+FoxP3), DC (CD11c) , NK/T (CD3+, CD1d), neutrophils (CD11b, Ly6G} and MDSC (CD14+,CD11b) in the tumor tissue before and after treatment, (when available). PD-L1 expression will be quantified from biopsies of tumors prior to treatment.

b) Serum Cytokine Analysis: Multiplex cytokine analysis in patient's plasma will be performed in precoated 96 well plates (Human TH1/TH2 10 plex ultrasensitive assay, Meso Scale Discovery – MSD, Maryland, USA) according to manufacturer's instructions. 25 µL of diluent 2 is dispersed into each well. The plate is sealed and incubated by vigorous horizontal shaking for 30 minutes at RT. 25 µL of the patient plasma is added per well and all samples measured in triplicates. Plates are sealed and incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS. 25 µL of 1× detection antibody solution is placed per well and sealed plates are incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS. 150 µL of 2× Read Buffer T is added to each well. Plates are analysed using the MSD SECTOR Imager 2400 and Discovery Workbench 3.0 software (both from Meso Scale Discovery, USA). The mean value of two wells is taken as the recorded reading, provided that the coefficient of variation (CV) was less than 10%. Concentrations recorded lower than the standard curve are kept as absolute values. For purposes of logarithmic analysis, readings of 0 are adjusted to 0.01 pg/ml. The following cytokines will be measured before and after treatment for each patients at various timepoints(if possible) : Th1/Th2/Th17 cytokines, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4 and others including IL-6, TGF-β and HMGB1

9.4 Specimen Banking

Subject samples collected for this study will be retained at the department of pathologyand at the lab of Dr. Hannan (NC7. 208). Specimens will be stored labeled with study ID (no identifiers) and frozen in -80ºC until they are used up or for 10 years (whichever comes first). Only approved study personnel will have access to the blood samples for immunologic assays as listed above. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens. We will also analyze archival tissue from patients enrolled in this trial obtained from UTSW sources (clinical pathology and cancer center tissue repository) or outside institutions (with appropriate institutional release forms)."

10.0 Statistical Considerations

10.1 Study Design/Study Endpoints

This is a prospective one arm, single center phase 2 trial of the addition of SABR to Avelumab with the hypothesis that this is a durably effective means of potentiating the effects of PD-L1 blockade in inducing higher objective response rate (ORR) eventually leading to improvements in progression-free survival, complete response rate, overall survival in the ROPT patient population.

10.2 Sample Size and Accrual

In this phase II study (with safety lead-in) we will begin with a 6 patient cohort of PD-LIt blockade combined with 3 fraction SABR to an acceptable dose of the site radiated to determine the safety and feasibility of this regimen. We will enroll 3 patients at a time, evaluating DLTs at 8 weeks and follow the patients for 8 weeks before enrolling an additional 3 patients if 0 or 1/3 patients has a DLT. If ≤2/6 patients develops a DLT we will open up to an expansion cohort evaluating PDL-1 inhibition + SABR to assess response rates, PFS, OS and collect further toxicity data.
The best ORR for ROCC with anti pD-1 inhibitor was 10-15 % from the Japanese reported phase 2 study[50].The additional estimated benefit from SAbR-IT is 25 % based upon data from Oregon phase 1 study[51] and also the UTSW RCC study.
For efficacy evaluation, we plan to enroll 23 patients for the phase II part of this protocol.
Simon's two-stage design will be used for the phase II study. The null hypothesis that the true response rate is 15% will be tested against a one-sided alternative. In the first stage, 11 patients will be accrued (6 of the lead-in patients will be evaluated for response and included in the first stage). If there are 2 or fewer responses in these 11 patients, the study will be stopped. Otherwise, 18 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 8 or more responses are observed in 29 patients. This design yields a type I error rate of 0.05 and power of 85% when the true response rate is 40%.

10.3 Data Analyses Plans

Safety data (all AEs and SAEs) will be tabulated for both phase I and II parts. Rates of AEs and SAEs will also be calculated along with their exact 95% confidence intervals.
For efficacy, response rate will be calculated along with its exact 95% confidence intervals, and compared with historical response rate of 15% using normal approximation test (one-sided).
Tumor biopsy TIL assay and tumor PD-L1 levels will be assayed and correlated with response using Spearman rank-correlation.

11.0 Study Management

11.1 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 by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.1.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

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 subject 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 subject and the investigator is assured that the subject understands the implications of participating in the study, the subject 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 subject and by the person who conducted the informed consent discussion.

11.1.2 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Radiation Oncology Clinical Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- 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 {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.2 Registration/Randomization Procedures

All subjects must be registered with the Radiation Oncology Clinical Research Office before enrollment to study. All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. The eligibility checklist and confirming documentation will be entered electronically through the system.

Upon confirmation of eligibility and enrollment new subjects will receive a number beginning with 01 such that the first subject consented is numbered 01, the second subject consented receives the number 02, etc The subject will be assigned a secondary number in the order of enrollment.

Each newly registered subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.3 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management

and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity reviews will be performed at 6 monthly intervals. These reviews will be documented by electronic method and will be distributed to the sponsor and SCCC-DSMC.)

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

RADIATION ONCOLOGY DATA SAFETY MONITORING PLAN

1. The purpose of the Radiation Oncology Data and Safety Monitoring Plan is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants. The plan complies with the Simmons Cancer Center (SCCC) Data Safety Monitoring Plan and the University of Texas Southwestern Medical Center (UTSW) IRB guidelines.

2. The Radiation Oncology Safety Assurance Committee (ROSAC) is charged with developing, implementing, and maintaining the Data and Safety Monitoring Plan. The membership consists of a Medical Director of Clinical Research as well as representation from the following groups: clinical research, nursing, regulatory, pharmacy, physicists, radiation therapists, and faculty. Ad hoc members are contacted to participate as needed.

3. All clinical trials are reviewed by ROSAC on a monthly basis for enrollment. All local SAEs are reviewed by ROSAC monthly for severity and attribution. For investigator-initiated trials, SAEs at affiliated institutions are monitored as local SAEs. The principle investigator and study coordinator will present a study treatment summary and SAEs for review. Source documents will be available for the ROSAC members during the review. NCI Common Toxicity Criteria Version 4 will be used for grading and attributing adverse events. The documentation of these monthly reviews will be submitted to the SCCC DSMC on a monthly basis.

4. If a related SAE occurs on a multi-institutional clinical trial coordinated by the Radiation Oncology Clinical Research Office, the Clinical Research Manager or designee ensures that all participating sites are notified of the event and resulting action, within one (1) working day of the determination.

5. All participating sites will be monitored annually. At least 5 charts for each site will be reviewed each time a site is monitored. Monitoring will include verification of source documentation as per SCC DSMC plan. Results of data monitoring along with any necessary responses, if applicable, will be documented and filed within the Department of Radiation Oncology. These documents are available upon request at time of audit. All monitoring will be performed remotely, however on-site visits may be scheduled as necessary per DSMC policy.

6. In addition the pharmaceutical sponsor will be notified about any SAE per the safety policy outlined in the investigator brochure

11.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.4.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

11.4.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has 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.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. 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 IRB for approval prior to implementation.

11.6 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 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.

11.7 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 may 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.

12.0 References

References:

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): p. 5-29.
2. Ozols, R.F., *Treatment goals in ovarian cancer.* Int J Gynecol Cancer, 2005. **15 Suppl 1**: p. 3-11.
3. Pujade-Lauraine, E., et al., *Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial.* J Clin Oncol, 2014. **32**(13): p. 1302-8.
4. Brewer, C.A., et al., *Cisplatin plus gemcitabine in platinum-refractory ovarian or primary peritoneal cancer: A Phase II Study of the Gynecologic Oncology Group.* Gynecologic Oncology, 2006. **103**(2): p. 446-450.
5. Kandalaft, L.E., et al., *Immunotherapy for ovarian cancer: what's next?* J Clin Oncol, 2011. **29**(7): p. 925-33.
6. Galic, V., R.L. Coleman, and T.J. Herzog, *Unmet needs in ovarian cancer: dividing histologic subtypes to exploit novel targets and pathways.* Curr Cancer Drug Targets, 2013. **13**(6): p. 698-707.
7. Zhang, L., et al., *Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer.* N Engl J Med, 2003. **348**(3): p. 203-13.

8. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proceedings of the National Academy of Sciences, 2007. **104**(9): p. 3360-3365.
9. Yang, W., et al., *Increased expression of programmed death (PD)-1 and its ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia.* Immunology, 2013. **139**(4): p. 513-22.
10. Adachi, K. and K. Tamada, *Immune checkpoint blockade opens an avenue of cancer immunotherapy with a potent clinical efficacy.* Cancer Sci, 2015.
11. Ghebeh, H., et al., *The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors.* Neoplasia, 2006. **8**(3): p. 190-8.
12. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proc Natl Acad Sci U S A, 2007. **104**(9): p. 3360-5.
13. Thompson, R.H., et al., *Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up.* Cancer Res, 2006. **66**(7): p. 3381-5.
14. Wu, C., et al., *Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance.* Acta Histochem, 2006. **108**(1): p. 19-24.
15. Ohigashi, Y., et al., *Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer.* Clin Cancer Res, 2005. **11**(8): p. 2947-53.
16. Heery, C.R., et al., *Pharmacokinetic profile and receptor occupancy of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in a phase I, open-label, dose escalation trial in patients with advanced solid tumors.* ASCO Meeting Abstracts, 2015. **33**(15_suppl): p. 3055.
17. Thomas, G.M. and A.J. Dembo, *Integrating radiation therapy into the management of ovarian cancer.* Cancer, 1993. **71**(4 Suppl): p. 1710-8.
18. Lee, S.W., et al., *Radiation therapy is a treatment to be considered for recurrent epithelial ovarian cancer after chemotherapy.* Tumori, 2011. **97**(5): p. 590-595.
19. Yahara, K., et al., *Epithelial ovarian cancer: Definitive radiotherapy for limited recurrence after complete remission had been achieved with aggressive front-line therapy.* Journal of Radiation Research, 2013. **54**(2): p. 322-329.
20. Brown, A.P., et al., *Involved-field radiation therapy for locoregionally recurrent ovarian cancer.* Gynecologic Oncology, 2013. **130**(2): p. 300-305.
21. Albuquerque, K.V., et al., *Impact of tumor volume-directed involved field radiation therapy integrated in the management of recurrent ovarian cancer.* Gynecologic oncology, 2005. **96**(3): p. 701-4.
22. Potters, L., et al., *American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy.* Int J Radiat Oncol Biol Phys, 2010. **76**(2): p. 326-32.
23. Kavanagh, B.D., R.C. McGarry, and R.D. Timmerman, *Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases.* Semin Radiat Oncol, 2006. **16**(2): p. 77-84.
24. Milano, M.T., et al., *Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study.* Int J Radiat Oncol Biol Phys, 2012. **83**(3): p. 878-86.

25. Salama, J.K., et al., *Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease.* Cancer, 2012. **118**(11): p. 2962-70.
26. Long, B., R.N. Eskander, and K.S. Tewari, *Use of stereotactic radiosurgery in the treatment of gynecologic malignancies: A review.* World J Radiol, 2014. **6**(6): p. 366-73.
27. Kunos, C.A., et al., *Phase II Clinical Trial of Robotic Stereotactic Body Radiosurgery for Metastatic Gynecologic Malignancies.* Front Oncol, 2012. **2**: p. 181.
28. Cheng, X., et al., *Structure and interactions of the human programmed cell death 1 receptor.* J Biol Chem, 2013. **288**(17): p. 11771-85.
29. Hirano, F., et al., *Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity.* Cancer Res, 2005. **65**(3): p. 1089-96.
30. Chen, L. and X. Han, *Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future.* J Clin Invest, 2015. **125**(9): p. 3384-91.
31. Lugade, A.A., et al., *Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor.* J Immunol, 2005. **174**(12): p. 7516-23.
32. Ruocco, M.G., et al., *Suppressing T cell motility induced by anti-CTLA-4 monotherapy improves antitumor effects.* J Clin Invest, 2012. **122**(10): p. 3718-30.
33. Taube, J.M., et al., *Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape.* Sci Transl Med, 2012. **4**(127): p. 127ra37.
34. Parsa, A.T., et al., *Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma.* Nat Med, 2007. **13**(1): p. 84-8.
35. Marzec, M., et al., *Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1).* Proc Natl Acad Sci U S A, 2008. **105**(52): p. 20852-7.
36. Vivier, E., et al., *Innate or adaptive immunity? The example of natural killer cells.* Science, 2011. **331**(6013): p. 44-9.
37. Manjunath, S.R., et al., *Autologous immune enhancement therapy in recurrent ovarian cancer with metastases: a case report.* Case Rep Oncol, 2012. **5**(1): p. 114-8.
38. Tseng, H.C., et al., *Increased lysis of stem cells but not their differentiated cells by natural killer cells; de-differentiation or reprogramming activates NK cells.* PLoS One, 2010. **5**(7): p. e11590.
39. Bauer, S., et al., *Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA.* Science, 1999. **285**(5428): p. 727-9.
40. Benson, D.M., Jr., et al., *The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody.* Blood, 2010. **116**(13): p. 2286-94.
41. Webb, J.R., et al., *PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer.* Gynecol Oncol, 2016. **141**(2): p. 293-302.
42. Berger, A., *Th1 and Th2 responses: what are they?* BMJ, 2000. **321**(7258): p. 424.
43. Kidd, P., *Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease.* Altern Med Rev, 2003. **8**(3): p. 223-46.
44. Seymour, L., et al., *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* The Lancet Oncology, 2017. **18**(3): p. e143-e152.

45. Hartsell, W.F., et al., *Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases.* J Natl Cancer Inst, 2005. **97**(11): p. 798-804.
46. Koswig, S. and V. Budach, *[Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study].* Strahlenther Onkol, 1999. **175**(10): p. 500-8.
47. Agarwala, A.K. and N.H. Hanna, *Long-term survival in a patient with stage IV non-small-cell lung carcinoma after bone metastasectomy.* Clin Lung Cancer, 2005. **6**(6): p. 367-8.
48. Schefter, T.E., et al., *A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases.* Int J Radiat Oncol Biol Phys, 2005. **62**(5): p. 1371-8.
49. Timmerman, R. and F. Lohr, *Normal tissue dose constraints applied in lung stereotactic body radiation therapy.*, in *Stereotactic Body Radiation Therapy.* , R. Timmerman and B. Kavanagh, Editors. 2005, Lippincott, Williams, and Wilkins: Philadelphia.
50. Hamanishi, J., et al., *Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer.* J Clin Oncol, 2015. **33**(34): p. 4015-22.
51. Seung, S.K., et al., *Phase 1 study of stereotactic body radiotherapy and interleukin-2--tumor and immunological responses.* Sci Transl Med, 2012. **4**(137): p. 137ra74.