MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2018-1059
Protocol Title	DNA DAMAGE REPAIR (DDR) INHIBITOR-BASED BASKET OF BASKETS PHASE I/II TRIAL IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING ABERRATIONS IN DDR GENES (D-BOB)
Protocol Phase	I/II
Protocol Version	08
Version Date	18Nov2022
Protocol PI	[redacted]
Department	Investigational Cancer Therapeutics
IND Sponsor	MD Anderson Cancer Center
IND #	146604

DNA DAMAGE REPAIR (DDR) INHIBITOR-BASED BASKET OF BASKETS PHASE I/II TRIAL IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING ABERRATIONS IN DDR GENES (D-BOB)

Principal Investigator: [redacted]

Sponsor: The University of Texas MD Anderson Cancer Center (MDACC)

Supporter: EMD Serono

Study Drug(s): Avelumab, M6620 (formerly VX-970)

Clinical Phase: Phase I/II

Indications: Patients with advanced cancers with aberrations in genes involved in DNA Damage Response (DDR)

IND #: 146604

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List of MDACC Study Contacts

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STUDY SYNOPSIS

MDACC Protocol Number	2018-1059
Protocol Version (Date)	November 18, 2022
Trial Center/Country	Single Institution Trial (MDACC)/USA
Planned Trial Period (First Subject In/Last Subject Out)	January 2020/January 2025
Trial Registry	February 12, 2020 clinicaltrials.gov
Study Population	Patients with advanced solid tumors with DNA Damage Response aberrations
Study Design	This is an open label, single center Phase I/II dose escalation and expansion study that will evaluate the safety and clinical benefit of the following combinations: • IV ATR inhibitor (M6620) in combination with avelumab. **Note: Additional arms involving agents, such as an oral ATR inhibitor, DNA-PK inhibitor, a PARP inhibitor, an ATM inhibitor, and other agents will be added following a substantial amendment to the current protocol.**
Objectives	Primary Objectives 1. To determine the safety and tolerability of the combination of M6620 and avelumab in patients with DDR deficient advanced solid tumors. 2. To establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination of M6620 and avelumab in patients with DDR deficient advanced solid tumors. Secondary Objectives 1. To determine the clinical benefit of the combination of M6620 and avelumab, as defined by clinical benefit rate (CBR) - complete response [CR] + partial response [PR] + stable disease [SD] > 6 months (CR + PR + SD > 6 months). 2. To assess clinical benefit of the combination as defined by objective response rate (ORR = CR + PR), overall survival (OS), and progression free survival (PFS). Exploratory Objectives 1. To evaluate clinical benefit of the combination of M6620 and avelumab based on specific DDR aberrations.

	2. To evaluate clinical benefit of the combination of M6620 and avelumab based on DDR gene expression signatures. 3. To evaluate the impact of treatment on PD-L1 expression and immune cell populations. 4. To assess potential mechanisms of resistance by comparing pre- and on-treatment biopsies in responders and non-responders. 5. To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of M6620 in combination with avelumab in patients with DDR deficient advanced solid tumors.
Endpoints	<u>Primary Endpoints</u> 1. Incidence and severity of adverse events (AEs) and serious adverse events (sAEs) (as graded by NCI CTCAE version 5.0), including significant changes in laboratory parameters, ECGs, and vital signs. 2. Incidence of dose-limiting toxicities (DLTs) (see Section 3.3). <u>Secondary Endpoints</u> 1. Clinical benefit will be assessed radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and immune-related RECIST (irRECIST). Post-baseline imaging will occur every 2 cycles or 8 weeks (± 7 days) for the first year of treatment. Thereafter, tumor assessments will be performed every 3 cycles or 12 weeks (± 7 days), independent of cycle delays. 2. ORR, OS, and PFS by radiographic disease assessments per RECIST v1.1 and irRECIST. Post-baseline imaging will commence after 2 cycles (8 weeks) of therapy. <u>Exploratory Endpoints</u> 1. Correlation between clinical benefit (CBR, ORR, PFS, or OS) and ATM mutations and/or protein loss. 2. Assessment of homologous recombination deficiency (HRD) score and replication stress response defect (RSRD) score. 3. Immunohistochemistry, immunofluorescence, and flow cytometry analysis of immune cell subsets and markers, including PD-L1. 4. Whole exome sequencing, RNA-sequencing, and Reverse Phase Protein Array (RPPA) analysis of pre-, on-treatment, and optional at-progression tumor biopsies. 5. PK summary statistics, concentration-time profiles and parameters (e.g. CL, AUC, C_{max}, T_{max}, half-life if estimable).

Study Considerations	• Actionable variant(s) in the following DDR genes, based on next generation sequencing (NGS), will be considered in this trial: *ARID1A*, *ATM, ATR, ATRX*, *BAP1, BARD1, BRCA1/2, BRIP1, CDK12, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, MSH2, NBN (NBS1), PALB2, RAD51, RAD51C, RAD51D, SMARCB1,* and *VHL*. Other appropriate aberrations may be considered for patient selection at the discretion of the PI depending on emerging data. • CLIA-approved immunohistochemistry analysis of ATM protein loss may also be considered. • Interim analysis of toxicity will be performed in cohorts of 10 patients. • Interim analysis for futility will be performed in cohorts of 10 patients.
Planned Sample Size	3-6 patients for dose escalation. 30 patients for dose expansion. The accrual may be up to 36 patients

STUDY CALENDAR

Assessments		Treatment Period														Post-Treatment		
	Screening	Cycle 1						Cycle 2				Cycle 3 and Beyond				End of Treatment (EOT)	Short-term Follow-Up	Long-term Follow-up
Day **Visit Window in days**	**≤ 28 days prior to 1st dosing of study drug**	**D1** **± 3**	**D2-4**	**D8** **± 2**	**D15** **± 2**	**D16-18**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**+ 7**	**Day 30, 60, and 90 after last dose** **± 7**	**Every 12 weeks** **± 14**
Informed Consent[1]	X																	
Verify Eligibility	X	X																
Medical History[2]	X																	
Tumor History	X																	
Serum or urine Beta-hCG[3]	X	X						X				X				X	Day 30 and 60 only	
Protocol/Safety Evaluations																		
Physical Exam and ECOG[4]	X	X			X			X		X		X		X		X	X	
Vital Signs[5]	X	X		X	X		X	X		X		X		X		X	X	
Weight[5]	X	X			X			X		X		X		X		X	X	
Height	X																	
12-lead ECG[6]	X							X										
ECHO/MUGA[7]	X											X				X		

Assessments		Treatment Period														Post-Treatment		
	Screening	Cycle 1						Cycle 2				Cycle 3 and Beyond				End of Treatment (EOT)	Short-term Follow-Up	Long-term Follow-up
Day **Visit Window in days**	**≤ 28 days prior to 1st dosing of study drug**	**D1 ± 3**	**D2-4**	**D8 ± 2**	**D15 ± 2**	**D16-18**	**D22 ± 2**	**D1 ± 2**	**D8 ± 2**	**D15 ± 2**	**D22 ± 2**	**D1 ± 2**	**D8 ± 2**	**D15 ± 2**	**D22 ± 2**	**+ 7**	**Day 30, 60, and 90 after last dose ± 7**	**Every 12 weeks ± 14**
AE/SAE Assessment[8]	X	X			X			X		X		X		X		X	X	
Concomitant Medications	X	X			X			X		X		X		X		X		
Survival Status[9]																		X
Laboratory Evaluation																		
Hematology[10]	X	X			X			X		X		X		X		X	X	X
Chemistry[11]	X	X			X			X		X		X		X		X	X	X
Thyroid Function[12]	X	X										X				X	X	
Urinalysis[13]	X	X						X				X				X		
Coagulation Test[14]	X	X						X				X				X	X	
Hepatitis B and C (Hepatitis B surface antigen and core antibody; anti-hepatitis C antibody)	X																	

Assessments		Treatment Period														Post-Treatment		
	Screening	Cycle 1						Cycle 2				Cycle 3 and Beyond				End of Treatment (EOT)	Short-term Follow-Up	Long-term Follow-up
Day **Visit Window in days**	**≤ 28 days prior to 1st dosing of study drug**	**D1** **± 3**	**D2-4**	**D8** **± 2**	**D15** **± 2**	**D16-18**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**+ 7**	**Day 30, 60, and 90 after last dose** **± 7**	**Every 12 weeks** **± 14**
Study Treatment																		
Avelumab[15]		X			X			X		X		X		X				
M6620[16,17]		X		X	X		X	X	X	X	X	X	X	X	X			
Tumor Measurement																		
CT, MRI, or PET-CT[18]	X											Every 8 weeks for up to 1 year, then every 12 weeks thereafter. Confirmation ≥ 4 weeks following initial OR PD.				X		X
Relevant Tumor Markers[19]	X	X						X				X				X		X
Research Studies (PK/PD)																		
Tumor biopsy[20]	X				X											X		
Liquid biopsy[21]	X				X							X				X		
PK Blood Samples		X			X							X						

Assessments		Treatment Period														Post-Treatment		
	Screening	Cycle 1						Cycle 2				Cycle 3 and Beyond				End of Treatment (EOT)	Short-term Follow-Up	Long-term Follow-up
Day **Visit Window in days**	**≤ 28 days prior to 1st dosing of study drug**	**D1** **± 3**	**D2-4**	**D8** **± 2**	**D15** **± 2**	**D16-18**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**D1** **± 2**	**D8** **± 2**	**D15** **± 2**	**D22** **± 2**	**+ 7**	**Day 30, 60, and 90 after last dose** **± 7**	**Every 12 weeks** **± 14**
-Avelumab[22]		X			X							X				X		
-M6620[23]		X	X		X	X												

Footnotes:

1. Informed consent must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period. The use of remote consenting to obtain informed consent from clinical trial participants using paper or electronic consent forms is allowed in this study

2. Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

3. For female patients of childbearing potential, who do not fit the definition of 'female patients who are not of childbearing potential' in the inclusion criterion, a serum or urine pregnancy test, will be performed on 2 occasions prior to starting study therapy: once at the start of screening (within 28 days of first dose of study treatment), and once at the baseline visit (Cycle 1 Day 1), immediately before administration of investigational agent. Pregnancy tests will also be routinely repeated on Day 1 of every cycle during the active treatment period.

4. Physical examination and ECOG will be performed at screening, on Days 1 and 15 of each cycle, and at the End of Treatment (EOT) visit. Physical examinations during the study should be symptom directed.

5. Vital signs: temperature, pulse, respiratory rate, blood pressure, body surface area, and body weight will be measured at the start of each treatment cycle (up to 3 day before the start of a new cycle) and on day 15 (± 1 day) of each cycle. Weight will be used to calculate doses per institutional SOP. Height will be obtained from the electronic medical record.

6. 12-lead ECG (single) will be performed at screening, and on Cycle 2 Day 1. Thereafter, ECGs will be performed as clinically indicated.

7. ECHO/MUGA: will be performed at screening, and on Cycle 3 Day 1. Thereafter, ECHO/MUGA will be performed as clinically indicated.

8. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 5.0. Patients must be followed for AEs for 90 days after the last dose of study drug, or until all drug related toxicities have resolved, whichever is later; or earlier than 30 days should the patient commence another anticancer therapy in the meantime.

9. Survival status: investigators will collect survival data for patients after progression of disease unless patient fully withdraws consent to consent to participate in the study. Approximately 1 year after the last dose of treatment, a chart review, patient visit, or telephone call will be conducted. The telephone call should be less than 5 minutes in duration, to obtain information regarding survival status.

10. Hematology: complete blood count (CBC), differential, and platelets.

11. Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose (non-fasting), calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin (total, direct, indirect), lactate dehydrogenase (LDH), total protein, albumin, uric acid, amylase, lipase, creatinine kinase, Adrenocorticotropic hormone (ACTH) and Testosterone (at screening only for CRPC patients), Gamma Glutamyl Transferase (GGT) and C-reactive Protein (CRP). No need to assess on Cycle 1 Day 1 if baseline assessment was performed within 2 days prior to that date. Chemistry labs will be performed on Days 1 and 15 of every cycle.

12. Thyroid Function: thyroid-stimulating hormone (TSH), free thyroxine (T4), and total triiodothyronine (T3) will be assessed at screening, Cycle 1 Day 1, and every 2 cycles or 8 weeks thereafter (C3D1, C5D1 etc.,) until disease progression or unacceptable toxicity, and also at the EOT visit.

13. Urine analysis will include color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, and microscopy including WBC/high power field (HPF), and RBC/HPF, if clinically indicated. Dipstick is acceptable. Urine analysis will be at screening and Day 1 of every cycle. No need to repeat on Cycle 1 Day 1 if baseline assessment was performed within 2 days prior to that date.

14. Coagulation test includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation tests will be performed at screening, and Day 1 of every cycle. No need to repeat on Cycle 1 Day 1 if baseline assessment was performed within 2 days prior to that date.

15. Avelumab will be administered to patients at 800 mg, IV every 2 weeks, starting on Cycle 1 Day 1 (Days 1 and 15 of every cycle).

16. M6620 may be administered to patients in the dose escalation phase at 1 of 3 doses: 240 mg/m^2 (dose level 1), 480 mg/m^2 (dose level 2), or 120 mg/m^2 (dose level -1) IV weekly, starting on Cycle 1 Day 1 (Days 1, 8, 15, and 22 of every cycle). M6620 will be administered to patients in the dose expansion phase of at the recommended phase 2 dose (RP2D) established in the dose escalation phase.

17. When M6620 and Avelumab are to be administered on the same day (e.g. C1D1, C1D15), avelumab will be infused first, with an interval of at least 1 hour before infusion of M6620.

18. CT, MRI, or PET-CT scans will be performed at screening, and then every 2 cycles or 8 weeks (± 7 days) for the first year of treatment. Thereafter, tumor assessments will be performed every 3 cycles or 12 weeks (± 7 days) independent of cycle delays. Confirmatory scans will also be obtained ≥ 4 weeks following initial documentation of objective response (OR) or progression of disease (PD). The type of scan obtained is at the discretion of the investigator as appropriate for the disease. However, the same method should be used for the duration of the study. Baseline brain CT or MRI scan is required for all high risk patients (such as breast, melanoma and other cancer types as determined by the PI/sub I) at baseline (screening). Patients with stable brain metastases present at baseline (screening) will have brain CT or MRI scans performed at each tumor assessment. If bone metastases are present at baseline (screening), then repeat bone imaging is required every 8 weeks for the first 52 weeks of study treatment and every 24 weeks thereafter. Bone imaging is required at the time of confirmation of CR for patients who have bone metastases.

19. Relevant tumor markers (e.g., CA125, PSA, and CEA) will be assessed at screening, and on Day 1 of every cycle (± 7 days) this will include blood draws at EOT and Long Term Follow-up.

20. One tumor biopsy is mandatory (C1D15), although not mandatory all other tumor biopsies will be strongly encouraged. A core tissue biopsy may be required at baseline if no leftover tissue is available for screening, tissue is older than 1 year, or there is not enough tissue for testing. Tumor biopsies may be performed at baseline (pre-treatment), Cycle 1 Day 15, and at the time of progression/EOT (where feasible).

21. Blood samples, including for liquid biopsy (cfDNA), will be collected at baseline (pre-treatment), Cycle 1 Day 15, Cycle 3 Day 1, every other cycle thereafter (C5D1, C7D1 etc.,), and at the time of progression/EOT

22. Blood draw for Avelumab PK: 3.5 mL whole blood) will be collected (in 3.5 mL SST (VPGOL35) tubes to prepare serum) at: (i) Pre dose and EOI: Cycle 1 Day 1 and cycle 1 Day 15, (ii) Pre dose only: Cycle 3, 6 and (iii) End of treatment sample.

23. Blood draw for M6620 PK: (2 mL whole blood in Vacutainer® tubes containing K2EDTA anticoagulant for plasma) will be collected at: pre dose and EOI: Cycle 1, day 1 and Day 15, (ii) Cycle 1, day 2-4 (one sample during this timeframe) and (iii) Cycle 1 day 16-18 (one sample during this timeframe).

1. INTRODUCTION

Genomic instability is a hallmark of cancer, arising from a combination of replication stress and errors in DNA damage response (DDR). DDR deficiency (DDR-D) enables the cancer cell's acquisition of driver gene mutations but also engenders targetable vulnerabilities to treatment strategies that induce insurmountable DNA damage, such as platinum chemotherapies, and/or further suppress DDR leading to catastrophic instability[1]. In addition, multiple pre-clinical and clinical studies have shown significant cross-talk between DDR-D, tumor immune infiltrate, and response to immuno-oncology agents (IO) [2-5]. Thus, identifying DDR aberrations in cancers is extremely important for therapeutic decision making with the advent of immune checkpoint blockade and new classes of DDR inhibitors (DDRi), such as poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi), ataxia telangiectasia mutated and rad3-related (ATR) inhibitors (ATRi). Multiple PARPi are FDA-approved for the treatment of recurrent *BRCA1/2* mutant ovarian cancers, as well as *BRCA1/2* mutant breast cancers[6]. However, the clinical response to PARPi and DNA damaging agents such as platinum-based chemotherapies, is limited by almost inevitable drug resistance, culminating in short-lived antitumor responses. Therefore, there remains a significant unmet clinical need for novel antitumor strategies beyond just PARPi and platinum to increase the depth and duration of response, and survival benefits for patients with advanced cancers harboring DDR aberrations.

1.1 Mechanisms of Action/Indication

1.1.1 Avelumab, PD-L1 immune checkpoint inhibitor

Avelumab is an immune checkpoint-blocking antibody which targets programmed death ligand 1 (PD-L1), thereby disrupting the interaction with and signaling through the programmed death receptor 1 (PD-1), resulting in activation of T cells. Clinically, avelumab is approved for patients with Merkel cell carcinoma and for patients with locally advanced or metastatic urothelial carcinoma following disease progression during or after platinum-based chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. Ongoing clinical studies have demonstrated meaningful clinical activity across multiple tumor types and treatment settings, with ongoing responses > 1 year (NCT01772004, JAVELIN Solid Tumor).

1.1.2 M6620, ATR inhibitor (formerly VX-970)

M6620 is a first in class, potent inhibitor of ataxia telangiectasia mutated and Rad3-related protein (ATR). Supporting pre-clinical studies have demonstrated that PARPi-resistant *BRCA1*-deficient cells are exquisitely dependent on ATR for survival; ATR inhibitors (ATRi) disrupt BRCA1-independent RAD51 loading to DNA DSBs in PARPi-resistant *BRCA1*-deficient cells, overcoming such resistance mechanisms[7,8]. ATRi may therefore potentially overcome PARPi-resistance in *BRCA*-deficient cancers. In addition, the ATR/CHK1 and ATM/CHK2 axes have multiple interconnected and overlapping functions in regards to DDR, cell cycle regulation, and mitigation of replication stress. Preclinical and early clinical studies of ATR inhibitors have shown functional loss of ATM to predict for ATR inhibitor sensitivity[9]. Deficiency in ARID1A, a key chromatin regulator, have also been shown to lead to homologous repair deficiency (HRD) and in particular susceptibility to ATR inhibition in preclinical models[10]. Other pre-clinical *in vitro* studies have demonstrated that M6620 sensitizes many cancer cell lines to the cytotoxic effects of numerous DNA-damaging drugs[11]. *In vivo*, M6620 has also been shown to potentiate the antitumor activity

of DNA-damaging agents and radiotherapy. For example, in patient-derived xenograft mouse models of non-small cell lung cancer (NSCLC), the combination of M6620 with cisplatin resulted in significantly greater tumor control in comparison to either single agent[12]. Additionally, in a xenograft mouse model of gastric cancer, treatment with the ATRi AZD6738, decreased proliferation (by Ki67 expression) and increased apoptosis (by TUNEL assay), resulting in greater tumor control[13]. In a recent phase I clinical trial, the combination of M6620 and Topotecan, was demonstrated to be active in platinum-refractory small-cell lung cancer (SCLC), which is notably resistant to Topotecan monotherapy. Partial response or prolonged stable disease (≥ 6 months) was observed in 3 of 5 SCLC patients enrolled in this study[14]. Additionally, phase I studies of M6620 led by Dr. Yap, have also demonstrated promising clinical activity in patients harboring *BRCA1/2* mutant cancers[15-17].

1.2 Rationale for the combination of DDR and immune checkpoint inhibitors

There is strong preclinical and clinical evidence that DDR-D and S-phase specific DNA damage leads to activation of innate immune pathway activity including the stimulator of interferon gamma (STING) axis, increased tumor immune infiltrate, increased PD-L1 expression, and improved response to immune therapy (IO)[18-20]. Preclinical data has also shown DDRi can have similar effects on PD-L1, innate immune activity, and immune response as genetic deficiencies in DDR[4,5]. However, the clinical response to single-agent DDRi, including PARPi, is limited by drug resistance, with short-lived antitumor responses, even in tumors with DDR gene aberrations. In addition, single agent IO response is not uniform, even within a single tumor type, and predictive functional biomarkers are lacking. Therefore, there remains a significant unmet clinical need for novel antitumor strategies to increase the depth and duration of response to both IO and DDRi, and improve survival benefits for patients with advanced cancers harboring DDR aberrations.
Recent preclinical data provide rationale to combine DDR inhibitors such as ATRi with immunotherapies in an effort to increase clinical outcomes for patients with cancers carrying mutations in DDR genes. In a study of DNA repair-deficient breast cancers, Parkes et al., identified a mechanism of immune response where STING-mediated chemokine production occurred in response to DNA damage. This resulted in an inflammatory microenvironment in DDR-deficient breast tumors. They also found that expression of PD-L1 was associated with tumors deficient in DDR, supporting the investigation of immunotherapies in tumors harboring DDR defects[19]. Other studies have demonstrated that PARPi treatment can increase the expression of PD-L1 on breast cancer cells, and that the combination of PARPi and anti-PD-L1 therapy significantly increased antitumor response in mouse models of breast cancer in comparison to either monotherapy[4]. In a Phase I modular study led by Dr. Yap, the combination of the ATRi AZD6738 with the PD-L1-targeting antibody durvalumab, was shown to be well tolerated with signals of antitumor activity[21].

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary, Secondary, and Exploratory Objectives

2.1.1 Arm A: M6620 + Avelumab

Primary Objectives:

1. To determine the safety and tolerability of the combination of M6620 and avelumab in patients with DDR deficient advanced solid tumors.

2. To establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination of M6620 and avelumab in patients with DDR deficient advanced solid tumors.

Secondary objectives:

1. To determine the clinical benefit of the combination as defined by clinical benefit rate (CBR) - complete response [CR] + partial response [PR] + stable disease [SD] > 6 months (CR+PR+SD>6months).

2. To assess clinical benefit of the combination as defined by objective response rate (ORR), overall survival (OS), duration of response (DoR) and progression free survival (PFS). Patients will be followed for 6 months after a confirmed response.

Exploratory objectives:

1. To evaluate clinical benefit of the combination of M6620 and avelumab based on specific DDR aberrations.

2. To evaluate clinical benefit of the combination of M6620 and avelumab based on DDR gene expression signatures.

3. To evaluate the impact of treatment on PD-L1 expression and immune cell populations.

4. To assess potential mechanisms of resistance by comparing pre- and on-treatment biopsies in responders and non-responders.

5. To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of M6620 in combination with avelumab in patients with DDR deficient advanced solid tumors

2.2 Primary, Secondary, and Exploratory Endpoints

2.2.1 Arm A – M6620 + Avelumab

Primary Endpoints:

1. Incidence and severity of adverse events (AEs) and serious adverse events (sAEs) (as graded by NCI CTCAE version 5.0), including significant changes in laboratory parameters, ECGs, and vital signs.

2. Incidence of dose-limiting toxicities (DLTs) (see Section 3.3).

Secondary Endpoints:

1. Clinical benefit will be assessed radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and immune-related RECIST (irRECIST).

2. ORR, OS, DOR and PFS by radiographic disease assessments per RECIST v1.1 and irRECIST.

Exploratory Endpoints:

1. Correlation between clinical benefit (CBR, ORR, PFS, DOR or OS), and ATM mutations and/or protein loss.

2. Assessment of homologous recombination deficiency (HRD) score and replication stress response defect (RSRD) score.

3. Immunohistochemistry, immunofluorescence, and flow cytometry analysis of immune cell subsets and markers.

4. Whole exome sequencing, RNA-sequencing, and Reverse Phase Protein Array (RPPA) analysis of pre-, on-treatment, and optional at-progression tumor biopsies.

5. PK summary statistics, concentration-time profiles and parameters (e.g. CL, AUC, C_{max}, T_{max}, half-life if estimable)

3. STUDY DESIGN

3.1 Study Overview

This is a single-center, investigator-initiated, open-label, study of M6620 in combination with avelumab (Arm A), in adult patients with advanced solid tumors with aberrations in DNA Damage Response (DDR) genes.

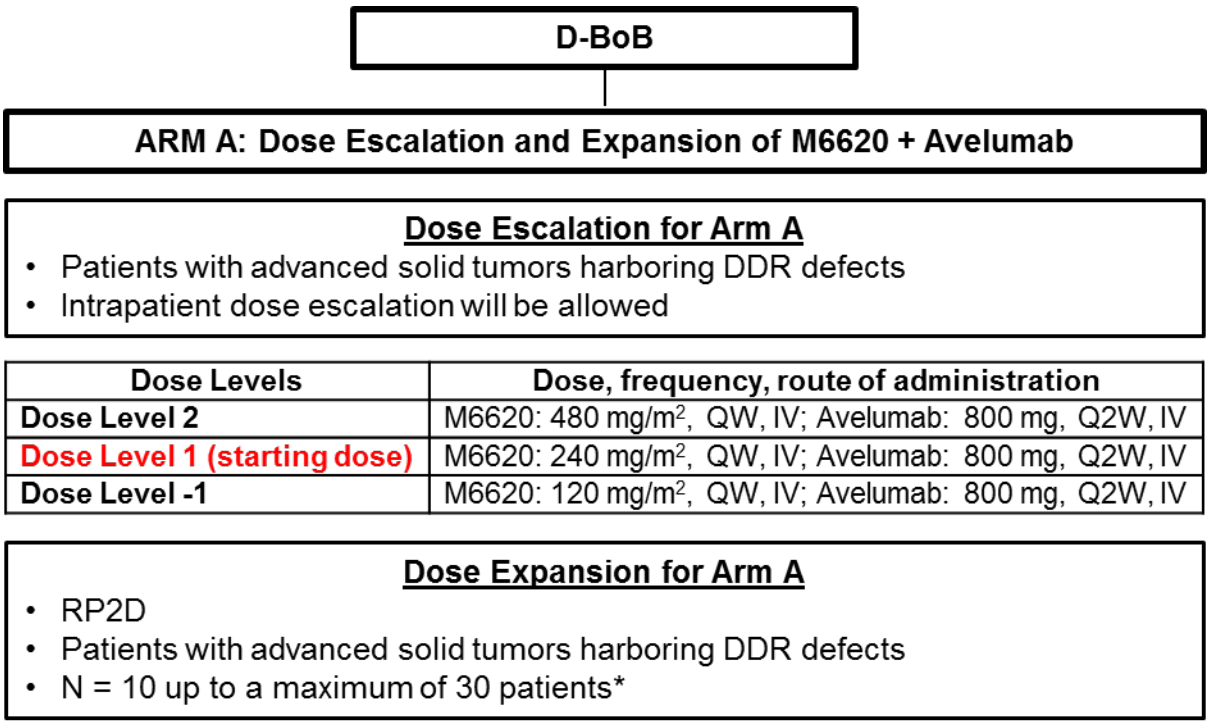
Note: Additional arms will be developed based on evolving molecular and clinical data, and will be added to this protocol following a substantial amendment.

This is an adaptive program of trials, which will be set up sequentially depending on the development and/or availability of the individual agents. In this adaptive study, patients with DDR deficient biomarker positive advanced solid tumors entered on study may crossover to other available combination baskets upon disease progression, depending on evolving molecular and/or immune profiling data.

The number of patients in each basket may be increased depending on pre-defined signals and early stopping rules for futility or toxicity as described in Section 3.2 and Section 9.6. Patients will have pre and on-treatment tumor biopsies for correlative translational studies described in Section 7.5. All patients will have serial testing of blood parameters for DDR aberrations (e.g. ctDNA) and immune profiling.

3.2 Study Treatment Arms

Figure 1: DNA Damage Repair (DDR) Inhibitor-based Basket of Baskets Trial (D-BoB)



***Note:** a 3-stage decision with 10 patients at each stage will be used for each regimen in the dose expansion phase of the trial. We will stop after the 1st stage if we see 0 successes in 10 patients,

after the 2nd stage if we see < 2 successes in 20 patients, and we will declare the treatment worthy of further study if we see > 3 successes in 30 patients.
QW = weekly; Q2W = every two weeks; MTD = Maximum Tolerated Dose; RP2D = Recommended Phase 2 Dose

3.2.1 Arm A: M6620 + Avelumab

This basket study will begin with dose escalation and expansion of the combination of M6620 and avelumab. During the dose escalation phase, patients with advanced solid tumors who meet eligibility criteria may be treated at 1 of 3 doses of M6620 in combination with a fixed dose of avelumab, and will be evaluated for dose limiting toxicities (DLTs). Intrapatient dose escalation will be allowed in this trial.

Intra-patient dose escalation for patients enrolled in dose level 1 may be considered in consultation with the Principal Investigator. Once the respective dose level has been declared safe, patients who have completed at least 2 Cycles of treatment at the original enrolled dose level may escalate to the next higher dose level that has cleared the DLT observation period of 28 days. For the safety analysis, patients will be considered at both dose levels.

All patients must have DDR aberrant advanced solid tumors to be eligible. The dose expansion phase will be enriched for patients with advanced solid tumors with aberrations in the following DDR genes: *ARID1A*, *ATM, ATR, ATRX*, *BAP1, BARD1, BRCA1/2, BRIP1, CDK12, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, MSH2, NBN (NBS1), PALB2, RAD51, RAD51C, RAD51D, SMARCB1,* and *VHL*. Other appropriate aberrations may be considered for patient selection at the discretion of the PI depending on emerging data. Variant interpretation for actionability will be performed by the MD Anderson Cancer Center (MDACC) Institute for Personalized Cancer Therapy (IPCT) Precision Oncology Decision Support (PODS) group. The PODS team facilitates a real-time mutation-by-mutation assessment of actionability. High-throughput literature retrieval from the MEDLINE database, along with natural language processing (NLP), is performed to identify scientific literature that potentially shed light on whether there is experimental evidence showing if a genomic alteration increases the cellular processes of tumorigenesis. The literature is then manually reviewed by expert scientists to validate and record the experimental assessment of each alteration.

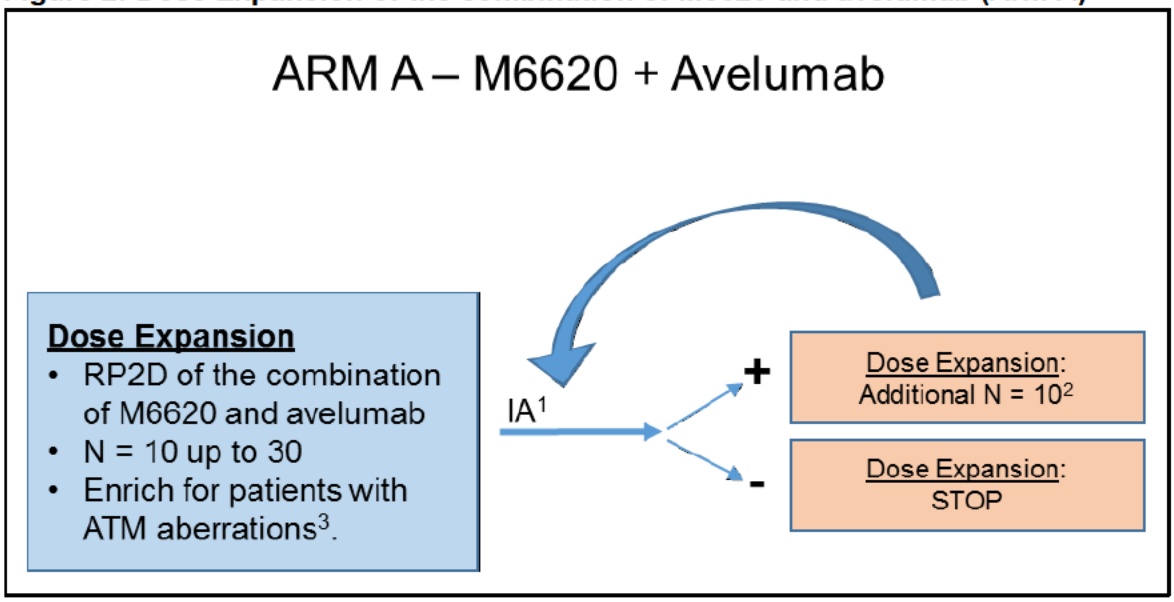
Table 1: Dose Escalation of the combination of M6620 and avelumab (Arm A)

Dose Level	Dose, frequency, and route of administration
Dose Level 2	M6620: 480 mg/m^2, QW, IV; Avelumab: 800 mg, Q2W, IV
Starting Dose Level 1	M6620: 240 mg/m^2, QW, IV; Avelumab: 800 mg, Q2W, IV
Dose Level -1	M6620: 120 mg/m^2, QW, IV; Avelumab: 800 mg, Q2W, IV

Note: other intermediate doses of M6620 may be considered following discussion with EMD Serono.

When avelumab and M6620 are to be administered on the same day, avelumab will be administered first, with an interval of at least 1 hour between infusions.

Figure 2: Dose Expansion of the combination of M6620 and avelumab (Arm A)



[1]**Interim Analysis for Safety:** Patients can have any qualifying DDR aberration for interim safety analysis. We will stop if, at any time during the study, we determine that there is more than an 80% chance that the posterior probability of toxicity (i.e., DLT) is more than 30%.

[2]**Interim Analysis for Futility**: Using a 3-stage design with 10 patients in each stage, we will stop after the 1st stage if we see 0 successes in 10 patients, after the 2nd stage if we see <2 successes in 20 patients, and we will declare the treatment worthy of further study if we see >3 successes in 30 patients. If we set p0 (highest success rate for unacceptable treatment) =5% and p1 (lowest success rate for acceptable treatment) =20%, this design has alpha=5%, 80% power and probability of early termination under p0 of 60% after 1st stage and 79% after either 1st or 2nd stage.

[3]**Note:** This study will not be rejected for efficacy until at least N=10 patients with ATM variants have been evaluated for efficacy.

3.3 Dose Limiting Toxicity (DLT) Definition

Severity of adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. A DLT is defined as any death not clearly due to the underlying disease or extraneous causes or as any Grade ≥ 3 non-hematologic AE or any Grade ≥ 4 hematologic AE according to the NCI-CTCAE v 5.0, occurring during the DLT observation period that is related to any of the study interventions as determined by the Investigator or Sponsor at any dose and judged not to be related to the underlying disease or any previous or concomitant medication. A DLT must be confirmed by the SMC.

Any of the following adverse events occurring in the first 28 days of study participation are considered DLTs:

1. Grade 4 neutropenia ≥ 7 days or febrile neutropenia will be considered dose limiting.
2. Grade 3+ thrombocytopenia with bleeding or Grade 4 thrombocytopenia >7 days will be considered dose limiting.
3. A study intervention-related TEAE that in the opinion of the Safety Monitoring Committee (SMC) is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk.
4. Delay by more than 4 weeks (28 days) in receiving the next scheduled cycle of study drug(s) due to persisting toxicities attributable to the study drug(s).
5. Non-hematologic toxicities:
    a. Grade ≥ 3 nausea/vomiting or diarrhea lasting ≥ 72 hours while receiving optimal supportive medications,
    b. Grade ≥ 3 fatigue lasting ≥ 7 days,
    c. Grade3 pneumonitis of any duration,
    d. Grade ≥ 3 rash lasting ≥ 7 days despite treatment,
    e. Any Grade 4 immune related toxicities
    f. Any other Grade ≥ 3 non-hematological toxicity (except for electrolyte abnormalities that are reversible and asymptomatic or hair loss which is not dose-limiting; as well as Grade 3 infusion-related reaction of any duration,
    g. AST or ALT >3 × ULN and concurrent total bilirubin >2 × ULN of any duration without initial findings of cholestasis (elevated alkaline phosphatase, e.g., findings consistent with Hy's law or FDA definition of potential IP-induced liver injury).. For patients with hepatic metastases: AST, ALT >8X ULN; AST or ALT >5X ULN lasting ≥14 days.

The following treatment-related AEs are exceptions to the above mentioned DLT definition and are **not** considered to be DLTs:

1. Isolated Grade 4 lymphopenia without clinical correlate.
2. Any Grade 4 neutropenia < 7 days duration not associated with any clinical symptoms.
3. Other single laboratory values out of normal range that have no clinical correlate, and resolve to Grade ≤ 1 or to baseline within 7 days with adequate medical management.
4. Any Grade 3 autoimmune thyroid-related toxicity that clinical resolves to Grade ≤ 2 within 7 days of initiating therapy.
5. Grade 3 diarrhea persisting < 72 hours after initiation of medical management.
6. Grade 3 non-recurrent skin toxicity that resolves to Grade ≤ 1 in < 7 days after initiation of medical management.
7. Transient Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, nausea, and emesis that resolve to Grade ≤ 1 in < 48 hours after initiation of medical management.
8. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 6 days.
9. Grade 3 infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management.

Elevation of amylase and/or lipase without clinical and/or radiographic evidence of pancreatitis are not considered DLTs, and the patient may resume treatment at any grade at the discretion of the treating physician in consultation with the PI.

During dose escalation, patients who receive <75% of the planned dose of the investigational products in the combination during Cycle 1 for reasons unrelated to study drug(s) are not evaluable for DLT and will be replaced.

In rare instances, an event may fall within the definition of a DLT as defined above but the event may not be considered a DLT (e.g. not clinically meaningful or significant). If this occurs, the PI will thoroughly review the event and supporting data, and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition, other events may occur that do not meet the definition of a DLT but are concerning to the PI, may then be considered to be DLTs.

In the event that a DLT is at least possibly related to the study drug(s), patients will halt treatment with the study drug(s) until symptoms resolve to the grade outlined in Section 5.2.5.2. Study drug(s) may be restarted as described in Section 5.2.5.

3.4 Maximum Tolerated Dose (MTD) Definition

In the dose escalation phase for the combination of M6620 and avelumab, patients will be assigned sequentially in groups of up to 6 patients at each dose level. Three to 6 patients will initially be enrolled at each dose level for DLT observation. A total of 6 patients will be enrolled at each dose level in the event that a DLT is observed in 1 of the first 3 patients and/or additional safety data are needed.

The MTD is defined as the highest dose level with less than 2 patients with DLT out of at least 6 patients at the dose level. Management and dose modifications associated with adverse events are outlined in subsequent protocol sections.

The DLT assessment window is 28 days (1 cycle). In the absence of DLTs, patients may continue consecutive treatment. For patients who experience a DLT, they may continue treatment with modifications if the toxicity resolves and at the discretion of the treating physician and the PI. In the absence of clinical deterioration and if the investigator believes that the patient continues to receive benefit from the treatment, patients may continue to receive study drug(s) after the first indication of progressive disease until a confirmatory scan is obtained.

To understand and safeguard against potential cumulative toxicities the study team will continue to monitor the occurrence of study drug related SAEs and AEs throughout the treatment period and during potential treatment extensions to allow for dose correction in the event of cumulative immune-mediated toxicities.

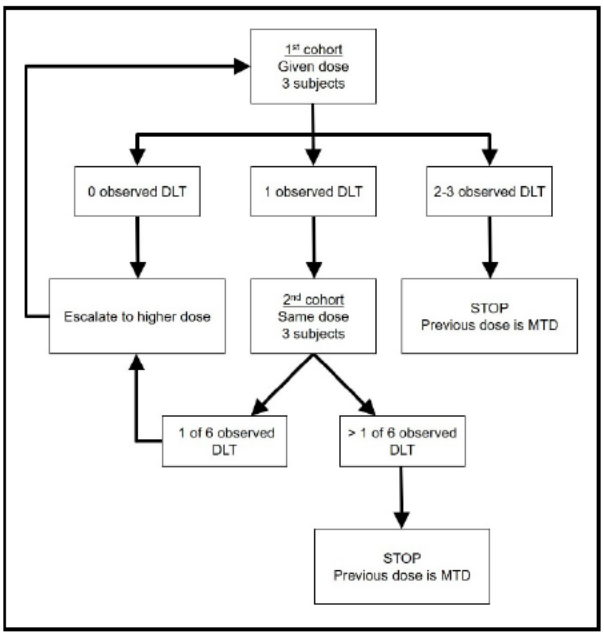
Delayed onset of significant toxicities will be evaluated on a case-by-case basis at the discretion of the PI in consultation with the Safety Monitoring Committee (SMC). At minimum, a review and discussion of potential delayed onset of significant toxicity will take place at review prior to a dose escalation decision.

3.5 Dose Escalation and Stopping Rules

The decision to proceed to the next dose level will be made after the first 3 patients in a dose level have completed 28 days (1 cycle) of dosing. Prior to advancing/changing dose levels, a dose

level summary will be completed and submitted to SMC for review and approval. The data discussed at the SMC during escalation/expansion phases and the minutes of the meetings will be submitted to the IND Office Medical Affairs & Safety group.

Figure 4: Dose Escalation Rules:



Dose escalation will occur at the planned dose levels until the MTD is determined. The MTD is defined as the highest dose level with less than two patients with DLT out of at least six patients. The recommended phase 2 dose (RP2D) will be based on the safety and preliminary efficacy data from the dose escalation and dose expansion arms. Intra-patient dose escalation will only be allowed if the patient experienced grade ≤1 AEs at the current dose.

All enrolled participants will be considered in the DLT analysis. If any patient should be excluded from the analysis, the reason(s) should be clearly documented (see Section 3.3). If a DLT occurs at a dose level with 3 patients within the first 28 days, 3 additional patients will be enrolled at that dose level. If at any time, at least one third of the participants at a dose level (33%) experience DLTs, the MTD will be reassessed and the next lowest dose level will be considered the MTD.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the study.

1. Age ≥18 years.

2. Subjects must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective.

3. Subjects will be eligible for this study based on the presence of actionable aberrations in one or more of the following DNA Damage Response (DDR) genes: *ARID1A*, *ATM, ATR, ATRX*, *BAP1, BARD1, BRCA1/2, BRIP1, CDK12, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, MSH2, NBN (NBS1), PALB2, RAD51, RAD51C, RAD51D, SMARCB1, and VHL,* or other related genes at the discretion of the principal investigator in consultation with the MD Anderson Cancer Center Institute for Personalized Cancer Therapy Precision Oncology Decision Support (PODS) group. Variant interpretation for actionability will be performed by PODS.

4. Subjects with germline defects in DDR genes are eligible for this trial.

5. The collection of archival tumor tissue (within 1 year prior to study enrollment) will be mandatory. Tumor biopsies on Cycle 1 Day 15 will be mandatory. Subjects will not be put at undue risk to obtain the biopsy at C1D15. A biopsy at C1D15 will not be required if it poses a serious/severe complication risk greater than 2%. All other biopsy timepoints are not mandatory but will be strongly encouraged where feasible. These include at baseline and at disease progression. Archival and fresh tissue requests can be waived in exceptional circumstances with PI approval and only where rationale is documented.

6. Subjects must have received at least 1 line of systemic therapy in the advanced/metastatic setting. Subjects with diseases without known effective options, and subjects who had declined standard of care therapy prior to study introduction are also eligible.

7. Subjects enrolling in the dose escalation should have progressed on or be intolerant to all therapies known to confer a clinical benefit. Subjects must not have refused all available therapies.

8. Subjects who have received prior therapy with immune checkpoint inhibitors (ICIs) are eligible for this trial. Subjects with a standard-of-care option for an Immune Checkpoint Inhibitor are eligible.

9. Subjects must have measurable disease per RECIST v1.1, or patients may have bone metastatic disease evaluable by Prostate Cancer Working Group 3 (PCWG3) for subjects with metastatic castration-resistant prostate cancer (CRPC), or according to tumor evaluation criteria best suited and accepted for the tumor type to be evaluated.

10. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

11. Subjects must have a life expectancy ≥12 weeks.

12. Subjects must have normal organ and marrow function as defined below:

a. Absolute neutrophil count ≥1.5 x 10^9/L;
b. Platelets ≥100 x 10^9/L;
c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
d. Total bilirubin ≤1.5X the institutional upper limit of normal (ULN);
e. AST(SGOT)/ALT(SGPT) ≤2.5X institutional ULN or ≤5X institutional ULN in the presence of liver metastases;
f. Renal function defined by serum creatinine ≤ 2X ULN or estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault formula.

13. Female patients of childbearing potential must have a negative serum or urine pregnancy test at screening (and again at baseline just prior to first administration of study drugs).

    Female patients of non-childbearing potential must meet at least 1 of the following criteria:
    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months, with no alternative pathological or physiological cause;
    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    c. Have medically confirmed ovarian failure.

    All other female patients are considered to be of childbearing potential.

14. Women of childbearing potential and fertile men must agree to use adequate contraception when sexually active from signing of the informed consent form for the full study until at least 6 months after the last study drug administration. Patients must agree to utilize 2 reliable and acceptable methods of contraception simultaneously. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy. Men taking part in this study are advised not to father a child during and up to 6 months after treatment; prior to treatment, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment. Female partners of childbearing potential from male study patients have to use adequate contraception / birth control between signing of the informed consent and 6 months after the last administration of the study drug if the male study patient is not sterilized. The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods, when used consistently and correctly, include:

    - Combined (estrogen and progestin containing: oral, intravaginal, transdermal) and progestin-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
    - Intra-uterine device or intrauterine hormone-releasing system.
    - Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
    - Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).

Male patients with a female partner of reproductive potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 6 months after last study drug administration. Patients must agree to utilize 2 reliable and acceptable methods of contraception simultaneously.

15. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

16. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

17. Human Immunodeficiency Virus (HIV)-infected (HIV1/2 antibody-positive) patients may participate IF they meet all the following eligibility requirements:
    a. They must be on an anti-retroviral regimen with evidence of at least two undetectable viral loads within the past 6 months on this same regimen; the most recent undetectable viral load must be within the past 12 weeks.
    b. They must have a CD4 count ≥250 cells/mcL over the past 6 months on this same anti-retroviral regimen and must not have had a CD4 count <200 cells/ mcL over the past 2 years, unless it was deemed related to the cancer and/or chemotherapy-induced bone marrow suppression.
        i. For patients who have received chemotherapy in the past 6 months, a CD4 count <250 cells/mcL during chemotherapy is permitted as long as viral loads were undetectable during this same chemotherapy.
    c. They must have an undetectable viral load and a CD4 count ≥250 cells/mcL within 7 days of enrolment.
    d. They must not be currently receiving prophylactic therapy for an opportunistic infection and must not have had an opportunistic infection within the past 6 months.

4.2 Exclusion Criteria

Patients who meet any of the exclusion criteria listed below will not be eligible for participation in the study.

1. Anticancer systemic therapy or radiotherapy within 4 weeks or 5 half-lives, whichever is shorter prior to starting the study agents. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 2 weeks prior to study enrollment, and no clinically significant toxicities are expected (e.g., mucositis, esophagitis).

2. Known symptomatic brain metastases requiring steroids. Patients with previously treated diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

3. Current use of immunosuppressive medication at the time of study enrollment, EXCEPT for the following permitted steroids:
   a. Intranasal, inhaled, topical steroids, eye drops, 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).

4. Subjects who had major surgery within 4 weeks prior to study enrollment.

5. Known prior severe hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5 Grade ≥ 3).

6. Active infection requiring systemic therapy.

7. Known history of immune-mediated colitis, inflammatory bowel disease, pneumonitis, and pulmonary fibrosis.

8. Subjects with radiographic evidence of pneumonitis on baseline imaging.

9. Active or prior autoimmune disease that may deteriorate when receiving an immunostimulatory agent. Patients with type I diabetes, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

10. Prior organ transplantation including allogenic stem cell transplantation.

11. Diagnosis of Myelodysplastic Syndrome (MDS).

12. Vaccination within 4 weeks of study enrollment and while on trial is prohibited except for the administration of inactivated vaccines.

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

14. Other acute or chronic medical or psychiatric conditions including but not limited to recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results, and in the judgement of the Investigator, would make the patient inappropriate for entry into this study.

15. Pregnant female patients, breastfeeding female patients, fertile male patients, and female patients of childbearing potential who are unwilling or unable to use 2 highly

effective methods of contraception as outlined in this protocol for the duration of the study, and for at least 6 months after the last dose of study drug administration.

16. 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 is positive).

17. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for ≥ 2 years.

18. Persisting toxicity related to prior therapy (NCI CTCAE v5 Grade > 1); however, alopecia and sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 AEs not constituting a safety risk, based on the Investigator's judgement, are acceptable.

19. Subjects receiving treatment with strong inhibitors or inducers of CYP3A4 that cannot be discontinued before start of investigational treatment and for the duration of study.

20. Subjects with ongoing toxicity (any grade) and/or resolved ICI toxicity (grade 3 or higher only.

5. STUDY TREATMENTS

The trial regimen will be administered in 28-day cycles. The investigational products to be administered in this trial are: M6620 and avelumab. For both dose escalation and expansion, treatment will continue until disease progression, unacceptable toxicity, and/or withdrawal of patient consent.

5.1 Allocation to Treatment

Eligible patients will be enrolled to receive one of the study drug combinations in an open-labeled, unblinded manner. Patients will be registered and successively assigned to the next available treatment slot at a dose level decided on after the safety evaluation and ongoing observations of earlier enrolled patients. Dose level allocation will be performed after patients have given their written informed consent and have completed the necessary baseline assessments.

5.2 Investigational Product Supplies

M6620 and avelumab will be supplied for the study by EMD Serono. The Investigational Pharmacy will receive a supply of study drug(s) prior to activation with instructions on how to confirm drug receipt. Resupplies will be made during the course of the study based on need.

5.2.1 Formulation and Packaging

Packaging and labeling for all study drugs will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. The information on each study drug will be in accordance with approved submission documents.

5.2.1.1 M6620

M6620 drug product will be supplied as a 20 mg/mL solution for injection, in 10 mL clear vials in cardboard boxes with foam inserts, designed for single-use only. M6620 drug product is intended for intravenous administration, only after dilution with 5% dextrose solution in water (D5W).

5.2.1. 2 Avelumab

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by EMD Serono in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum flip-off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Avelumab will be packed in boxes each containing 8 vials.

Avelumab will be supplied by EMD Serono and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by an EMD Serono qualified person under Good Manufacturing Practice conditions. Avelumab will be shipped and must be stored under refrigerated conditions (2ºC to 8ºC) that are monitored with temperature control monitoring devices.

5.2.2 Preparation and Dispensing

5.2.2.1 M6620

M6620 solution for injection must be diluted with 5% dextrose in water solution prior to administration. Do not use 0.9% Sodium Chloride due to incompatibility with M6620. To prepare the infusion solution add the dose volume of M6620 to a non-polyvinyl chloride (non-PVC), di(2-ethylhexyl) phthalate (DEHP)-free EVA infusion bag containing 5% dextrose in water. Gently invert the IV bag 5-10 times to mix the solution. Confirm the solution is clear and free of precipitates and/or particulates. The final concentration must be between 0.075 mg/mL to 1 mg/mL. Place the IV bag into an opaque cover to protect from light.

5.2.2.2 Avelumab

Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g. physician, nurse, physician’s assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Each single-use vial contains 200mg of Avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing mannitol, and polysorbate 20 (Tween 20). For administration, avelumab drug concentrate must be diluted with 0.9% saline solution (sodium chloride for injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed. Detailed information

on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Investigational Product Manual.

Any unused portion of the avelumab solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

5.2.3 Administration, Pre-medications, and Infusion Reactions

5.2.3.1 M6620

All doses of M6620 will be administered at the investigator site by well-trained medical staff. The start and stop times of the M6620 infusion, along with the total dose and volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of M6620 infusion will also need to be recorded in the patients' medical records. The vials of M6620 that are assigned and prepared for patients will be recorded in the pharmacy records. These records will all be available for MDA IND Office representatives to verify compliance.

To minimize the possibility of phlebitis, M6620 should be administered through a large bore catheter into a large caliber peripheral vein. The IV infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth.
If any participant develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the participant cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein). If standard procedures to limit symptoms of injection site reaction, or pruritus or acute hypersensitivity are insufficient, then the infusion time may be extended beyond 60 minutes, but no more than 90 minutes.

If a patient remains on therapy after 6 months, then treating physician/investigator may consider changing M6620 dosing from every week to every 2 weeks for ease of schedule for the patient. The physician/investigator will maintain the same dose of M6620 when changing from every week to every 2 weeks scheduling. This option will be discussed with every patient remaining on therapy after 6 months, and the decision will be at the discretion of the patient and investigator.

5.2.3.2 Avelumab

All doses of avelumab will be administered at the investigator site by well-trained medical staff. The start and stop times of the avelumab infusion, along with the total dose and volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of avelumab infusion will also need to be recorded in the patients' medical records. The vials of avelumab that are assigned and prepared for patients will be recorded in the pharmacy records.

Avelumab will be administered as a 1-hour infusion dose of 800 mg administered IV once every 2 weeks.

As a routine precaution, participants enrolled in this study must be observed for 1-hour post infusion for the first 4 infusions, in an area with resuscitation equipment and emergency agents. At all times during avelumab treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be

assured. In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

The treatment recommendations for infusion-related reactions are outlined in **Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications** (Section 5.2.5.3.2).

Investigators should also monitor participants closely for potential irAEs, which may become manifest at any time during treatment. Such events include but are not limited to pneumonitis, hepatitis, colitis, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, and type 1 diabetes mellitus), myocarditis, myositis, and rash. See Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications details on the management of irAEs.
Investigators should also monitor participants closely for potential irAEs, which may become manifest earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto antibodies like anti-nuclear antibodies or anti-neutrophil cytoplasmic antibodies. **See Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications** (Section 5.2.5.3.2) for details on the management of irAEs.

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

5.2.3.3 Pre-medications

For avelumab, premedication with an antihistamine (for example, 25 to 50 mg diphenhydramine) and with paracetamol (acetaminophen; 500 to 650 mg) IV or oral equivalent approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory, and thereafter is based upon clinical judgment and presence/severity of prior infusion reactions. Standard prophylactic premedication with corticosteroids is not recommended; however, prophylactic steroids to prevent recurrence of infusion-related reaction are not prohibited, based on the Investigator's clinical judgment. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Premedication with a corticosteroid and/or an antihistamine should be given to participants who have developed acute hypersensitivity and/or pruritus with M6620 infusion and who continue to receive treatment with M6620.

5.2.3.4 Administration of Avelumab and M6620 on the same day

On days when both avelumab and M6620 are to be administered (e.g., C1D1, C1D15), avelumab infusion will precede infusion of M6620, with at least 1 hour in between infusions to observe patients for infusion-related reactions.

5.2.3.5 Food Requirements

The investigational products may be administered without regard to food.

5.2.4 Patient Compliance

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded in the CRF. The investigator will make sure that the information entered into the CRF regarding drug administration is accurate for each patient. Any reason for non-compliance should be documented.

5.2.5 Recommended Dose Modifications

Every effort should be made to administer the study drugs on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. Toxicity will be graded according to NCI CTCAE, version 5.0. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur:

- Within a cycle: dosing interruption until adequate recovery and dosing reduction, if required, during a given treatment cycle.
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

5.2.5.1 Dose Interruptions

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in Dose Delays (Section 5.2.5.2).

Doses may be held as needed until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Dose Modifications (Section 5.2.5.3), unless expressly agreed otherwise following discussion between the Investigator and the SMC.

In the event of a treatment interruption for reasons other than treatment-related toxicity (e.g. elective surgery) lasting >28 days, treatment resumption will be decided in consultation with the SMC.

5.2.5.2 Dose Delays

Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted/delayed. Appropriate follow-up assessments should be done until adequate recovery (or until deemed irreversible) occurs as assessed by the Investigator. A treatment delay of more than 4 weeks due to lack of recovery will result in discontinuation of the patient from the treatment, unless continuation (with dose reduction) upon subsequent recovery is considered in the patient's best interest by the investigator (e.g. proven clinical benefit).

A new cycle of treatment may begin only if:

a. ANC ≥ 1000/μL
b. Platelet count ≥ 100,000/μL
c. Hemoglobin ≥ 8.5 g/dL
d. Non-hematologic toxicities have returned to baseline or Grade ≤ 1 severity (or, at the investigator discretion, Grade ≤ 2 if not considered a safety risk for the patient).

Withhold scheduled dose for liver function test related AEs (including asymptomatic) Grade ≥ 3 until return to baseline or Grade ≤ 1 severity. In cases of potential liver injury, consultation with a hepatologist should be considered in the decision to initiate treatment with anti-inflammatory medications.

If these conditions are not met, treatment must be delayed by 1 week. If, after a 1-week delay, all toxicities have recovered within the limits described above, treatment with study drugs, can be resumed. Both study drugs should be delayed simultaneously if applicable. If the patient has not recovered after 1 week of delay, treatment may be delayed by 1 more week. However, initiation of the next cycle can only be delayed by a maximum of 4 weeks (28 days). Therefore, if persisting toxicity does not allow for the resumption of treatment, the patient will be permanently discontinued.

For all ≥ Grade 3 hematological or non-hematological AEs that are NOT study drug-related, after consultation with the Medical Monitor and at the discretion of the treating physician, study drug dosing may be continued.

Elevation of amylase and/or lipase without clinical and/or radiographic evidence of pancreatitis are not considered DLT, and the patient can resume treatment at any grade at the discretion of the treating physician in consultation with the PI.

Patients continuing on protocol after more than a 28 days delay in treatment can continue on a case by case basis after discussion with the Medical Monitor and at the discretion of the treating physician.

Each dose modification or treatment delay has to be documented in the eCRF, including the respective reason.

5.2.5.3 Dose Modifications

In the event that a DLT that is at least possibly related to one of the study drugs occurs, patients will halt treatment with study drugs until symptoms resolve to the grade outlined in Section 5.2.5.2, and then treatment can be restarted. After the first two cycles reduction in the frequency of dosing in study drug(s) may be required based on the worst toxicity experienced in the previous cycle.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

During the dose escalation arm for the combination of M6620 and avelumab, patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level or at a decreased frequency once recovery to ≤ Grade 1 or baseline is achieved. Patients enrolled in the expansion arms may resume dosing, once recovery to ≤ Grade 1 or baseline is achieved after experiencing recurrent and intolerable ≥ Grade 2. If a dose or frequency reduction is required due to the treatment related toxicity, this may be allowed as an alternative to discontinuation of treatment, upon agreement with the MDACC IND Office.

Once a patient has a dose reduction or reduction in the frequency in the dosing for a drug-related toxicity, the dose will not be re-escalated. Patient requiring more than two dose reductions will be withdrawn from treatment unless otherwise agreed between the investigator and the MDACC IND Office.

Adverse events (both non-serious and serious) associated with study drug(s) exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. The immunotherapy drug avelumab must be withheld for drug-related toxicities and severe or life threatening AEs as per Table 3. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. The dose modification guidelines are intended to be applied when the physician determines the events to be related to avelumab.

For subjects whose dose was withheld due to toxicity, subjects may resume immunotherapy study drug (avelumab) upon resolution of toxicity to Grade 0-1 or baseline.

Note: The general treatment recommendations outlined in Sections 5.2.5.1, 5.2.5.2, and 5.2.5.3 can be used **unless** more specific treatment guidelines are outlined in Sections 5.2.5.3.2.1 and 5.2.5.3.2.2 below.

5.2.5.3.1 Adverse Drug Reactions Requiring M6620 Treatment Discontinuation or Modifications

In the case of occurrence of an AE attributed to M6620, treatment may be interrupted and may resume when all toxicities have returned to Grade 2 or less, at the discretion of the Investigator. Except for participants in Part A during the DLT observation period, doses of M6620 may be reduced after occurrence of a related AE using the following guidelines, any exceptions to this dose modification criterion will need to be agreed between the PI and IND Office:

a. For Grade 4 hematologic toxicity: the dose of M6620 will be reduced by 25%.
b. For Grade 3 non-hematologic toxicity: M6620 will be discontinued.
c. For Grade 4 non-hematologic toxicity: M6620 will be discontinued.

Guidelines for dose modification for toxicity are provided below. The final dose reduction or delay for each participant may be determined by the Investigator. However, these guidelines provide the minimum dose reduction or delay criteria. Additionally, if a participant who is responding to treatment experiences toxicity even after 2 dose reductions, the participant may continue to receive treatment if in the judgment of the Investigator it is in the best interest of the participant. In this case the dose of M6620 will further be reduced by at least 25%.

In case of M6620 Grade 3 or higher toxicity (excluding fatigue or nausea/vomiting/diarrhea adequately managed by supportive care), treatment will be interrupted and may be resumed when all toxicities have returned to Grade 2 or lower, at the discretion of the Investigator.

For the following hematologic toxicities, once the toxicity has returned to Grade 2 or lower, dosing can be resumed with 1 dose level reduction. If, after 1 dose level reduction, any of the below drug-related hematologic toxicities are subsequently observed, then dosing may be resumed with 2 dose level reductions:

a. Grade 4 thrombocytopenia;
b. Febrile neutropenia (growth factor support, per site protocol, may be used in lieu of dose reduction) except during the DLT assessment period prior to occurrence of a DLT. Once a DLT has occurred, it is acceptable to use growth factor support even during the DLT period;
c. Grade 4 neutropenia lasting more than 7 days.

If any of the drug-related toxicity listed below is subsequently observed, the M6620 dose will be reduced by 1 dose level:

a. Grade 3 non-hematologic toxicity (except for fatigue or nausea, vomiting, or diarrhea adequately controlled by medication). For infusion reactions, hypersensitivity, or allergic reactions related or possibly related to M6620, see below for additional guidelines for management;
b. Any Grade 2 or lower non-hematologic toxicity requiring dose delay of more than 2 weeks.

For Grade 4 non-hematologic toxicity, treatment will be interrupted and may be resumed with 2 dose level reductions when toxicity has returned to Grade 2 or lower.

If any toxicity not described above results in a delay in dosing during any part of the study and the participant may be benefitting from therapy, then the doses of M6620 may be reduced by 1 dose level at the discretion of the Investigator.

5.2.5.3.2 Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications

Treatment with avelumab should be permanently discontinued, if any of the following ADRs occurs:
Any Grade 4 ADRs:

- Permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.

Any Grade 3 ADRs:

- Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate;
- Permanently discontinue avelumab if toxicity does not resolve to Grade ≤ 1 or Baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks is not permitted.
Infusion-related reactions and irAEs should be handled according to guidelines as outlined in table below.

5.2.5.3.2.1 Management of Infusion-Related Reactions

To mitigate infusion-related reactions associated with avelumab, participants have to be pre-medicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and the presence/severity of prior infusion reactions.

Management of symptoms should follow the guidelines shown in Table 2.

Table 2: Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab.

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated.	• Decrease the 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 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the participant. • Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

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

5.2.5.3.2.2 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE v5 grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines as shown in Table 3.

Table 3: Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate participant 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 to 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 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs

Grade of Rash	**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 Grade 2 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	**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	Reassess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Reassess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 × ULN and/or Total bilirubin > ULN to 1.5 × 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 × ULN and/or total bilirubin > 1.5 to ≤ 3 × 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 × ULN and/or total bilirubin > 3 × 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	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increase 1.5 × baseline or creatinine increased > ULN to 1.5 × 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 × baseline and ≤ 6 x ULN or creatinine increased > 1.5 and ≤ 6 × 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 × 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. [a] Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, restart 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.[a] 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).

[a] Local guidelines, or e.g., ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
https://professional.heart.org/professional/GuidelinesStatements/UCM_492626_Guidelines-Statements-Search-Page.jsp

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	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	(i.e., hypopituitarism/hypophysitis)	
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 thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone) • 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-	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	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.	
Other irAEs (not described above)		
Grade of other irAEs	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider restarting 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 Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
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	Permanently discontinue avelumab therapy Specialty consult	

Persistent Grade 2 or 3 irAE lasting 12 weeks or longer		

ADL=activities of daily living, AHA=American Heart Association, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BNP=B-type natriuretic peptide, CK-MB=creatine kinase MB, CT= computed tomography, ESC=European Society of Cardiology, 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.

5.2.5.4 Treatment beyond Progression

5.2.5.4.1 Treatment beyond Initial Progression

Participants will receive avelumab as outlined in the study design until PD. Avelumab may continue past the initial determination of PD according to RECIST v1.1, as long as the following criteria are met:

a. Treatment with avelumab is ongoing.
b. No new unacceptable treatment or disease-related toxicity.
c. Tolerance of study interventions.
d. Stable ECOG PS.
e. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

5.2.5.4.2 Treatment beyond Confirmed Progression

Participants who experience PD may continue treatment with study interventions if the Investigator believes the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

If the participant continues with treatment after confirmed PD, they should remain on the study and continue to receive monitoring according to the Study Calendar. Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule.

Treatment should be discontinued permanently upon documentation of further, unequivocal PD, unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met (See Section 6.5).

5.2.5.4.3 Continuation of Study Intervention after Local Treatment of Disease Progression

If PD is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions with respect to the criteria defined in Section 4.2, and provided that the above criteria are met in addition to the following:

a. Tumor assessment showing PD has been performed and was documented according to RECIST v1.1, prior to the procedure.
b. Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of study interventions.
c. There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
d. Participants must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
e. Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if PD is mainly due to a metastatic lesion, which in the opinion of the Investigator may be surgically removed, participants may continue study interventions after the local treatment of such a lesion provided that:

a. Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1, prior to the procedure.
b. It has been at least 2 weeks and the participant has fully recovered from the surgery.
c. Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

5.3 Drug Storage and Accountability

The investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. The storage conditions stated in the investigator brochure may be superseded by the label storage.

The storage conditions and temperatures will be recorded on the Investigational Pharmacy temperature logs.
The Investigator or an approved representative (e.g. pharmacist) will ensure that all investigational product is stored in a strictly controlled, secure area, at appropriate temperatures and in accordance with applicable regulatory requirements.

The Investigator or designated personnel must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product(s). Accountability Logs will be maintained by the Investigational Pharmacy. The forms must identify the investigational product,

including batch or code numbers, and account for its disposition on a patient by patient basis, including specific dates and quantities.

Destruction of investigational product will be performed per the MDACC policy.

5.3.1 M6620 Storage

Store intact vials protected from light inside cardboard boxes at room temperature, 25ºC (77ºF), with excursions allowed between 15 and 30ºC (59 and 86ºF).

Note: If a temperature excursion is identified, promptly return M6620 to between 15 and 30ºC and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to the CMO (Fisher) for determination of suitability.

Stability testing of the intact vials is on-going. Prepared solutions must be protected from light and used within 4 hours from time of preparation if stored at room temperature or 24 hours if stored refrigerated (2ºC-8ºC)

5.3.2 Avelumab Storage

Avelumab must be stored in the refrigerator at 2ºC – 8ºC (36ºF – 46ºF). Do not freeze. Protect from light. Do not shake vigorously.

Note: If a temperature excursion is identified, promptly return Avelumab to 2ºC – 8ºC (36ºF – 46ºF) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to the CMO (Fisher) for determination of suitability.

5.4 Concomitant Treatment

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant medications and treatments, including herbal supplements, supportive care drugs (e.g. antiemetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, blood products, and nondrug interventions (e.g. paracentesis) will be recorded from 28 days prior to the start of study treatment (i.e. the screening period) and up to 90 days after the last dose of investigational product (i.e. the Short Term Follow up Day 90 Visit). If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new treatment is started. All concomitant medications will be captured in the EMR, but not the EDC.

5.4.1 Other Anticancer or Experimental Drugs

No additional anticancer therapy will be permitted while patients are receiving one of the study drug combinations.

Additionally, the concurrent use of vitamins or herbal supplements should be considered with caution.

Palliative and supportive care for disease related symptoms may be administered at the Investigator's discretion.

5.4.2 Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines and as deemed necessary by the treating investigator.

5.4.3 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the DLT period – Cycle 1 (Please See Section 5.2.5.3.1), but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines (J Clin Oncol, 2006. 24(19):3187-3205).

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Erythropoietin or darbepoetin may be used at the investigator's discretion for the supportive treatment of anemia.

5.4.4 Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted at the investigator's discretion. The choice of the prophylactic drug, as well as the duration of treatment, is up to the investigator and assuming the drug is not included in Prohibited Concomitant Medications and Therapies (Section 5.4.11).

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

5.4.5 Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered, as needed, assuming the drug is not included in Prohibited Concomitant Medications and Treatments (Section 5.4.11).

5.4.6 Corticosteroids

Chronic, systemic corticosteroid use (more than 10 mg/day of prednisone equivalent) for palliative or supportive purpose is not permitted. Use of corticosteroids as symptomatic treatment may be allowed on an individual basis and upon discussion with the SMC. Steroids for replacement therapy (physiologic replacement) are allowed. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.4.7 Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and the study drug(s) required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping study drug(s) is recommended at least 14 days prior to surgery.

Postoperatively, the decision to reinitiate study drug(s) treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.4.8 Radiation Therapy

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions and other sites of disease if considered medically necessary by the treating physician, provided that the bony lesions and/or other sites of disease to be irradiated were present at the time of screening tumor assessments and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. All attempts should be made to rule out disease progression in the event of increased localized pain.

Study treatment should be suspended for at least 5 half-lives of M6620, prior to the start of palliative radiotherapy to exclude synergistic toxicities between DDR inhibitors and radiation therapy.

5.4.9 Bisphosphonates or Denosumab

Bisphosphonates or denosumab treatment is allowed and it will be given as per local practice. The need to initiate treatment with bisphosphonate or denosumab or to increase the dose of these therapies while on study treatment (for patients who started bisphosphonate or denosumab therapy > 2 weeks before study enrollment), may be considered as a symptom of disease progression that should be considered as a symptom of disease progression that should be confirmed radiologically.

5.4.10 Androgen Deprivation Therapy for Patients with CRPC

Patients with CRPC must receive androgen deprivation therapy with a GnRH agonist/antagonist or bilateral orchiectomy (medical or surgical castration).

5.4.11 Prohibited Concomitant Medications and Therapies

The following treatments must not be administered during the trial:

- Immunotherapy not specified in this protocol, and immunosuppressive drugs, i.e., chemotherapy or systemic corticosteroids except:
    a. When required for the treatment of immune-related adverse events or infusion-related reactions/hypersensitivity.
    b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent.
    c. Systemic corticosteroids for the management of patients with allergy to CT IV Radiographic Contrast Media.

- Administration of a live vaccine within 30 days prior to study treatment.

- Strong inhibitors or inducers of CYP3A4 (See Appendix F).

- Herbal remedies with immunostimulating properties (e.g., mistletoe extract), or known to potentially interfere with major organ function (e.g., hypericin).

Any additional concomitant therapy that becomes necessary during the trial and any changes to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication for each drug.

6. STUDY PROCEDURES

For screening, treatment period, and follow up procedures see the Study Calendar.

For the treatment period discussed below, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to, where possible, in order of the most important to the least important:

a. Clinical safety lab tests – obtain prior to study drug administration
b. Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to study drug administration.
c. ECGs – obtain within 30 minutes of study drug administration
d. Other procedures – all other procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection, unless sampling is determined by the study personnel to potentially impact the results.

During the COVID-19 pandemic, alternative methods for conducting study assessments should be considered when compliance, feasibility, and safety can be assured. These methods may include:

- Telemedicine visits, e.g., via telephone/video (using compliant video-conference tools as permitted by health authority regulations)
- Use of primary care centers and local laboratories for blood draws

If alternative methods are used, local laboratory reference ranges will be documented. Local laboratory test results, laboratory accreditation, and reports should be retrieved and documented in the participant's study records.

6.1 Screening Period

All screening activities must take place within 28 days prior to enrollment into the study, unless otherwise indicated.

The required screening assessments and laboratory tests are summarized in the Study Calendar and Section 7 (Assessments). Following completion of the screening assessments and confirmation of eligibility, patients may initiate study treatment.

6.2 Study Treatment Period

Treatment will continue until progression of disease (PD) or unacceptable toxicity, withdrawal of consent by the patient, or non-compliance by the patient with protocol requirements. Safety assessments will be performed as illustrated in the Study Calendar.

Per the physician's discretion, a patient may continue treatment even if there is progression of disease as long as the patient remains clinically stable and/or pseudoprogression is assumed (in the case of combinations involving avelumab).

Clinical and radiological examinations for disease status are performed per the study calendar.

If a patient discontinues treatment due to any other reason than disease progression/death/ withdrawal of informed consent, the disease evaluations shall continue until disease progression. This includes patients who wish to discontinue treatment, but agree that further data is captured for the purpose of the study (partial withdrawal).

6.3 End of Treatment Visit

Patients that discontinue from treatment will undergo an end of treatment (EOT) visit, regardless of the reason of discontinuation, per the study calendar.

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess adverse events and concomitant medications and treatment is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the patient is acceptable.

6.4 Follow up Phase

Patients who discontinue treatment for reasons other than progression of disease (and withdrawal of consent for participation in the trial) will continue to visit the clinic for evaluation of their disease by CT/MRI scan approximately every 12 weeks until progression of disease is determined or patient receives additional anti-neoplastic medication.

Of note, a patient may decide to discontinue study treatment. This is not the same as full withdrawal of consent to participate in the trial and these patients should be encouraged to continue to be followed up as for other patients until progression of disease. If a patient chooses to have no further interaction regarding the study (fully withdrawal of consent), the investigator must provide written documentation of the patient's decision to fully withdraw from the study.

Investigators will collect survival data for patients after progression of disease unless patient fully withdrew consent to participate in the study. Approximately one year after last dose of treatment, a chart review, patient visit, or telephone call will be conducted. The telephone call will be less than five minutes to obtain information regarding survival status.

6.5 Patient Withdrawal

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/ removed if necessary in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Patients who are withdrawn from the study outside of the DLT period will not be replaced.

Patients will be removed from further treatment for the following reasons:

a. Confirmed evidence of true disease progression (See Section 5.2.5.4)
b. Non-compliance
c. Need for treatment with medications not allowed by the study protocol (unless the medication is temporary and continuation of study treatment following cessation of that medication is reasonable at the discretion of the Investigator and Study Monitor)
d. Patient no longer consents to participate in the study
e. Intercurrent illness that interferes with study assessments
f. Incidence or severity of AEs in this study indicates a potential health hazard to the patient
g. Investigator's discretion
h. Pregnancy
i. Termination of the study

Reasons for withdrawal from study follow up may include:

a. Completed study follow up
b. Study terminated by Sponsor
c. Lost to follow up
d. Refusal of further follow up for survival
e. Death

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT and the follow-up visits should be performed, if possible. The reason for discontinuation has

to be documented in the eCRF in all cases. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form.

If a patient withdraws consent for further study treatment, the patient should still be followed for progression and survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described.
All procedures should be followed within the allowed flexibility windows as outlined in the Study Calendar.

7.1 Safety Assessments

7.1.1 Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product - 1 negative pregnancy test during screening period (within 28 days of first dose of study drugs), and 1 at the baseline visit immediately before administration of investigational product.

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient receives the investigational products. Pregnancy tests will also be routinely repeated on Day 1 of every cycle (prior to dosing of study drugs) during the active treatment period, at the end of study therapy, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test and confirmed pregnancy, the patient will be withdrawn from administration of investigational products and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by the Institutional Review Board (IRB) or if required by local regulations.

7.1.2 Contraception Check

Male patients who are able to father children and female patients who are of childbearing potential, who are, in the opinion of the investigator, sexually active and at risk of pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of 2 highly effective (<97% failure rate) methods of contraception.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception;
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment and thus are not considered to be of child-bearing potential. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment;
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject;
- Combination of any of the following two (a+b or a+c or b+c):
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception;
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.

    In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

    Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

The investigator or his/her designee will discuss with the patient the need to use 2 contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

7.1.3 Adverse Events

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signed information consent and study entry. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Assessment of AEs will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0) timing, seriousness, and relatedness.

AEs that occur during the study, including baseline signs and symptoms, will be recorded in MOCLIA. The active reporting period begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

7.1.4 Laboratory Safety Assessments

The required safety laboratory tests are listed in Table 4 below. Required safety laboratory tests including at minimum: hematology (hemoglobin, platelets, and white blood cells), and chemistry (ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose) must be reviewed prior to study drug administration per the study calendar.

Table 4: Required Safety Laboratory Tests

Hematology	**Chemistry**	**Coagulation**	**Urinalysis (Dipstick is acceptable)**	**Pregnancy Test**
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive (≥ 2+), collect 24hr urine or collect spot urine and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine with a sensitivity of ≥ 25 mIU/mL
Platelets	AST	PTT		
WBC	Alkaline Phosphatase			
Absolute Neutrophils	Sodium		Urine dipstick for urine blood: If positive and clinically indicated collect a microscopic (Reflex Testing)	
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium			
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Total Bilirubin Direct Bilirubin Indirect Bilirubin			
Thyroid Function Tests:	Blood urea nitrogen (BUN) or Urea			
TSH, Free T4	Creatinine			
Total T3	Uric Acid			

	Glucose (non-fasted)			
Other Tests:	Albumin			
ACTH	Phosphorus or Phosphate			
HBV surface antigen	Total Protein			
Anti-HCV antibody	Amylase			
If Anti-HCV antibody test positive, then HCV RNA	Gamma Glutamyl Transferase (GGT)			
Testosterone (at screening only for CRPC patients)	Creatine Kinase			
	C-reactive Protein (CRP)			
	LDH			
	Lipase			

7.1.5 Physical Examinations and Vital Signs

Patients will have a physical examination (PE) per the study calendar, and will include the measurement of body weight, vital signs and assessment of ECOG performance status. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF. At screening only, height will be obtained from the electronic medical record.

Abbreviated PEs should be performed as appropriate at each visit where complete physical exams are not required, with special attention to skin and mucosa, and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.

For treatment involving M6620, a patient's body weight will be measured per study calendar at Day 1 of each dosing cycle, and it will be used to calculate the patient's dose of M6620 for that cycle.

Vital signs will include measurements of blood pressure, pulse rate and temperature (oral, tympanic, temporal or axillary). On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) of first study drug (if more than one study drug is given) and 1 hour after the start of the infusion of last study drug (if more than one study drug is given). The blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices for measuring BP and pulse rate is acceptable.

7.1.6 (12-Lead) Electrocardiograms

A standard 12-lead (with a 10 second rhythm strip) tracing will be used for all electrocardiogram (ECG) assessments.

All patients require a single ECG measurement at baseline and C2D1. Thereafter, on treatment ECGs will be performed as clinically indicated.

Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc > 500 msec, a subsequent ECG should be repeated to verify the result. If ECG is confirmed > 500 msec, local guidelines (e.g. Repeat ECGs, review by cardiologist) should be followed.

7.2 Pharmacokinetic Assessments

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. For samples where nominal time coincides with end of infusion, a sample collected within 10 minutes post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g., CRF). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and sponsor. PK sampling schedule may be modified based on emerging PK data. Details on processes for collection, processing, handling, storage and shipment of these samples will be provided in the Laboratory Manual.

PK samples would be stored in Institutional Tissue Bank (ITB) for ~1.5-2 years, while the clinical data mature and await sample analyses.

7.2.1 Blood for PK Analysis of Avelumab

Blood samples (3.5 ml whole blood at each time point) will be collected for serum PK analysis of avelumab as outlined in the Study Calendar. Pre-dose avelumab PK samples will be collected within 1 hour prior to avelumab infusion. The post-dose avelumab samples should be taken within 10 minutes after the avelumab infusion ends. PK sampling for avelumab will occur as follows: (i) Pre dose and EOI: Cycle 1 Day 1 and cycle 1 Day 15, (ii) Pre dose only: Cycle 3, 6 and (iii) End of treatment sample.

Storage & Processing for PK evaluation:

1. Do not draw blood for serum as the first tube. When using a winged blood collection, a **2mL Red tube (optional discard tube)** should be used prior to the first specimen collection. The discard tube is used to fill the blood collection set tubing's "dead space" with blood. The discard tube does not need to be filled completely and should be a non-additive or coagulation tube, thus SST cannot be used as discard tube. This step ensures maintenance of the proper blood-additive-ratio of the specimen.
2. Collect **3.5 mL** of blood in a SST tube with Silica Clot Activator and Polymer Gel.
3. Gently invert the tube 5 times to mix the clot activator with blood.
4. Allow blood to clot for 30 minutes at room temperature in a vertical position.
5. After allowing clot to form, centrifuge the tube for 15 minutes at 1100-1300 x g at +25 degrees Celsius (if refrigerated centrifuge is available, set the temperature at 25 degrees Celsius in

order to prevent heating during centrifugation and to optimize flow of the barrier material; flow may be impeded if chilled before or during centrifugation).
6. Carefully collect and aliquot the serum equally in **2** separate micronics tubes.
7. Put the tubes immediately in the freezer in an upright position at -80 degrees Celsius. If not available, store at –20 degrees Celsius (for a maximum of one month). **In case of temperature deviations, the affected samples, the length of deviation and maximum temperature reached should be tracked and promptly communicated to the CRA/CTL.**

If shipment is required: Ship the samples to the Central Lab in batches in dry ice. Material stored at –20 degrees Celsius must be shipped within a maximum of 1 month from blood draw to central laboratory

8. Do not draw blood for serum as the first tube. When using a winged blood collection, a **2mL Red tube (optional discard tube)** should be used prior to the first specimen collection. The discard tube is used to fill the blood collection set tubing's "dead space" with blood. The discard tube does not need to be filled completely and should be a non-additive or coagulation tube, thus SST cannot be used as discard tube. This step ensures maintenance of the proper blood-additive-ratio of the specimen.
9. Collect **5 mL** of blood in a SST tube with Silica Clot Activator and Polymer Gel.
10. Gently invert the tube 5 times to mix the clot activator with blood.
11. Allow blood to clot for 30 minutes at room temperature in a vertical position.
12. After allowing clot to form, centrifuge the tube for 15 minutes at 1100-1300 x g at +25 degrees Celsius (if refrigerated centrifuge is available, set the temperature at 25 degrees Celsius in order to prevent heating during centrifugation and to optimize flow of the barrier material; flow may be impeded if chilled before or during centrifugation).
13. Carefully collect and aliquot the serum equally in **3** separate micronics tubes.
14. Put the tubes immediately in the freezer in an upright position at -80 degrees Celsius. If not available, store at –20 degrees Celsius (for a maximum of one month). **In case of temperature deviations, the affected samples, the length of deviation and maximum temperature reached should be tracked and promptly communicated to the CRA/CTL.**

Ship the samples in batches in dry ice. Material stored at –20 degrees Celsius must be shipped within a maximum of 1 month from blood draw to central laboratory

7.2.2 Blood for PK Analysis of M6620

Blood samples (2 ml whole blood at each time point) will be collected for plasma PK analysis of M6620, as outlined in the Study Calendar. Pre-dose M6620 PK samples will be collected within 1 hour prior to M6620 infusion. The end-of-infusion M6620 PK samples should be taken within 10 minutes after the M6620 infusion ends and the sample taken during days 2-4 may be taken at any time within this visit window

PK sampling for M6620 will occur as follows: I) M6620 predose and EOI: cycle 1 day 1 and day 15; II) cycle 1 day 2-4 (one sample during this timeframe) and cycle 1 day 16-18 (one sample during this timeframe) to capture a sample during the terminal phase of M6620.

Storage & Processing for PK evaluation:
Blood sample: **The total duration between blood sample collection at room temperature and final storage of the plasma sample must not exceed 60 minutes**

- The blood samples have to be collected into 2 mL K2 EDTA tubes
- Store blood samples until centrifugation at ambient temperature

- Centrifuge blood samples at approx. 1500 g for approx. 15 minutes at room temperature
- After centrifugation, split the plasma into 2 aliquots and transfer plasma into 2 labeled polypropylene tubes (PK M6620 primary and back-up sample) and lock them with push caps. The primary sample tube must contain at least 0.4 mL plasma, the other back-up sample tube the rest of the plasma.
- Freeze the 2 plasma aliquots (tubes) immediately after centrifugation and aliquotation at - 20°C±5°C and store in upright position

Plasma sample: Store samples in an upright position until shipment at –20°C±5°C in a temperature controlled freezer
Analyte stability in matrix: Stability in matrix at room temperature: 1 day
Long term frozen stability in matrix at -20ºC and -75°C: 3 months (Stability for 6 and 12 months will be analyzed at a later timepoint) Freeze/thaw cycles: -20ºC and -75°C: four times.

7.3 Tumor Response Assessments

The tumor assessment for inclusion must be recorded and measured within 28 days prior to treatment start. Clinical benefit rate will be evaluated based on RECIST v 1.1 and irRECIST using CT scan or MRI scan or PET-CT scan. For patients with multiple measurable lesions, up to 5 lesions in total and 2 lesions per organ should be identified.

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Baseline Brain CT or MRI scan is required for all high risk patients (such as breast, melanoma and other cancer types as determined by the PI/sub I) at baseline (screening). Patients with stable brain metastases present at baseline (screening) will continue to have brain CT or MRI scans performed at each tumor assessment. Otherwise, brain CT or MRI scan is required only when clinically indicated if new brain metastases are suspected.

Whole body bone scintigraphy (bone scans) should be performed at screening and at regular imaging intervals as defined in the study calendar for all patients with prostate cancer. If clinically indicated per investigators' discretion, participants with other tumor types may undergo bone scan at baseline to assess the presence of bone lesions. If bone metastases are present at baseline (screening), then repeat bone imaging is required at regular intervals with other imaging as defined in the study calendar thereafter. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of CR for patients who have bone metastases.

The exact technique used for measurement of lesions (i.e., CT, MRI, or PET/CT scan) will be left to the discretion of the investigator, however, for each patient the same technique must be used throughout the study, assessed whenever possible by the same individual. The CT/ MRI abdomen must include the pelvis. A PET/CT is allowed, but ultrasound and x-ray of thorax is not allowed.

In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled tumor assessment should be performed. In case a detected increase in tumor size is below the resolution limit of the CT/ MRI scanner, it is acceptable to continue with treatment until a second assessment at a later time point unequivocally confirms progressive disease. Partial response requires confirmation with a follow-up scan at least 4 weeks apart.

If the increase in tumor burden is ≥ 20% relative to nadir, then in the absence of rapid clinical deterioration, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented is recommended. Patients will continue with study drug until confirmation scan is obtained.

The following are defined as non-target lesions: bone lesions, leptomeningeal disease, pleural/pericardial effusion, ascites, inflammatory breast disease, lymphangitis, cystic lesions and lesions not measurable by CT or MRI. All non-target lesions are described over time and need not be measured.

The first evaluation of disease status by imaging will be done after 2 cycles or 8 weeks (± 7 days) of treatment and every 2 cycles or 8 weeks (± 7 days) thereafter at the physician's discretion. After completion of 1 year of treatment, tumor assessments will be performed every 3 cycles or 12 weeks (± 7 days) independent of cycle delays.

Patients will also be eligible for the study if their disease is evaluable outside irradiated field on CT/ MRI.

In case palliative radiation becomes necessary during the treatment within the study, there must be at least two target lesions left outside the irradiated filed for continuous assessment for response.

7.4 Tumor Biopsies and Blood Samples

Archival tumor tissue samples, tissue from biopsies performed at baseline, while on treatment, and at disease progression, will be used to analyze candidate DNA, RNA, or protein markers, or immune changes, which may contribute to the response or resistance to the combinations being tested in this study. Archival tissue available from a biopsy or surgery that was performed within 1 year prior to study enrollment, will be acceptable. While not mandatory, tumor biopsies will be strongly encouraged. Patients may have pre-treatment (baseline), and on-treatment (Cycle 1 Day 15) tumor biopsies for correlative studies. In the event that clinical benefit is not observed or is transient, an understanding of the mechanisms of resistance may help guide optimal patient selection for future development of the combination. Therefore, an optional tumor biopsy will also be performed at disease progression, unless clinically contraindicated. Target lesions may be used for tumor biopsies as long as there are other target lesions that are accessible for RECIST measurement.

Given the limited ability to assess tumor tissue-based biomarkers longitudinally, a number of biomarkers will also be measured in peripheral blood at a number of time points. Blood samples will be obtained at baseline, Cycle 1 Day 15, Cycle 3 Day 1, every other cycle thereafter, and at disease progression.

7.5 Correlative Studies

To allow for the correlative studies detailed below to be performed, a subset of patients will undergo pre-treatment, on-treatment, and where feasible at-progression tumor biopsies. Serial blood sampling will also be undertaken to longitudinally assess pharmacodynamic and/or

mechanistic biomarkers for the combination of M6620 and avelumab. Correlative studies to be undertaken are outlined below.

7.5.1 To determine baseline molecular markers (DNA, RNA, and protein) or other markers (e.g. HRD or RSRD score, somatic mutation burden, immune profiling) that may predict clinical benefit.

We will undertake DNA whole exome sequencing (WES), RNA sequencing (RNA-seq), and reverse phase protein array (RPPA) studies, as well as immune profiling on tumor biopsies obtained from patients at baseline to assess if baseline markers are correlated with clinical benefit. We will use ROC curve analysis with Wilcoxon rank sum testing. With 30 patients, if the clinical benefit rate is 33%, and we assume a 10% alpha level, then we have 90% power to detect a ROC area of 0.83 as different from the null value of 0.5.

7.5.1.1 Genomic Sequencing Plan

Whole exome sequencing will be performed to an average depth of 100x. Normal samples (blood will be collected when possible) will be sequenced to a similar depth to distinguish germline and somatic aberrations. All samples will be assessed using a Nimblegen pull down SeqCap EZ human Exome Library and sequenced with four samples per lane on the Illumina HiSeq 2000 in our CCSG sequencing core. This approach provides an average 100-fold depth across the human exome. All computational analysis will use shared resources within the Research Information Systems and Technology Services (RISTS) at MDACC. RISTS provides a high performance computing environment that consists of an 8064 processor computer cluster (336 nodes) with 794 TB data storage capacity for CPU-intensive large-scale computing. Similar to our previous studies and participation by Ken Chen in the TCGA analysis platform at the WashU Genome Center, sequence analysis will consist of 4 major steps: 1) read alignment, 2) variant calling, 3) variant stratification, and 4) report (Figure 5). We will align reads in the FASTQ format to several different versions of reference sequences using BWA. We will use Samtools, VarScan and MuTect to call somatic SNVs and indels and GATK to detect germline SNVs and indels. We will use Pyclone and ABSOLUTE to estimate tumor purity and clonal architecture. We will perform variant annotation using the variant effect predictor (VEP), AnnoVar, InterVar, CanDrA, CHASM, MutationAssessor, SIFT and PolyPhen and OncoKB. The Institute for Personalized Cancer Therapy (IPCT) precision oncology decision support (PODS) team will further review these annotations and identify additional preclinical evidences in the literature.

7.5.1.2 Homologous Recombination Deficiency (HRD) Score

We will focus on HRD scores that we have previously defined[22-24]. An HRD score was defined as an unweighted summation of the 1) loss of heterozygosity (LOH) scores, defined as the number of LOH regions >15 Mb, but less than a whole chromosome in length, within a tumor genome, 2) telomeric allelic imbalance (TAI) score, defined as the number of allelic imbalances (DNA segments having unequal maternal and paternal copies) extending to the telomeric end of the chromosome and 3) large-scale state transition (LST) score, defined as the number of chromosomal breaks between adjacent regions of at least 10 Mb. The accuracy of these scores is critically dependent on accurate estimation of allele specific copy numbers (ASCNs). We will use ASCAT, FACET, Sequenza and TITAN to perform ASCN analysis from heterogeneous tumor samples and calculate HRD scores.

7.5.1.3 Replication Stress Response (RSR) Defect Score

Using isogenic cell line models, we recently developed a gene expression signature to predict defects in replication stress response (RSR)[24]. We functionally validated this gene signature in a panel of 16 breast cancer cell lines, with 8 of 9 signature high cell lines exhibiting defects in RSR (Figure 2A). As the ATR/CHK1 signaling cascade plays a critical role in replication stress response, we hypothesized that high RSR defect scores would correspond to increased sensitivity to inhibitors of this pathway, which was validated by the strong negative correlation with IC50 values for the CHK1 inhibitor AZD7762 (Figure 2B). Emerging evidence also suggests that PARP is activated at stalled replication forks during replication stress and this function may largely contribute to PARP sensitivity. Upon analyzing the correlation between RSR defect score and olaparib sensitivity, we found that they were likewise negatively correlated (Figure 2C).

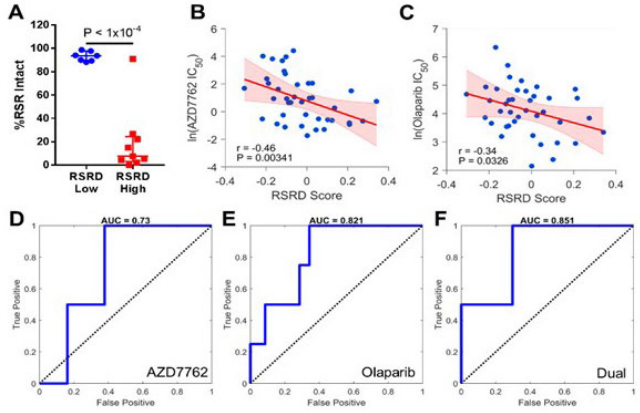


Figure 2. Replication stress response defect (RSRD) gene signature. (A) Breast cancer cell line gene expression data from the Cancer Cell Line Encyclopedia was used to determine RSRD signature score and bifurcate cell lines into "RSRD low" and "RSRD high" groups by maximization of the F-statistic between groups. The ability of cells to respond to replication stress was assessed by ability to recover from hydroxyurea-induced stalled replication forks, and is reported as percentage of replication stress response (RSR) intact cells. (B-C) RSRD gene signature score negatively correlates with IC50 values from the GDSC/COSMIC database for CHK1 inhibitor AZD7762 (B) and PARP inhibitor olaparib (C). (D-F) Receiver operating characteristic curve plots for the ability of the RSRD gene signature to predict drug response in colorectal cancer cell lines (n = 39) for AZD7762 (D), Olaparib (E), and dual sensitivity (F). Drug responders were defined as one standard deviation below the mean of the log-transformed IC50 values for single drugs and for dual sensitivity as an average of 0.75 standard deviations below the average for both drugs.

To investigate if these findings are conserved in colorectal cancer cell lines, we tested the ability of our RSR defect signature to predict response to CHK1 inhibition (AZD7762, Figure 2D), PARP inhibition (olaparib, Figure 2E), and dual inhibition of CHK1 and PARP (Figure 2F). We found that while the gene signature independently predicted activity of either CHK1 or PARP inhibition alone, the signature was best at predicting dual drug sensitivity. Based on this, we hypothesize that this RSR defect gene signature may be predictive of response to DDR inhibitor-based combinations. To test this, RNA-sequencing data obtained from the analysis of pre-treatment tumor biopsies will be analyzed and used to assess the predictive power of the RSR defect signature with respect to the clinical benefit of each DDR inhibitor-based combination treatment. These preliminary results may be used as the basis to refine the signature for adaptation to large-scale clinical translation.

7.5.1.4 RNA-seq Analysis

We maintain a RNA Seq data analysis workflow that makes use of the high performance computing facilities, including several cluster systems at the MD Anderson Cancer Center to analyze next generation sequencing data from RNA extracted from human or animal tissues. Fresh frozen or FFPE samples are prepared by the IPCT genomics lab and sequenced by the Sequencing Core Facility. The workflow makes use of proven software and best practices to analyze single or paired-end data. The workflow completes in 2 to 5 days depending on size of data and status of clusters. Results from this workflow are deposited to a centralized location and are used for second-stage analysis to answer specific questions.

7.5.1.5 Reverse Phase Protein Array (RPPA)

We will perform an RPPA-based proteomic analysis using 181 high-quality antibodies that target total (n=128), cleaved (n=1), acetylated (n=1) and phosphorylated forms (n=51) of proteins in patient samples. The function space covered by the antibodies used in the RPPA analysis

encompasses major functional and signaling pathways of relevance to human cancer. We will merge different batches of RPPA data using an algorithm, called Replicates Based Normalization (RBN), which mitigates batch effects facilitating creation of a single protein dataset merging samples across different batches. We will use a two-way unsupervised hierarchical clustering analysis to discover the groups of biological objects sharing common characteristics, and a two-dimensional heat map to visualize protein expression patterns. To detect the discriminating biomarkers for each cluster (obtained by hierarchical clustering using the RPPA data normalized by RBN), LIMMA will be used to select biomarkers by comparing samples in each cluster with samples in all the other clusters together. In addition, we will compute pathway activity scores using a series of pathway predictors developed based on member proteins selected by literature review.

7.5.1.6 Immuno-profiling

We will assess the immunomodulatory effects of the study drugs using the assays described. These assays will be undertaken in collaboration with [redacted]

7.5.1.6.1 Immunohistochemistry (IHC)

Histology sections obtained from FFPE tumor samples will be utilized for IHC. IHC will be performed using autostainers. All antibodies to be used have been optimized for IHC by examination of positive and negative controls and testing of the antibodies in standard assays including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software using Aperio Image Toolbox™ (Leica Biosystems). Five random 1-mm square areas within the tumor region will be selected for analysis. The expression of markers of interest in malignant cells will be evaluated using the Aperio™ digital H-score system, which includes the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300. Quantification of markers expressed in immune cells will be expressed by cell density (number of cells per mm^2). In the event that image analysis quantification of expression in malignant cells cannot be performed, microscopic analysis will be performed by a trained pathologist using H-score as follows: intensity is classified as 0 (absent), 1 (weak, apparent only on 100X magnification), 2 (moderate, apparent on 50X magnification), and 3 (strong, apparent on 16X magnification). This scoring system provides criteria that can be reproduced more consistently by pathologists. The data and digital images will be deposited into a central database for review by pathologists.

7.5.1.6.2 Multiplex Immunofluorescence (mIF)

Assessments by mIF may include, but are not limited to, assessment of infiltrating immune cell number and phenotype, relative expression of genes representative of immune activation versus suppression. For mIF analysis, we will use Opal chemistry and multispectral microscopy Vectra™ 3.0 and Polaris™ (Perkin-Elmer) which includes the Nuance software. Image analysis will be performed using the inForm software. A variety of immune markers will be assessed across two panels including: CD68, PD-1, CD3, CD8, PD-L1, FOXP3, Granzyme B, CD45RO, pan-cytokeratin and DAPI. Additional markers may be selected based on the results of gene expression analysis and may include other immunotherapy targets (e.g. OX-40, Vista, GITR, TIM-3, LAG-3, ICOS).

7.5.1.6.3 Flow Cytometry Analysis

High order flow cytometry panels will be designed to assess lymphocyte subsets and phenotype in peripheral blood. Flow cytometry panels will focus on effector and regulatory T cells by analyzing the expression of markers such as: CD3, CD4, CD8, ICOS, Ki67, CD25, FOXP3, Perforin, IFN-γ, TIM3, Granzyme B, and PD-1.

7.5.1.6.4 Cytokine Analysis (MSD)

The Meso Scale Discovery (MSD) platform will be used for the detection of soluble factors (e.g. from serum or plasma). This technology allows for the detection of up to 40 analytes per well and uses a very low sample volume. This method has a sensitivity of up to 1000X higher than traditional ELISA assays with a large linear range of 3-4 logs. The instrument performs immunoassays utilizing electrochemiluminescense to detect the signal in a 96 well plate format. This technology can be utilized for either single agent detection or in multiplex format. A wide menu of validated single or multiplex kits for the detection of 1 to 40 analytes are available from the manufacturer and can be customized. Cytokines available for testing include: IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, and TNF-α.

7.5.1.6.5 HTG EdgeSeq Immuno-Oncology Panel Analysis (IOP)

HTG has developed a novel technology known as quantitative nuclease protection assay (qNPA™), or HTG Edge Chemistry that enables extraction and amplification-free quantification of mRNA or miRNA. This process does not require RNA extraction from FFPE, and is amenable to small clinical specimens, as it requires very little sample input (~ 1-2 mm^2 FFPE tissue or 1.56 ng RNA). We will obtain the gene expression profile of 549 genes implicated in the host immune response to tumors, allowing us to profile tumor infiltrating lymphocytes, immune response in tumors, and potential prognostic drug signatures.

7.5.1.6.6 HTG EdgeSeq Oncology Biomarker Panel Analysis (OBP)

HTG has developed a novel technology known as quantitative nuclease protection assay (qNPA™), or HTG Edge Chemistry that enables extraction and amplification-free quantification of mRNA or miRNA. This process does not require RNA extraction from FFPE, and is amenable to small clinical specimens, as it requires very little sample input (~ 1-2 mm^2 FFPE tissue or 1.56 ng RNA). We will obtain the gene expression profile of 2568 oncology-related biomarkers (distributed across 24 pathways) from FFPE tumor samples by using next generation sequencing detection technology. Profiling tumor tissues will allow us to identify new biomarkers and analyze tumor cell signaling pathways. The demonstrated performance of the assay in breast, lung, colon, and prostate cancers, and melanoma FFPE samples enables multiplex oncology biomarker profiling of these and other malignant neoplasms with a simple workflow using next generation sequencing detection technology (no RNA extraction, rapid sequencing library preparation). Please see Table 6 below.

Table 6: HTG EdgeSeq Oncology Biomarker Panel Pathways

AMPK Pathway	Angiogenesis	FGFR Pathway
Cell Cycle	Cluster of Differentiation	JAK/STAT Pathway

EGF/PDGF Pathway	EGFR/HER Pathway	PI3K/AKT Pathway
Hypoxia	Stress Toxicity	Cardio Toxicity
NF-KB Pathway	Apoptosis	DNA Repair
Stem Cells	DMPK	Hedgehog Pathway
MAPK Pathway	Wnt Pathway	

7.5.2 To evaluate underlying mechanisms of action of the combinations by assessing pharmacodynamic (PD) biomarkers in serial tumor and blood samples.

We will use RNA-seq, RPPA and other assays as well as immune profiling to assess changes in PD biomarkers with treatment. Immuno-profiling will include multiplex immunofluorescence (mIF) and immunohistochemistry (IHC) to characterize immune cell infiltrates and immune checkpoint proteins (e.g. PD-1, PD-L1) on serial tumor samples. Flow cytometry analysis will also be conducted on serial blood samples to analyze circulating T cell populations. Cytokine analysis will also be performed on blood specimens. We will compare post-baseline values to baseline values using t-tests or Wilcoxon signed rank test if the data are clearly not Gaussian. With 30 patients, we will have 90% power to detect a mean difference of 0.55*s (where “s” is the standard deviation of the paired differences) assuming a two-sided 10% alpha. Dot plots of marker values over time will be produced to visualize changes.

7.5.3 To assess response and resistance in circulating tumor DNA (ctDNA), and concordance of genomic alterations between serial tumor biopsies and ctDNA.

We will undertake targeted NGS studies using serially collected ctDNA samples (at baseline, different timepoints on treatment, and at progression), and plot levels of target DNA anomalies over time in patients and correlate these with levels of tumor burden over time. In particular, we will assess ctDNA levels in responding patients and identify new resistance mechanisms in samples from progressing patients. NGS will also be used to assess ctDNA changes on treatment, and also to assess the correlation between serially collected biopsies and ctDNA samples.

7.5.4 To evaluate potential mechanisms of drug resistance through profiling of tumor progression biopsies.

By comparing molecular profiles of tumors collected at disease progression with baseline profiles through the use of WES, RNA-seq, and RPPA studies as well as immune profiling, we will attempt to identify new DNA anomalies, as well as changes in gene and protein expression levels.

7.5.5 To develop response biomarkers for the assessment of ATR and PD-L1 inhibition.

We will attempt to identify signatures of response and resistance by comparing biomarker profiles of tumor biopsies collected on-treatment to baseline profiles, and correlating these with tumor response.

7.5.6 To develop and characterize patient-derived xenografts (PDXs) to determine mechanisms of antitumor response and resistance.

Patient-derived xenografts will be established in mice using tumor biopsies obtained from patients at baseline and at time of drug resistance. Molecular profiling will be undertaken with whole exome

sequencing, RNA-seq and RPPA studies to assess mechanisms of antitumor response and resistance. By comparing profiles in PDX tumors from responding and progressing patients, we will attempt to identify signatures of response and progression.

8. ADVERSE EVENT REPORTING

8.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the Safety Project Manager (MDACC IND Office). For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the MDACC IND Office concurs with that assessment.

As part of ongoing safety reviews conducted by the MDACC IND Office, any non-serious AE that is determined by the MDACC IND Office to be serious will be reported by the MDACC IRB as an SAE per MDACC institutional policy. To assist in the determination of case severity, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

The active reporting period begins from the time that the patient provides informed consent through 90 calendar days after the last administration of the investigational product(s) unless other anti-cancer therapy is commenced, at which time toxicity follow up will cease at the discretion of the treating physician .

8.2 Definition of Adverse Event

An adverse event is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) as ‘any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment,’ (ICH E6:1.2).

An adverse event cab therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

8.3 Definition of Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered ‘serious’ if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

a. Death.
b. A life threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, may have caused death.
c. Inpatient hospitalization or prolongation of existing hospitalization.
d. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
e. A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the PI or the IND Sponsor (IND Office).
- All events occurring during the conduct of a protocol and meeting the definition of an SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in 'The University of Texas MD Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices.' Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life threatening or fatal events, that are unexpected, and related to the study drug(s), must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90 day time period, which are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

SAEs in screening will only be captured if they are related to a protocol procedure. Hospitalizations clearly documented as disease progression will not be captured as SAEs unless the patient continues on study.

8.4 Reporting to the Federal Drug Administration (FDA)

Serious adverse events will be forwarded to the FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the Sponsor's guidelines, and the IRB policy.

8.5 Investigator Communications with EMD Serono

For SAEs, the active reporting period to EMD Serono or its designated representative begins from the time that the patient provides informed consent through 90 calendar days after the last administration of the investigational product. SAEs occurring in a patient after the active reporting period has ended, should be reported to EMD Serono if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product(s) are to be reported to EMD Serono.

AEs (serious and non-serious) should be reported on the case report form (CRF) from the time the patient has taken at least one dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

The investigator's primary responsibilities in safety reporting are to identify and follow up on SAEs experienced by participants in the study, and to forward the information to the IRB, IND Office, and EMD Serono, as required by local regulations (for regulatory reporting) and Investigator-Initiated Research (IIR) agreement (for reporting to EMD Serono).

The following reportable events must be submitted to EMD Serono within 24 hours (or immediately for death or life threatening events) using the MDACC SAE form with the EMD Serono Reportable Events Fax Cover Sheet with each SAE submission:

a. SAEs,
b. Exposure during pregnancy or breastfeeding (even if not associated with an AE),
c. Occupational exposure (even if not associated with an AE),
d. Potential drug-induced liver injury (Hy's Law cases): these events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to EMD Serono:

[redacted]
OR
Email: [redacted]

Specifying:

- PROTOCOL NUMBER and/or Title
- EMD Serono assigned Study Number
- SUBJECT Number
- SITE Number/PI Name

The MDACC SAE form will be submitted to EMD Serono. The following details must be recorded for each SAE in the SAE report form:

a. A description of the AE in medical terms according to NCI CTCAE v5.0, not as reported by the subject,
b. The severity grade as assessed by the investigator according to the definitions in NCI CTCAE v5.0,
c. The date of becoming serious and the date of becoming known (if different),
d. The reason for seriousness,
e. The outcome of the SAE at the time of the report,
f. Information on administration of the study drug(s),
g. Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history.

If in any one subject the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time. The investigator is required to submit SAE Follow up reports until the SAE has resolved or stabilized, and all queries have been answered.

8.6 Recording of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the study participants, are properly recorded in the participant's medical records and the electronic case report form.

The following adverse event attributes must be assigned by the investigator:

a. Adverse event term according to NCI CTCAE v5.0
b. Severity grade according to NCI CTCAE v5.0
c. Start date and stop date (or date of last assessment)
d. Outcome
e. Causality to study drug(s) (assessed as either related or unrelated)
f. Any action taken.

Adverse events will be followed until they resolve to baseline or are considered stable. It will be left to the investigator's clinical judgement to determine whether an AE is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms resolve or the condition becomes stable.
Pre-existing diseases, when worsening during study therapy, have to be considered as AEs. They can lead to SAEs, if they meet the criteria described in Section 8.3.
Intensity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. If an adverse event occurs which is not described in the CTCAE version 5.0, the four-point scale below will be used:

- Mild: discomfort noticed but no disruption of normal daily activity.
- Moderate: discomfort sufficient to reduce or affect daily activity.
- Severe: inability to work or perform normal daily activity.

- Life threatening: represent an immediate threat to life.

8.6.1 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the eCRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Laboratory test value abnormalities as such should not be reported on the AE page of the eCRF as adverse events unless they are treatment-emergent and they satisfy one or more of the following conditions for clinical significance:

a. Accompanied by clinical symptoms.
b. Lead to a change in study medication (e.g. dose modification, interruption or permanent discontinuation).
c. Require a change in concomitant therapy (e.g. addition, interruption, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

Please note: any laboratory result abnormality fulfilling the criteria for a serious adverse event should be reported as such, in addition to being recorded as an adverse event in the eCRF.

8.6.2 Pregnancy

Pregnancy per se is not considered an AE. A medical occurrence observed in the mother or fetus/newborn would be considered an AE.

Female patients must be instructed to immediately inform the investigator if they become pregnant during the study. The study treatment must immediately be stopped and the patient withdrawn from the study. Pregnancies occurring up to 6 months after completion of the last treatment cycle must also be reported to the investigator. The investigator must report all pregnancies within 24 hours of knowledge to EMD Serono. The investigator should counsel the patient, discuss the risks of continuing the pregnancy, and the possible effects on the fetus. The patient should be monitored until the conclusion of the pregnancy.

Pregnancy occurring in the partner of a patient participating in the study should also be reported to the investigator, MDACC IND Office, and EMD Serono. The partner should be counseled and followed as described above.

8.6.3 Adverse Drug Reactions with Concomitant Medications

The investigators must be aware that for all concomitant medications, the regulations of post-marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

9. DATA ANALYSIS/STATISTICAL METHODS

Ying Yuan, Ph.D. (Professor, Department of Biostatistics, MDACC) will perform all statistical analyses. Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented as outlined below.

9.1 Analysis Sets

9.1.1 Safety Analysis Set

The safety analysis set includes all enrolled patients who receive at least one (1) dose of study medication.

9.1.2 DLT Analysis Set

The DLT analysis set is a subset of the safety analysis set and includes all enrolled patients in the dose escalation phase, receive at least one dose of the combination treatment, and either experience DLT during the first cycle (28 days) of treatment, or complete the DLT observation period for the first cycle of treatment.

Patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of each of the investigational products in the combination in Cycle 1 for reasons other than toxicity, which are attributable to the investigational products are not evaluable for DLT. Additional patients will be enrolled in the specific cohort to replace patients who are not considered DLT evaluable.

9.1.3 Response Analysis Set

All enrolled patients who receive at least one (1) dose of study medication with baseline assessment and have at least one post-baseline tumor assessment will be considered evaluable for response.

9.2 Statistical Methods and Properties

The study will be monitored for futility and excessive toxicity in cohorts of 10 as described below. If the trial does not stop early, we will estimate the clinical benefit rate and the response rate separately with appropriate 95% confidence intervals. We will also estimate the progression free survival (PFS) and overall survival (OS) using Kaplan-Meier methods.

9.4 General Statistical Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum,

and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

No imputation of missing efficacy data is planned. For time-to-event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0.

For AEs, missing dates will not be imputed, however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

Evaluations will be performed separately for each trial arm.

9.4.1 Demographics and Baseline Characteristics

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race and Hispanic origin, the summary statistics will be the number and percentage of patients within each group or the total sample. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

Baseline characteristics include: Performance status, duration from initial diagnosis, response to previous therapy (Y/N).

9.3 Sample Size Determination

There will be 3-6 patients enrolled per dose level in the dose escalation phase of the combination of M6620 and avelumab.

Each dose expansion arm may have up to 30 patients each. A 3-stage design with 10 patients in each stage will be utilized. We will stop after the 1st stage if we see 0 successes in 10 evaluable patients on RP2D, after the 2nd stage if we see < 2 successes in 20 evaluable patients, and we will declare the treatment worthy of further study if we see > 3 successes in 30 evaluable patients. If we set p0 (highest success rate for unacceptable treatment) = 5% and p1 (lowest success rate for acceptable treatment) = 20%, this design has alpha = 5%, 80% power and probability of early termination under p0 of 60% after 1st stage and 79% after either 1st or 2nd stage.

9.4 General Statistical Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum,

and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

No imputation of missing efficacy data is planned. For time-to-event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0.

For AEs, missing dates will not be imputed, however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

All evaluations will be performed separately for each trial arm.

9.4.1 Demographics and Baseline Characteristics

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race and Hispanic origin, the summary statistics will be the number and percentage of patients within each group or the total sample. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

Baseline characteristics include: Performance status, duration from initial diagnosis, response to previous therapy (Y/N).

9.5 Efficacy Analysis

The efficacy population will consist of all patients who receive at least one dose of study medication with baseline assessment and have at least one (1) post-baseline tumor assessment. This population will be used for primary analyses of efficacy.

9.5.1 Efficacy Evaluation

Clinical efficacy will be measured by clinical benefit rate (CBR) per RECIST v1.1 and irRECIST. CBR is defined as complete response (CR) + partial response (PR) + stable disease (SD) > 6 months. Overall response rate (ORR) will be measured using RECIST 1.1 criteria. Secondary efficacy endpoints include objective response (CR+PR), progression free survival (PFS), Duration of Response (DoR), overall survival (OS) and ORR. A 95% CI of response rate will be estimated based on the binomial distribution.

9.6 Safety Monitoring

The safety population will consist of all patients who have received any amount of study medications. We will employ Thall and Simon methods (1994) to perform interim safety monitoring every 10 patients for up to 30 patients. Formally, denote q_T as the probability of toxicity and assuming a non-informative beta(0.3,0.7) prior for q_T, we will stop the study if we determine that

there is more than an 80% chance that the posterior probability of toxicity is more than 30%. Specifically, our interim monitoring rule for toxicity is: Pr [q_T >30% | data] >0.8. The stopping boundaries corresponding to the above monitoring rule are to terminate study if (# patients with DLT) / (# patients evaluated) >=5/10, 8/20. The calculations were performed using MultcLean Desktop v 2.0.1. We will compare the proportion of patients with CTCAE grade 3 or higher treatment-related toxicities between treatments using chi-squared test or Fisher exact test as appropriate for the data.

Table 7: Expected early stopping probability

True toxicity probability	Early stopping probability	Expected number of patients enrolled before stopping
0.2	0.05	29.1
0.3	0.28	25.7
0.4	0.63	19.9
0.5	0.89	14.9
0.6	0.98	11.8

9.6.1 Safety Evaluation

Safety analyses will be conducted using the safety population. For the objective of describing the toxicity profile, descriptive statistics will be provided on the grade and type of toxicity by dose level.

9.6.2 Adverse Events

Adverse Events (AEs) will be coded using the NCI CTCAE v5.0 (or MedDRA if code is not available in CTCAE) and displayed separately for patients. Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 90 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE preferred term. The number and percentage of patients with any treatment-emergent AE will be summarized separately for patients in the trial. The number and percentage of patients with treatment-emergent AEs assessed by the Investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any grade ≥ 3 treatment-emergent AE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations.

Serious AEs will also be tabulated. No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs (treatment emergent and post-treatment) will be listed in patient data listings. By-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

9.6.3 Laboratory Data

The actual value and change from baseline to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, separately for all study patients. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g. those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

9.6.4 Vital Signs and Physical Examinations

The actual value and change from baseline to each on study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data were to be recorded on the AE eCRF. All examination findings will be presented in a data listing.

9.6.5 Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

9.7 Pharmacokinetic Analysis

Pharmacokinetic analyses for avelumab and M6620 will consist of summary statistics and plots of concentration-time data. Additionally the pharmacokinetic data may be utilized in a population pharmacokinetic analysis to determine typical and individual PK parameters (e.g. CL, V_{ss}, AUC, C_{max}, T_{max}, half-life if estimable).

9.8 Biomarker Analysis

Biomarker studies outlined in Section 7.5 will be mostly exploratory in nature and considered hypothesis-generating. Statistical methods employed will depend on the extent and nature of the data obtained.

9.9 Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameter, and biomarkers. Data will also be displayed graphically where appropriate.

9.10 Final Analysis

The final analysis will take place after the MTD expansion has been completed. Additional data summarization may take place after all available survival data are collected, or after investigator decision, as appropriate.

9.11 Data Safety Monitoring Committee

Routine safety monitoring will be performed by the Medical Monitor. Safety monitoring, including analysis of PK, will be performed by a Safety Monitoring Committee, consisting of the Principal Investigator (and co-investigators as needed), Sponsor representatives (e.g., designee from the IND Office), the study-specific Medical Monitor, and EMD Serono. Additional investigators and study team members will participate in reviews as needed. An Independent Data Monitoring Board will not be utilized for this open-label study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

11. DATA HANDLING AND RECORD KEEPING

11.1 Case Report Form/Electronic Data Record

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD Anderson Cancer Center at Houston. Data will be collected and stored in the Investigational Cancer Therapeutics database, Molecular and Clinical Data Integrated Portal (MOCLIA).

11.2 Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: investigator’s study file and subject/ patient data.

The investigator’s study file will contain all essential documents such as the protocol/amendments, case report and query forms, patient information and informed consent form, institutional review board and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities (if applicable), drug records, staff curriculum vitae and authorization forms, and other appropriate documents/correspondence, etc.

Patient data includes patient hospital/clinic records (e.g. medical reports, surgery reports appointment book, medical records, pathology and laboratory reports, ECG, etc.), signed informed consent forms and patient screening and eligibility screening forms.

The investigator must keep these two categories of documents on file for at least 15 years (or longer, as legally required) after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material.

12. ETHICS

12.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.2 Patient Information, Consent and Sample Storage

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any samples collected, reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to EMD Serono and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by EMD Serono in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, EMD Serono will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The investigator site will store any patient samples in a secure storage space with adequate measures to protect confidentiality.

The informed consent document and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent document used during the informed consent process and any patient recruitment materials must be reviewed and approved by the IRB, and EMD Serono, and be available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

The consent discussion can occur in person, over the phone, during a telemedicine visit, or over a videocall. Alternatively, prospective participants may be provided an informed consent form via email or MyChart message, which they review independently.

Subjects can electronically sign the consent via iConsent (when in clinic) or KLIC-Sign (when remote consenting), which are both 21 CFR Part 11 compliant. Alternatively, subjects can sign a hard copy of the consent form while in clinic, which will be scanned into their electronic medical record.

12.3 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e. clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that may influence the evaluation of the benefits and risks of the investigational product, the IRB should be informed immediately.

In addition, the investigator will inform the IRB immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of trial is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in the opinion of the IRB, drug safety problems, or at the discretion of the MDACC IND Office. In addition, EMD Serono retains the right to discontinue the development of the involved study drugs at any time.

If a study is prematurely terminated or discontinued, EMD Serono or the MDACC IND Office will promptly notify the investigator. As directed by EMD Serono, all study materials must be collected and all CRFs completed to the greatest extent possible.

Appendix A: ECOG Performance Status

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

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)[25].

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to start of study treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE (i.e., Not Evaluable), PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case should be discussed with the radiologist and the Principal Investigator to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Not evaluable (NE): Progression has not been documented, and one or more target lesions have not been assessed; or
- Assessment methods used were inconsistent with those used at baseline; or
- One or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure); or
- One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Not evaluable (NE): Progression has not been determined and one or more non-target lesion sites have not been assessed or assessment methods used were inconsistent with those used at baseline or one or more non-target lesions cannot be assessed (e.g., poorly visible or unclear images) or one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal

Determination 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 sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment at a minimum interval of 6 weeks.

Appendix C: Immune-related RECIST (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.
This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1\anti PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T-cells, thus leading to tumor infiltration by T-cells and tumor regression rather than direct cytotoxic effects. Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.
Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.
On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST). For irRECIST, with the exception of a CR assessment, only target and new measurable lesions are taken into account.
In contrast to RECIST v1.1, the irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by $\geq$20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the study.

irRECIST responses are defined as follows:

- **Overall immune-related complete response (irCR):** Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- **Overall immune-related partial response (irPR)**: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.
- **Overall immune-related stable disease (irSD)**: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions does not meet criteria for irCR or irPR (compared to baseline), or immune-related progressive disease (irPD, compared to nadir).
- **Overall immune-related progressive disease (irPD)**: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (i.e., added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up

to 5 new lesions in total can be added to the measurements. New non-measurable lesions: Do not define progression but preclude irCR.

Measurable disease	**Non-measurable disease**		
Target and New Measurable Lesions (Tumor Burden)[a]	**Non-Target Lesions**	**New, non-measurable Lesions**	**Overall response using irRECIST[b]**
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

[a] Decreases assessed relative to baseline.

[b] Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix D: Assessment of Radiographic Response and Progression in Patients with CRPC

Radiographic imaging for patients with CRPC is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis). Bone imaging including a whole body radionuclide bone scan (scintigraphy) is required at baseline and at regular image screening intervals in all patients with prostate cancer enrolling on trial.
The investigator will assess response of soft tissue disease by RECIST v1.1 (see Appendix 16.2). However, bone disease will not be considered as non-target lesions assessed by RECIST v1.1. An objective response is defined as a best overall response of CR or PR per RECIST v1.1 and must be confirmed on repeated imaging at least 4 weeks after initial documentation.
Bone disease will be assessed for progressive disease only by PCWG3.64. The documentation required for the determination of radiographic progression is shown in the table below.

Date Progression Detected[a]	**Criteria for Progression**	**Criteria to Confirm Progression**	**Criteria to Document Disease Progression on Confirmatory Scan**
Week 8	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: At least 6 weeks after progression identified or at Week 16 visit[b]	2 or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 16 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point[b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan[c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

- Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
- Confirmation must occur at the next available scan.

- For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3. See table below for the timing of confirmatory imaging requirements.

Confirmatory Imaging Requirements for Patients with mCRPC Based on RECIST v1.1 and PCWG3

Disease Site	Response	Progression[a]
Soft tissue	Must be confirmed at least 4 weeks later	No confirmation required
Bone	Not applicable	Must be confirmed at least 6 weeks later

a To inform permanent treatment discontinuation.

Radiographic PFS is defined as the time from the start of treatment to documentation of radiographic progression in soft tissue by investigator' assessment according to RECIST v1.1, in bone by investigator's assessment according to PCWG3, or death if within 2 tumor assessments after last completed tumor assessment, whichever occurs first.

Appendix E: Abbreviations and Definitions

Abbreviation	Definition
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AHA	American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related
AUC	Area under the curve
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CK-MB	Creatinine kinase MB
Cmax	Maximum plasma drug concentration
CMO	Contract Manufacturing Organization
CNB	Core needle biopsy
CPK	Creatinine phosphokinase
CR	Complete response(s)
CRF	Case report form
CRP	C-reactive protein
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDR	DNA Damage Response
DLT	Dose-limiting toxicity
DOR	Duration of response
DSB	Double strand break
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture (system)
EOI	End of Infusion
EOT	End of treatment
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	Gonadotropin-releasing hormone
Hb	Hemoglobin
HBsAg	Hepatitis B virus surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HGSOC	High grade serous ovarian cancer
HIV	Human immunodeficiency virus
HPF	High power field
HR	Heart rate
HRD	homologous recombination deficiency
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IGF-1	Insulin-like growth factor 1
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
IO	Immuno-oncology
IPCT	Institute for Personalized Cancer Therapy
IRB	Institutional review board
irAE	Immune-related adverse event
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITB	Institutional Tissue Bank
IV	Intravenous
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLN	Lower limit of normal
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MDACC	The University of Texas MD Anderson Cancer Center
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3
PD	Pharmacodynamic or progressive disease
PD-L1	Programmed death ligand 1
PDX	Patient-derived xenograft
PET	Positron emission tomography

PFS	Progression free survival
PK	Pharmacokinetic
PODS	Precision Oncology Decision Support
PR	Partial response
PRL	Prolactin
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
RPPA	Reverse phase protein array
RSRD	Replication stress response defect
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SMC	Safety Monitoring Committee
STING	Stimulator of interferon gamma
T4	Thyroxine
TBD	To be determined
TEAE	Treatment-emergent adverse event
Tmax	Time of maximum plasma concentration following drug administration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cells

Appendix F: List of Prohibited Medications and Therapies

The following medications should not be administered while participating in this trial.

CYP3A4 and CYP3A5 Inhibitors	CYP3A4 and CYP3A5 Inducers
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	carbamazepine
itraconazole1	enzalutamide
ketoconazole	glucocorticoids
nefazodone	modafinil
saquinavir	oxcarbazepine
telithromycin	phenobarbital2
aprepitant	phenytoin2
erythromycin	pioglitazone
fluconazole	rifabutin
grapefruit juice	rifampin1
verapamil2	St. John's Wort
diltiazem	troglitazone1
cimetidine	
amiodarone	
NOT azithromycin	
chloramphenicol	
boceprevir	
ciprofloxacin	
delaviridine	
diethyl-dithiocarbamate	
fluvoxamine	
gestodene	
imatinib	
m befradil	
mifepristone	
norfloxacin	
norfluoxetine	
starfruit	
telaprevir	
voriconazole	

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