MD Anderson IND Sponsor Cover Sheet

Protocol ID	2017-0014
Protocol Title	Phase I/II Study to Evaluate the Safety and Tolerability of Avelumab in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies
Protocol Phase	I/II
Protocol Version	11
Version Date	24 Jan 2023
Protocol PI	Aung Naing, MD
Department	Investigational Cancer Therapeutics
IND Sponsor	MD Anderson Cancer Center
IND #	135484

TITLE: PHASE I/II STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF AVELUMAB IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH ADVANCED MALIGNANCIES

Short title:	Phase I/II of Avelumab Combination with Other Anti-Cancer Therapies
Sponsor:	The University of Texas MD Anderson Cancer Center (MDACC)
Supporter:	Pfizer, Inc.
Coordinating Investigator:	Aung Naing, MD
Compounds:	Avelumab, Utomilumab (PF-05082566 (4-1BB)), PF-04518600 (OX40)

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Investigational New Drug (IND) Number:	135484
Protocol Committee:	Dr. Juhee Song (Statistical Consultant) Aung Naing, MD

SYNOPSIS

MDACC Protocol Number:	2017-0014
Protocol Version (Date):	Version 11 24 Jan 2023
Study Design:	Based on preclinical or clinical evidence of anti-tumor activity through PD-1/PD-L1/4-1BB/OX40 in tumor microenvironment and recommendations by Pfizer and MD Anderson physicians, as of Amendment 09, this is a four arm study (Parts A-D) that includes 2 treatment categories to evaluate safety, pharmacodynamics, and anti-tumor activity of avelumab in combination with other cancer immunotherapies in Pfizer pipeline with or without radiation (XRT), in patients with metastatic solid tumors. • Category 1: Checkpoint agonist(s) in combination with avelumab; • Category 2: Checkpoint agonist(s) + XRT in combination with avelumab. This is an open label, single center Phase I/II combination therapy study in metastatic cancers. Patients may be enrolled in this study if they have advanced staged cancer either unresponsive or relapsed following prior standard therapy or for whom there is no known effective therapy. Patients who meet these criteria may in some cases have received no prior chemotherapy.
Total Number of Sites:	1
Study Population:	Patients with metastatic solid tumors
Primary Objectives:	• For Arm D, to establish the safety, tolerability, and dose-limiting toxicities (DLTs) of different treatment combinations of avelumab when administered in combination with a checkpoint agonist with radiation in patients with metastatic solid tumors in order to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 dose (RP2D). • To correlate pre- and post-treatment CD8 expression with clinical benefit (complete response [CR], partial response [PR], or stable disease [SD] for > 6 months).
Secondary Objectives:	• To evaluate the efficacy of the different treatment combinations in patients with metastatic solid tumors by assessing objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related RECIST (irRECIST). • To evaluate the efficacy of the different treatment combinations in patients with metastatic solid tumors by assessing progression-free survival (PFS), duration of response (DOR), and overall survival (OS).
Exploratory Objectives:	• To understand the mechanism of action of the avelumab plus an immune modulator combination, as well as potential mechanisms of resistance. • To characterize the effect of avelumab combinations on immune biomarkers in peripheral blood and tumor tissue obtained from subjects pre- and post-treatment.

	• To compare the response in irradiated versus non-irradiated lesions in Arm D. • To investigate immune biomarkers that are potentially predictive of response and resistance with the combination of avelumab and an immune modulator.
Planned Sample Size:	Two dose levels may be examined in each combination arm during the dose escalation/de-escalation with a standard "3+3" design, and a total of 3-6 patients will be enrolled per dose level. After each escalation or MTD determination by Pfizer, there will be an MTD expansion cohort of up to 14 patients each. As of Amendment 09, the planned total maximum accrual in this study will be 128 patients (Escalation 36 + MTD Expansions 92). Please refer to Section 9.3 and Table 12 for the history of amendments impacting the accrual.
Treatment Scheme:	There are 4 active arms in this study: Arm A: Avelumab + Utomilumab (4-1BB) Arm B: Avelumab + PF-04518600 (OX40) Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40) Arm D: Avelumab + Utomilumab (4-1BB) + XRT Treatment will continue until progression of disease (PD) or unacceptable toxicity, withdrawal of consent by the patients, or non-compliance by the patient with protocol requirements.
Primary Endpoint:	• Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. • Evaluation of CD8 immune biomarkers from tumor and blood biospecimens.
Secondary and Exploratory Endpoints:	• Objective response rate determined by radiographic disease assessments per RECIST v1.1 and irRECIST. • Progression-free survival, defined as the time from Cycle 1 start date until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1 and irRECIST, or death due to any cause, if occurring sooner than progression. • Duration of response determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1 and irRECIST, or death due to any cause, if occurring sooner than progression. • Overall survival determined from the Cycle 1 start date until death due to any cause. • Response data in irradiated and non-irradiated lesions. • Evaluation of various immune biomarkers from tumor and blood biospecimens.

Efficacy Assessments:	Anti-tumor activity will be assessed by radiological tumor assessments at 8-week intervals (± 7 days), using RECIST v1.1. In the event that partial response (PR), complete response (CR), or progressive disease (PD) is observed according to RECIST v.1.1 and irRECIST, tumor assessments should be repeated at least 4 weeks after initial documentation. After 1 year of treatment on the study, tumor assessments will be conducted less frequently, at 12-week intervals (± 7 days), independent of cycle delays. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 8 weeks). 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).
Safety Assessments:	All adverse events (AEs), including immune-related adverse events (irAEs), occurring during the course of the trial and for up to 30 days after the last dose of study medication will be captured, documented and reported. Toxicity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If multiple toxicities are seen, the presence of DLT shall be based on the most severe toxicity experienced. DLTs are defined as adverse events (AEs) that are related to study events and occur during the first 2 cycles or 8 weeks of treatment. Toxicity must have possible, probable, or definite attribution to the study drugs.
Statistical Considerations:	All enrolled patients are eligible for the analyses of toxicity and compliance. All patients who received at least 1 dose of study medication are eligible for analysis.

SCHEDULE OF ASSESSMENTS FOR ARMS A, B, AND C (NON-RADIATION)

The Schedule of Assessments table provides an overview of the protocol visits and procedures for Arms A-C. Refer to the Section 7.0- Assessments of the protocol for detailed information on each assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Assessments	Treatment Period							Post-Treatment	
	Screening	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dosing of Study Drug	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
Informed Consent [1]	X								
Verify Eligibility Criteria	X	X							
Medical History [2]	X								
Tumor History	X								
Serum or Urine Beta- hCG [3]	X	X		X		X		X	
Protocol /Safety Evaluation									
Physical Exam and ECOG [4]	X	X	X	X	X	X	X	X	
Height [5]	X								
Weight[5]	X	X	X	X	X	X	X		
Vital Signs [5]	X	X	X	X	X	X	X	X	X
12-lead ECG [6]	X	X		X		X			

Assessments	Treatment Period							Post-Treatment	
	Screening	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dosing of Study Drug	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
ECHO/MUGA[7]	X					X[7]		X	
AE/SAE Assessment [8]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Survival Status[9]									X[9]
Laboratory Evaluation									
Hematology [10]	X	X	X	X	X	X	X	X	X
Chemistry [11]	X	X	X	X	X	X	X	X	X
Thyroid Function [12]	X					X[12]		X	
Urinalysis [13]	X	X		X		X			
Coagulation Test [14]	X	X		X		X			
Hepatitis B and C Testing (Hepatitis B surface antigen and core antibody; anti-hepatitis C anti-body)	X								
Cardiac Monitoring[15]	X	X		X		X		X	
Study Treatment									
Expansion Arms A-C: Avelumab Dosing [16]			X	X	X	X	X		
Arm A: Utomilumab (4-1BB) Dosing [17]		X		X		X			
Arm B: PF-04518600 (OX40) Dosing [18]		X	X	X	X	X	X		
Arm C: Utomilumab(4-1BB)[19]		X		X		X			
Arm C: PF-04518600 (OX40)[19]		X	X	X	X	X	X		

Assessments	Treatment Period							Post-Treatment	
	Screening	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dosing of Study Drug	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
Tumor Measurement									
CT or MRI or PET-CT [20]	X					Every 8 Weeks for up to 1 year, then Every 12 Weeks thereafter			Every 12 Weeks
Tumor Markers (if applicable) [21]	X					Every 8 Weeks for up to 1 year, then Every 12 Weeks thereafter			Every 12 Weeks
Correlative Studies									
Expansion Arms A-C: Tumor Biopsy [22]	X[26]		X			X		X	
Expansion Arms A-C: Immune Biomarkers [23]	X		X			X		X	
Escalation Arm C: Tumor Biopsy [24]	X[26]			X				X	
Escalation Arm C: Immune Biomarkers [25]	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.
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 for the definition of “female patients who are not of childbearing potential” in inclusion criterion, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening (within 7 days of first dose of study treatment) and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations

4. Full physical examination and ECOG will be performed at screening, Days 1 and 15 of each cycle and End of Treatment visit. Physical examinations during the study should be symptom directed.
5. Vital signs: temperature, pulse, respiratory, blood pressure, body surface area and body weight will be measured. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days pre-dose Day 1 of each cycle and Day 15 of each cycle. At screening, height will be obtained from the electronic medical record.
6. 12-lead ECG (single) will be performed at screening and predose of Day 1 of Cycle 1. 12-lead ECG (single) will be performed at predose of Day 1 of every subsequent cycle.
7. For patients on the PF-04518600 (OX40) Arms (B and C) who have had prior exposure to anthracyclines, echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed at screening, every 3 cycles (starting at Cycle 4 Day 1), and End of Treatment (if not performed within 3 months of discontinuation).
8. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 30 days after the last treatment administration 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 withdrew consent to participate in the study using information from a chart review, patient visit, or telephone call. The telephone call will be less than five minutes to obtain information regarding survival status.
10. Hematology: White blood cell (WBC) count with differential, Hemoglobin, Platelet count, Red blood cell count, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC). No need to repeat on Cycle 1 Day 1 if baseline assessment performed within 2 days prior to that date. Post Cycle 3, patients in all study arms will have hematology labs on Day 1 and 15 of each cycle.
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, Total Bilirubin, Lactate dehydrogenase (LDH), Total Protein, Albumin, Uric acid, Amylase, Lipase and Creatine Kinase. No need to repeat on Cycle 1 Day 1 if baseline assessment performed within 2 days prior to that date. Post Cycle 3, patients in all study arms will have chemistry labs on Day 1 and 15 of each cycle.
12. Thyroid function: (thyroid-stimulating hormone (TSH), free thyroxine (T4), and total triiodothyronine (T3). TSH, free T4, and total T3 for endocrine monitoring will be evaluated at screening and every tumor restaging (every 8 weeks).
13. Urine analysis will include Color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin and microscopy including WBC/high power field (HPF), 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 performed within 2 days prior to that date.
14. Coagulation test include 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 performed within 2 days prior to that date.

15. For patients on the PF-04518600 (OX40) Arms (B and C) who have had prior exposure to anthracyclines, cardiac enzyme monitoring will be performed at screening, Day 1 of every cycle, and End of Treatment. Troponin T and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) will be evaluated prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if the screening assessment is performed within 2 days prior to that date. Assessments performed on Cycle 2 Day 1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. Assessments should also be performed when clinically indicated.
16. For MTD Expansion Arms A-C, avelumab will be administered IV every 2 weeks starting on Cycle 1 Day 15 (and then Days 1 and 15 of Cycle 2 and beyond).
17. For Arm A, utomilumab (4-1BB) will be administered IV every 4 weeks starting on Cycle 1 Day 1 (Day 1 of every cycle).
18. For Arm B, PF-04518600 (OX40) will be administered IV every 2 weeks starting on Cycle 1 Day 1 (Days 1 and 15 of every cycle).
19. For Arm C, utomilumab (4-1BB) will be administered IV every 4 weeks starting on Cycle 1 Day 1 (Day 1 of every cycle). PF-04518600 (OX40) will be administered IV every 2 weeks starting on Cycle 1 Day 1 (Days 1 and 15 of every cycle).
20. CT, MRI, or PET-CT Scans will be performed at screening, 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 during treatment, independent of cycle delays.
21. Tumor markers (if applicable) will be collected at screening, 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 during treatment, independent of cycle delays.
22. For MTD Expansion Cohorts in Arms A-C, tumor tissue will be obtained pre- treatment (baseline), between Cycle 1 Day 12-15 (prior to study drug dosing), prior to Cycle 3 Day 1 study drug dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.
23. For MTD Expansion Cohorts in Arms A-C, blood samples will be collected at baseline, between Cycle 1 Day 12-15 (prior to study drug dosing), prior to Cycle 3 Day 1 study drug dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission) to evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers. Cell free DNA from patient's blood samples will also be analyzed.
24. For Escalation Cohorts in Arm C (patients enrolled prior to Version 05), tumor tissue will be obtained pre- treatment (baseline), prior to Cycle 2 Day 1 dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.
25. For Escalation Cohorts in Arm C (patients enrolled prior to Version 05), blood samples will be collected at baseline, prior to Cycle 2 Day 1 dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission) to evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers. Cell free DNA from patient's blood samples will also be analyzed.
26. Archival tissue may not be utilized for the baseline sample time point.

SCHEDULE OF ASSESSMENTS FOR ARM D (RADIATION)

The Schedule of Assessments table provides an overview of the protocol visits and procedures for Arm D. Refer to the Section 7.0-Assessments of the protocol for detailed information on each assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Assessments		Treatment Period							Post-Treatment	
	Screening	Radiation Lead-in[4]	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dose of Radiation	First Day of Radiation (+/- 3 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
Informed Consent [1]	X									
Verify Eligibility Criteria	X	X								
Medical History [2]	X									
Tumor History	X									
Serum or Urine Beta- hCG [3]	X	X			X		X		X	
Protocol /Safety Evaluation										
Physical Exam and ECOG [5]	X	X	X	X	X	X	X	X	X	
Height [6]	X									
Weight[6]	X		X	X	X	X	X	X		
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X
12-lead ECG [7]	X		X		X		X			

Assessments		Treatment Period							Post-Treatment	
	Screening	Radiation Lead-in[4]	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dose of Radiation	First Day of Radiation (+/- 3 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
AE/SAE Assessment [8]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Survival Status[9]										X[9]
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[12]		X	
Urinalysis [13]	X	X			X		X			
Coagulation Test [14]	X	X			X		X			
Hepatitis B and C Testing (Hepatitis B surface antigen and core antibody; anti-hepatitis C antibody)	X									
Study Treatment										
Arm D: XRT [15]		X								
Arm D: Avelumab Dosing [16]				X	X	X	X	X		
Arm D: Utomilumab (4-1BB) [17]			X		X		X			
Tumor Measurement										
CT or MRI or PET-CT [18]	X						Every 8 Weeks for up to 1 year, then Every 12 Weeks thereafter			Every 12 Weeks

Assessments		Treatment Period							Post-Treatment	
	Screening	Radiation Lead-in[4]	Cycle 1		Cycle 2		Cycle 3 and Beyond		End of Treatment (EOT)	Follow-Up Visits
	</= 28 Days prior to 1st Dose of Radiation	First Day of Radiation (+/- 3 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	Day 1 (+/- 2 Days)	Day 15 (+/- 2 Days)	30 Days after Last Dose of Study Drug (+/- 7 Days)	Every 12 Weeks (+/- 7 Days)
Tumor Markers (if applicable) [19]	X						Every 8 Weeks for up to 1 year, then Every 12 Weeks thereafter			Every 12 Weeks
Correlative Studies										
Arm D: Tumor Biopsy [20]	X[22]						X		X	
Arm D: Immune Biomarkers [21]	X		X	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.
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 for the definition of “female patients who are not of childbearing potential” in inclusion criterion, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening (within 7 days of first dose of radiation) and once in the radiation lead-in prior to initial radiation treatment. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations
4. The radiation lead-in will occur within Days -5 to -1 with a +/- 3 day window. There will be 3 fractions or days of radiation. In all cases, the radiation must initiate and end within the radiation lead-time. Cycle 1 Day 1 treatment should be within 3 days of last dose of radiation.
5. Full physical examination and ECOG will be performed at screening, within 3 days of first day of radiation, Days 1 and 15 of each cycle and End of Treatment visit. Physical examinations during the study should be symptom directed.

6. Vital signs: temperature, pulse, respiratory, blood pressure, body surface area and body weight will be measured. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days pre-dose Day 1 of each cycle and Day 15 of each cycle. At screening, height will be obtained from the electronic medical record.
7. 12-lead ECG (single) will be performed at screening and predose of Day 1 of Cycle 1. 12-lead ECG (single) will be performed at predose of Day 1 of every subsequent cycle.
8. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 30 days after the last treatment administration 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 withdrew consent to participate in the study using information from a chart review, patient visit, or telephone call. The telephone call will be less than five minutes to obtain information regarding survival status.
10. Hematology: White blood cell (WBC) count with differential, Hemoglobin, Platelet count, Red blood cell count, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC). Hematology will be performed at screening, within 3 days of first day of radiation, Days 1 and 15 of each cycle, and End of Treatment visit.
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, Total Bilirubin, Lactate dehydrogenase (LDH), Total Protein, Albumin, Uric acid, Amylase, Lipase and Creatine Kinase. Chemistry will be performed at screening, within 3 days of first day of radiation, Days 1 and 15 of each cycle, and End of Treatment visit.
12. Thyroid function: (thyroid-stimulating hormone (TSH), free thyroxine (T4), and total triiodothyronine (T3). TSH, free T4, and total T3 for endocrine monitoring will be evaluated at screening and every tumor restaging (every 8 weeks).
13. Urine analysis will include Color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin and microscopy including WBC/high power field (HPF), RBC/HPF if clinically indicated. Dipstick is acceptable. Urine analysis will be at screening, within 3 days of first day of radiation, and Day 1 of Cycle 2 and beyond.
14. Coagulation test include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation tests will be performed at screening, within 3 days of first day of radiation, and Day 1 of Cycle 2 and beyond.
15. For Arm D, radiation will be given to 1-3 metastatic lesions. Radiation as described in Section 3.2 will be given during the Radiation Lead-in (Days -5 to -1) or 3 consecutive business days (+/-3 days). Cycle 1 Day 1 treatment should be within 3 days of last dose of radiation.
16. For Arm D, avelumab will be administered IV every 2 weeks starting on Cycle 1 Day 15 (and then Days 1 and 15 of Cycle 2 and beyond).
17. For Arm D, utomilumab (4-1BB) will be administered IV every 4 weeks starting on Cycle 1 Day 1 (Day 1 of every cycle).
18. CT, MRI, or PET-CT Scans will be performed at screening, 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 during treatment, independent of cycle delays.

19. Tumor markers (if applicable) will be collected at screening, 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 during treatment, independent of cycle delays.
20. For De-Escalation and MTD Expansion Cohort in Arm D, tumor tissue will be obtained pre- treatment (baseline), prior to Cycle 3 Day 1 dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.
21. For De-Escalation and MTD Expansion Cohort in Arm D, blood samples will be collected at baseline (prior to radiation), prior to Cycle 1 Day 1 dosing, prior to Cycle 1 Day 15 dosing, prior to Cycle 2 Day 1 dosing, prior to Cycle 3 Day 1 dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission). Cell free DNA from patient's blood samples will also be analyzed.
22. Archival tissue may not be utilized for the baseline sample time point.

GLOSSARY OF ABBREVIATIONS

β-HCG	Beta human chorionic gonadotropin
1L	First Line Treatment
2L	Second Line Treatment
3L	Third Line Treatment
ADR	Adverse Drug Reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CA	Competent Authority
CDDP	Cisplatin
CHF	Congestive heart failure
CI	Confidence interval
CNB	Core Needle Biopsy
CNS	Central nervous system
CR	Complete Response
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
D	Day
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DRAE	Drug-related Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMR	Electronic Medical Record
EOT	End of treatment
FFPE	Formalin-Fixed Paraffin-Embedded
FIP	First-in-Patient
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GEJ	Gastroesophageal Junction
GI	Gastrointestinal

GLP	Good laboratory practice
Gy	Gray
H	Hour
HCC	Hepatocellular carcinoma
HNSCC	Head and Neck Squamous Cell Carcinoma
HIF	Hypoxia-Inducible Factors
HPV	Human papillomavirus
HR	Hazard ratio
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IIR	Investigator-Initiated Research
IMP	Investigational medicinal product
IMRT	Intensity-Modulated Radiation Therapy
INR	International normalization ratio
IR	Irradiation
IRB	Institutional review board
irAE	Immune-Related Adverse Event
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
ITB	Institutional Tissue Bank
IV	Intravenous
kg	Kilogram
LAFB	Left anterior fascicular block
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
m^2	Square metre (body surface area)
LMW	Low molecular weight
mAb	Monoclonal Antibody
MCC	Merkel Cell Carcinoma
MCL	Mantle Cell Lymphoma
mg	Milligram
MI	Myocardial infarction
min	Minute
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear cells
PCWG2	Prostate Cancer Working Group 2
PD	Progressive disease
PDn	Pharmacodynamics
PET	Positron emission tomography

PFS	Progression-free survival
PI	Principal Investigator
PLT	Platelets
PPS	Per protocol set
PR	Partial Response
PRN	as needed
PT	Prothrombin time
QoL	Quality of Life
RBBB	Right bundle branch block
RBC	Red blood cells
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
ROSE	Rapid on Site Evaluation
RP2D	Recommend Phase 2 Dose
RR	Response Rate
RT	Radiation Therapy
SAE	Serious adverse event
SD	Stable disease
SADR	Serious adverse drug reaction
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
T3	Total triiodothyronine
T4	Free thyroxine
TEAE	Treatment-Emergent Adverse Events
TIL	Tumor-Infiltrating Lymphocytes
TNBC	Triple Negative Breast Cancer
TSH	Thyroid-Stimulating Hormone
TSP	Tumor suppressor protein
ULN	Upper limit of normal
VMAT	Volumetric modulated arc therapy
Vs.	Versus
WBC	White blood cell
WHO	World Health Organization
XRT	Radiation

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1.0 INTRODUCTION

1.1 Indications

There is a broad literature of evidence that infiltration of tumor tissue by T cells is associated with improved survival in patients with melanoma, breast, ovarian, lung, renal cell, colorectal and bladder carcinoma among other solid tumors (1, 2). However, eliciting T cell mediated immune response is a challenge as tumor cells frequently develop a host of immunosuppressive defense mechanisms to escape immune surveillance through a process called immune tolerance (1). It is therefore critical to overcome these barriers to elicit clinical response to therapeutic agents.

Despite the success with checkpoint inhibitors, including cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death-ligand 1 (PD-L1) blockades, many patients are primarily resistant or develop resistance to treatment after an initial response (3). Among several mechanistic approaches being investigated in the clinic to overcome primary and secondary resistance to the immune checkpoint blockers, there is growing evidence that combination therapies are potentially synergistic and are far more effective than monotherapies to combat resistance mechanisms as tumors use multiple pathways to evade immune elimination (4). Further, few immunologic parameters have been identified as early markers of response including intra tumoral CD8+ T cells. (5-7). Therefore, this program has been conceived to identify fine-tuned combination therapies that would facilitate infiltration of CD8+ T cells into tumor cells and demonstrate synergistic anti-tumor activity, allowing the capability to hone in on combinations and tumor types of interest.

Based on preclinical or clinical evidence of anti-tumor activity through PD-1, PD-L1, 4-1BB, and OX40 in tumor microenvironment, a six-arm study that includes 2 treatment categories to evaluate safety, pharmacodynamics, and anti-tumor activity of avelumab in combination with other cancer immunotherapies in Pfizer pipeline with or without radiation (XRT), in patients with metastatic solid tumors was initially to be conducted.

- Category 1: Checkpoint agonist(s) in combination with avelumab;
- Category 2: Checkpoint agonist(s) + XRT in combination with avelumab.

As of Amendment 09, the study was re-assessed, and the Joint Steering Committee decided that Arms E and F of checkpoint agonist(s) and radiation combined with avelumab were to be discontinued.

This study will assess whether checkpoint agonist(s), initially drives CD8+ T cells intra-tumorally, which helps avelumab (PD-L1 inhibitor) to augment the response in a limited series of indications. Based on emerging preclinical and clinical data, studies to evaluate combinations of avelumab with other immune modulators may follow.

Table 1: Treatment Arms of Avelumab in Combination with Other Cancer Immunotherapies with or without Radiation.

Categories	Treatment Arm	Treatment	Projected Phase I Enrollment
I. Avelumab + Checkpoint Agonist(s)	**A**	Avelumab + Utomilumab (4-1BB)	*Max. 14
	B	Avelumab + PF-04518600 (OX40)	*Max. 14
	C	Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)	**Max. 18
II. Avelumab + Checkpoint Agonist(s) + XRT	**D**	Avelumab + Utomilumab (4-1BB) + XRT	***Max. 32

*In Arm A, B and C, the MTD will be provided by Pfizer. The projected number of patients to be enrolled in Phase I is for MTD expansion cohorts only. This number does not include patients enrolled on the previous avelumab dosing schedule (prior to Version 05).
** The projected number of patients to be enrolled in Phase I includes dose escalation and MTD expansion cohort.
***In Arm D, the projected number does not include patients enrolled on the previous avelumab and radiation dosing schedule (prior to Version 08 and Version 09).
Please refere to Section 9.3 for Sample Size Determination.

1.2 Background

Immune cells in the tumor microenvironment express a diverse array of co-stimulatory and co-inhibitory receptors, the immune checkpoints, which are potential targets in the immune system that could be exploited to augment/sustain the anti-tumor response (8). Agents that block the co-inhibitory receptors and “release the brakes” on the immune system (checkpoint inhibitors) and those that enhance the co-stimulatory response (checkpoint agonist) have demonstrated broad anti-tumor effects in clinic, representing a new chapter in cancer immunotherapy (9).

1.2.1 Avelumab (PF-06834635): Anti-PD-L1 Monoclonal Antibody

Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody (mAb). PD-L1 is the binding partner for the PD-1 receptor and serves as a brake, or checkpoint, on the immune response. PD-1/PD-L1 checkpoint inhibitors “release the brakes” on the immune system, allowing it to fight the cancer (10). Targeting PD-L1 is also expected to have fewer immune-related adverse events (irAE) than CTLA-4 blockade due to the distinct biologic features of the two pathways (10, 11). Avelumab is currently in clinical development with ongoing phase I studies in patients with solid tumors, phase II studies in patients with Merkel cell carcinoma, and Phase III studies in patients with NSCLC, gastric, and ovarian cancer. In a phase I trial with PD-L1 antibody, among patients with evaluable response, an objective response was observed in 9 of 52 patients with melanoma, 2 of 17 with renal cell cancer, 5 of 49 with non-small cell lung cancer, and 1 of 17 with ovarian cancer. Responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up (10).

In a Phase I Trial EMR 100070-001 in solid tumors, treatment-emergent adverse events (TEAEs) occurred in all 53 subjects (100.0%) participating in the dose escalation cohort, of which 43 subjects (81.1%) reported treatment-related TEAEs. The most frequently observed treatment related TEAE was fatigue reported in 21 subjects (39.6%), followed by influenza-like illness in 11 subjects (20.8%), and pyrexia in 8 subjects (15.1%). Nine of the 53 subjects (17.0%) in the dose escalation cohort experienced at least 1 Grade ≥ 3 treatment-related TEAE. These included event terms of autoimmune disorder (3 subjects; 5.7%), aspartate aminotransferase (AST) increased and blood creatine phosphokinase (CPK) increased (each in 2 subjects;

3.8%), and fatigue, abdominal pain lower, lipase increased, amylase increased, alanine aminotransferase (ALT) increased, blood alkaline phosphatase increased, and lymphocyte count decreased (each in 1 subject; 1.9%). Of the 9 subjects (17.0%) who had Grade ≥ 3 treatment-related TEAEs, 7 (13.2%) had Grade 3 events, 2 (3.8%) had Grade 4 events (blood CPK increased and autoimmune disorder), and no Grade 5 treatment-related TEAEs were observed. Overall, the TEAE profile was similar across different dose escalation cohorts and the incidences of TEAEs by TEAE category did not increase with increasing dose. In the 1300 subjects comprising the pooled expansion cohort including subjects from 16 tumor expansion cohorts, the most frequently reported TEAEs were fatigue (27.4%), followed by nausea (21.2%), infusion-related reaction (16.2%), diarrhea (15.8%), and constipation (15.7%) (12).

The safety data analysis for the Japanese Phase I Trial EMR 100070-002 consists of data from 17 subjects treated in the dose escalation phase (5, 6, and 6 subjects with solid tumor treated with 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 35 subjects with gastric cancer treated with 10 mg/kg of avelumab once every 2 weeks in the treatment expansion phase. Nineteen serious TEAEs were reported in 15 subjects. Fourteen serious TEAEs were reported as ≥ Grade 3 (including 10 Grade 3 events and 4 Grade 5 events; none were reported as Grade 4). Seventeen serious TEAEs in 14 subjects were assessed as not related to treatment. Three subjects experienced serious TEAEs resulting in a fatal outcome. Two serious TEAEs, in one subject, resulted in a fatal outcome and were considered as treatment-related: acute kidney injury (Grade 5) and tumor lysis syndrome (Grade 5). One subject died due to disease progression and the other subject due to myocardial infarction, both serious TEAEs were not considered to be treatment-related. In this trial, three cases in 2 subjects with potential immune related AEs (irAEs) were identified, including hyperthyroidism (Grade 1), hypothyroidism (Grade 2), and colitis (Grade 2). All 3 irAEs were regarded as non-serious events and considered as related to treatment. Thirteen cases of infusion-related reactions in 11 subjects were identified, including 12 non-serious events of infusion-related reaction (Grade 1 or 2; all treatment-related) and a single serious event of drug hypersensitivity (Grade 2; assessed as not related to treatment, as it was caused by subsequent chemotherapy with oxaliplatin after trial discontinuation) (12).

The safety data analysis for the Phase II Trial EMR 100070-003 consists of data from 88 subjects treated with 10.0 mg/kg avelumab for MCC once every 2 weeks. A total of 78 serious TEAEs were reported in 35 subjects. Fifty-seven serious TEAEs were reported as ≥ Grade 3 (including 39 Grade 3 events, 7 Grade 4 events, and 11 Grade 5 events). The majority of serious TEAEs (70/78) were assessed as not related to treatment. Eight serious TEAEs in 6 subjects were considered as treatment-related: chondrocalcinosis (2 events; both Grade 2), enterocolitis (Grade 2), synovitis (Grade 2), transaminases increased (Grade 3), tubulointerstitial nephritis (Grade 2), infusion-related reaction (Grade 2), and hypothyroidism (Grade 2). In this trial, 2 cases in 2 subjects with potential irAEs were identified including a serious event of encephalopathy (Grade 2; assessed as not related to treatment) and a serious event of hypothyroidism (Grade 2; treatment-related) (12).

The clinical efficacy information summarized in the Investigator's Brochure includes data from the NSCLC and ovarian cancer expansion cohorts of the ongoing Phase I Trial EMR 100070-001, and for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002. The NSCLC expansion cohort in the ongoing Phase I Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively. The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0 vs 5.9 weeks) and OS (8.9 vs 4.6 months) were both observed in PD-L1 positive compared with PD-L1 negative subjects. The ovarian cancer

expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% confidence interval (CI): 6.3 to 12.0 weeks). The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95% CI: 3.2% to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3 weeks) (12).

Currently avelumab has received FDA approval for metastatic Merkel cell carcinoma and metastatic urothelial carcinoma indications (13, 14)

1.2.2 Utomilumab: Anti-4-1BB Agonist Monoclonal Antibody

Utomilumab or PF-05082566 is a fully humanized monoclonal antibody that stimulates signaling through the co-stimulatory receptor 4-1BB (CD-137), a member of the tumor necrosis factor receptor superfamily. 4-1BB is an activation dependent protein expressed in many immune cells (8). Co-stimulation through 4-1BB activates multiple signaling cascades within the T cell, which enhances the anti-tumor immune function and promotes formation of immunological memory. However, there are conflicting reports on the impact of 4-1BB stimulation on Treg expansion and suppressive capacity (8). Paradoxically, 4-1BB agonist antibodies also alleviate auto immune diseases, suggesting that it may reduce the clinical signs of autoimmune response associated with its anti-cancer activity (15). This dual activity of 4-1BB to provide anti-tumor activity while dampening irAEs usually associated with immunotherapy approaches makes it an attractive target (8). Further 4-1BB agonists alter the phenotype of T cells, favoring a potent tumoricidal ThEO T cell phenotype over Th17 phenotype (16). This may be critical in the treatment of colon cancer, in which the Th17 polarized T cells play important roles in tumor formation (8). 4-1BB targeted

immunotherapy has demonstrated durable anti-tumor response in wide range of murine tumors including floor of mouth squamous cell cancer, lymphoma, hepatocellular carcinoma, melanoma and colon cancer (8).

Utolimumab has been administered in a total of 110 patients: as a single agent to 47 (Study B1641001 Portion A) patients with advanced cancer at dose levels between 0.006 and 10.0 mg/kg and in 40 (Study B1641001 Portion B) patients at dose levels between 0.03 and10.0 mg in combination with rituximab, and in 23 (Study B1641003) patients at dose levels between 0.45mg/kg and 5.0 mg/kg in combination with pembrolizumab (17).

In B1641001 Portion A, a total of 19 (40.4%) patients out of 47 experienced treatment-related AEs, and the most frequently reported treatment-related AE was pyrexia (5 patients, 10.6%), which was generally mild, followed by fatigue (4 patients, 8.5%), which was mild except for one patient treated at 10 mg/kg, which was the highest PF-05082566 dose studied. This case was considered as a Grade 3, non-serious AE. For B1641001 Portion B of this study, a total of 18 out of 40 treated patients (45%) experienced treatment-related AEs, with the most common AE being fatigue (22.5% of patients). AEs were mild to moderate with the exception of one case of Grade 3 thrombocytopenia (platelet count decreased) which lasted less than 7 days, and was not considered as a serious adverse event (SAE). No Grade 4 or Grade 5 treatment-related AEs were observed in either study portion (17).

For the anti-tumor activity of B1641001 Portion A single agent PF-05082566, best clinical responses observed have been one complete response (CR) and one partial response (PR) in Merkel cell carcinoma (MCC) patients who were treated at 0.24 mg/kg and 0.6 mg/kg respectively. In Portion B patients treated with a combination of PF-05082566 and rituximab, 2 patients both with FL and treated at 0.03 and 0.12 mg/kg respectively, achieved a CR and 2 additional FL patients, treated at 0.18, achieved PRs. Two FL patients at 1.2 mg/kg and a patient with CD20 + Hodgkin’s lymphoma treated at 1.2 mg/kg achieved a PR. A patient with Mantle Cell Lymphoma (MCL) treated at 2.4 mg/kg achieved a PR. No PR or CR was observed at doses above 2.4 mg/kg as of the data cutoff (17).

In the B1641003 Study, 14 of the 23 (60.9%) patients dosed experienced at least one treatment related AE. Fatigue was the most common treatment-related AE reported in 8 (34.8%) patients, (maximum Grade 2) which was followed by rash maculo-papular in 6 (26.1%) patients (maximum Grade 1). There were no Grade 3 or higher treatment related AEs reported and all treatment-related AEs were mild to moderate in severity (Grade 1/2). Summary data indicate that there were several system organ class categories with an incidence of very common (>/=10%) AEs that were treatment-related; gastrointestinal disorders (nausea), general disorders and administration site conditions (fatigue and pyrexia), metabolism and nutrition disorders (decreased appetite), skin and subcutaneous tissue disorders (rash maculopapular and pruritus) (17).

For the anti-tumor activity of PF-05082566 in combination with pembrolizumab in patients with advanced solid tumors in Study B1641003, all patients evaluated for tumor responses have been in dose-escalation cohorts. Of the 5 patients treated in Cohort 1 (0.45 mg/kg) two patients achieved a best response of PR, one patient with RCC and the other patient with NSCLC. Three patients discontinued due to progression. There were no responses reported for the 3 patients treated in Cohort 2 (0.90 mg/kg). One of patients discontinued treatment due to progression, one withdrew consent and the third discontinued due to a non-treatment related AE of pain management. Of the 3 patients treated in Cohort 3 (1.8 mg/kg) one patient with RCC achieved a PR. One patient in this cohort had not achieved a response to date and the third patient progressed. Of the 3 patients treated in Cohort 4 (3.6 mg/kg) one patient with anaplastic thyroid disease achieved a PR. The other two patients in the cohort have discontinued due to progression. Of the 9 patients treated at the MTD in Cohort 5 (5.0 mg/kg) response information on 6 of these patients are available as of the data cut-off date. Of those 6 patients, 3 patients have discontinued due to progression, and three patients have not achieved a response to date (17).

1.2.3 PF-04518600: Anti-OX40 Agonist Monoclonal Antibody

PF-04518600 is an agonistic antibody that recognizes the co-stimulatory receptor OX40, a member of the tumor necrosis factor receptor superfamily expressed by

activated effector T cells and Treg cells (18). OX40 mAb selectively binds with OX40 receptors and augments T cell differentiation and cytolytic function while counteracting the immunosuppressive effects of Tregs (19, 20), and generates long term memory (20) leading to enhanced anti-tumor immunity against a variety of tumors. However, there are conflicting reports that these agonists may promote or diminish Treg cell responses depending upon the context of stimulation and the cytokine milieu (21). Administration of soluble OX40L or OX40 agonist antibody enhanced anti-tumor responses and led to tumor free survival in mouse models of melanoma, sarcoma, colon cancer, breast cancer (22, 23), thymoma and glioma (18, 21, 24).

Agonist antibodies to OX40 are currently in phase I clinical trials for cancer (3, 21). Thirty patients with metastatic solid malignancies refractory to conventional therapy were enrolled in a phase I study using the 9B12 murin agonistic anti-human OX40 mAb (25). A single cycle of anti-OX40 mAb was administered on days 1, 3, and 5. mild to moderate side effects included a brief period of lymphopenia, fatigue, fever/chills, and mild rashes. Twelve out of the 30 patients had regression of at least 1 metastatic lesion with only 1 cycle of treatment. Regression and stable disease were observed in patients with melanoma, renal cancer, squamous cell carcinoma of the urethra, prostate cancer, and cholangiocarcinoma. The longest interval of stable disease lasted 470 days in a patient with renal cancer, who received no other therapy during that time. Patients receiving the OX40 agonist had an expansion of CD4 (non-Treg cells) and CD8 T cells following drug infusion with concomitant expression of activation markers CD38 and HLA-DR (21).

In the first-in-patient study (FIP), Protocol B0601002, PF-04518600 monotherapy (Part A) is being studied in cancers that are considered to be amendable to immunotherapy, including advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC), and head and neck squamous cell carcinoma (HNSCC) (26).
PF-04518600 was administered intravenously at increasing doses (0.01 – 3 mg/kg) every 2 weeks until disease progression or unacceptable toxicity. Additional biomarker cohorts (opened at each dose level except 0.01 mg/kg) enrolled patients who consented to baseline and on-treatment tumor biopsies for immune profiling by

immunohistochemistry and RNA sequencing. As of 09 March 2016, 31 patients have enrolled in the dose-escalation phase of PF-04518600 study: 0.01 mg/kg (2 patients), 0.1 mg/kg (10 patients), 0.3 mg/kg (8 patients), 1.5 mg/kg (7 patients) and 3 mg/kg (4 patients). There were 25.8% of patients that had previously received ≥ 4 prior therapies for advanced disease. There were no dose limiting toxicities, and no drug-related or immune related grade 3-5 adverse events (AEs) were observed. Drug-related AEs (DRAEs) were all grade 1/2 events and occurred in 21 patients (67.7%). The most common DRAEs were fatigue (29.0%) and decreased appetite (9.7%). Out of 25 patients evaluable for response, 1 patient experienced partial response (PR, -50%, confirmed), and 15 patients experienced stable disease (SD). Eleven patients remain on treatment, and 5 patients continued treatment for >13 weeks. Assessments of peripheral blood lymphocyte indicated full OX40 receptor occupancy at ≥0.3 mg/kg, and maximal memory T cell proliferation at 0.1 and 0.3 mg/kg. These preliminary results demonstrate that PF-8600 is safe up to 3 mg/kg (27).

PF-04518600 will also be studied in combination with utomilumab (PF-05082566 anti-4-1BB mAb) in Protocol B0601002 Part B in patients with advanced or metastatic melanoma, HNSCC, non-small cell lung cancer (NSCLC), bladder, gastric or cervical cancers, who are unresponsive to existing therapies, for whom no standard treatment is available, or who have declined standard therapy (26).

1.3 Rationale for Combinations

1.3.1 Combination of Checkpoint Agonist(s) with Avelumab

Checkpoint inhibitors have attracted much attention following the approval of ipilimumab for treating patients with Stage III metastatic melanoma. Nivolumab has also been approved for treating metastatic melanoma, metastatic non-small cell lung cancer, and metastatic renal cell cancer in patients who have already tried an angiogenesis inhibitor; whereas pembrolizumab has been approved for treating patients with metastatic melanoma, and metastatic non-small cell lung cancer whose tumors express the protein PD-L1 on a companion diagnostic test. Recently, the combination of ipilimumab and nivolumab was approved for metastatic melanoma. However, generating a robust therapeutic immune response requires not only release

of “brakes” on T cells, but also stepping on the “gas”. T cell co-stimulation through receptors, like OX40 or 4-1BB, provides a potent “go” signal that actively promotes the optimal “killer” CD8 T cell responses (21).

1.3.1.1 Combination of Utomilumab (anti-4-1BB mAb) with Avelumab

The activation of 4-1BB signaling usually results in production of a large amount of IFN-γ, robust proliferation of T cells with enhanced effector function and memory potential (28). However, the enhanced T cell effector function is counterbalanced by upregulation of PD-L1 (29, 30). Expression of PD-L1 in tumors is inversely correlated with survival of patients (31), implying a need for a combination to counteract the negative immunoregulatory elements of signaling through 4-1BB. Further, in a syngeneic orthotopic mouse model of epithelial ovarian cancer (ID8), PD-L1 blockade resulted in tumor rejection in 60% (7/12) of the mice, indicating that PD-1/PD-L1 pathway is highly relevant, and is active very early in the process of establishment of ovarian tumors. Co-administration of a PD-L1 antagonist with α4-1BB and a cellular vaccine expressing GM-CSF (GVAX) triggered rejection of ID8 tumors and was associated with increase in proliferation of CD8+ T cell with a concomitant decrease in regulatory T cells (32).

In another preclinical study, mice transplanted with ID8 ovarian cancer cells was treated with control, mAb against 4-1BB (two different clones of mAb against CD137), or PD-1, or CD137+PD-1. Synergistic anti-tumor effect was observed with anti-CD137+PD-1 mAbs compared to control, mAb against 4-1BB or PD-1 (33). Overall survival (OS) was prolonged in mice treated with a combination of anti-PD-1 mAb with either anti-CD137 mAb as opposed to monotherapy, with the mean survival time being doubled ($p<0.05$ compared with control and single mAb groups) (Figure 1).

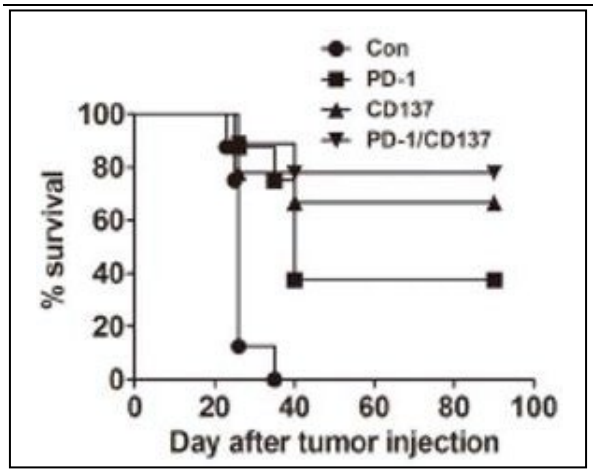

Figure 1: Survival in mice (8-9/group) transplanted intraperitoneal with ID8 cells. They were injected intraperitoneal twice at 4 days interval with 0.5 mg of control, anti-PD-1, anti-CD137 and anti-PD-1/CD137 mAb and their survival was recorded. *P < 0.05, **P < 0.01, compared with control mAb treated mice (28).

Presence of significantly increased CD8+ effector T cells and decreased immunosuppressive cells with anti-CD137/PD-1 mAbs suggests a systemic immune response (Figure 2).

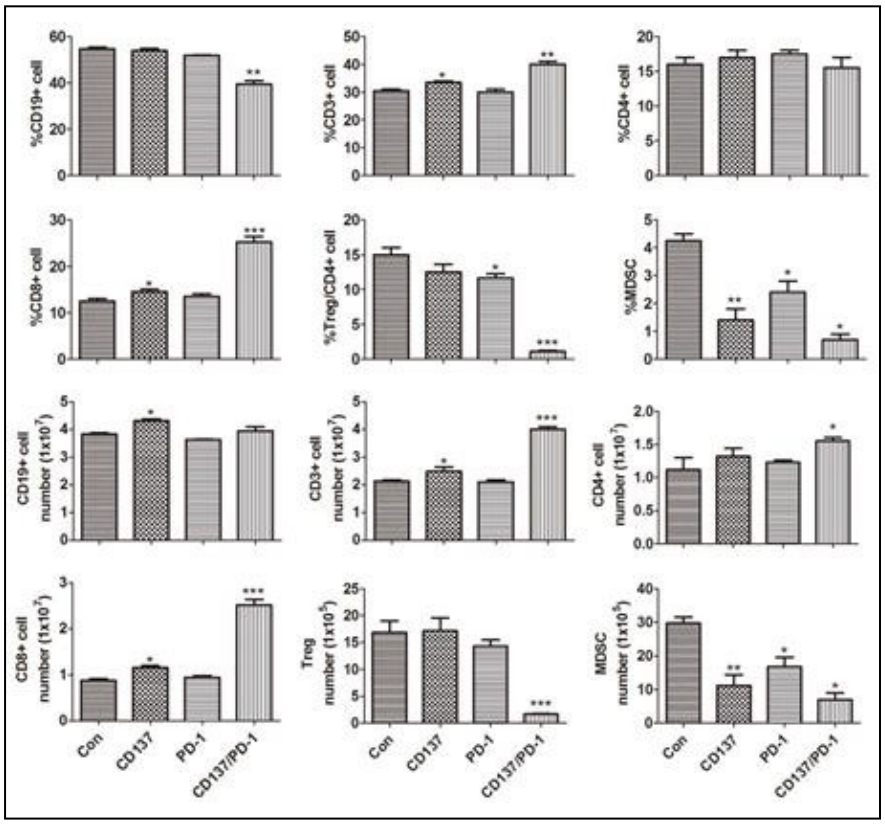

Figure 2: Analysis of lymphocyte components in spleens from mice treated with mAb combinations: The percentages and numbers of CD3+, CD4+, CD8+, CD19+, FoxP3+/CD4 and GR-1+CD11b+ cells in spleens (28).

Likewise, a robust anti-tumor effect of the anti–4-1BB/anti–PD-1 combination was observed in the 4-1BB agonist antibody resistant MC38 colon cancer model (Figure 3) (34). At the end of the study (Day 21 after tumor implant), tumor growth inhibition for the combination treatment was 63% relative to the control ($P < 0.0001$). The suppression was also significant when compared with the single agent alone ($P < 0.05$ versus (vs.) anti–4-1BB alone and $P < 0.001$ vs. anti–PD-1 alone). Anti-tumor efficacy of the combination was also evaluated in B16F10 melanoma model. Consistent with the above-mentioned results, pronounced tumor inhibition was reported when anti–PD-1 and anti–4-1BB were administered concomitantly. There was an 85% tumor growth inhibition compared to control ($p<0.0001$), and the response was dependent on IFNγ and CD8+ T cells (34). The combination treatment significantly increased both the central memory and effector memory CD8+ T cells in the spleen in both the models (34).

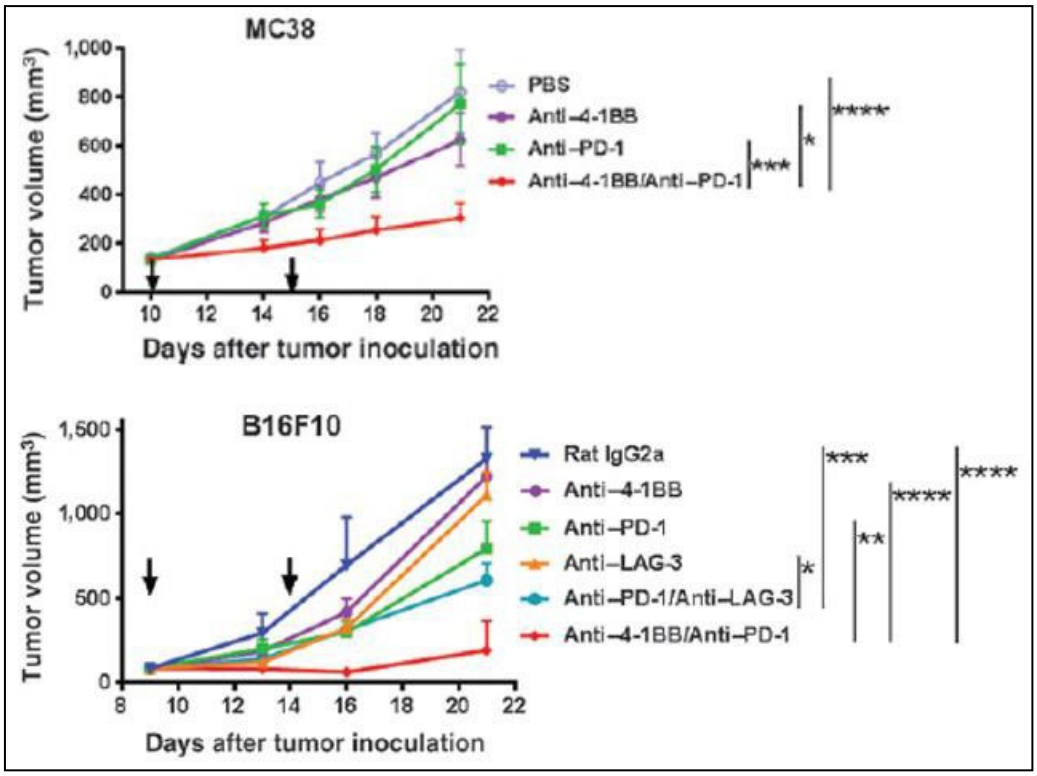

Figure 3: 4-1BB activation and PD-1 blockade synergistically amplify the antitumor effects in B16F10 melanoma and MC38 colon carcinoma models. C57BL/6 mice were inoculated subcutaneous (day 0) with 1 106 B16F10 or 1 106 MC38 cells. Animals were administered intraperitoneal rat IgG2a (isotype control, 10 mg/kg), anti–4-1BB (1 mg/kg), anti–PD-1 (10 mg/kg), or anti–LAG-3 (10 mg/kg) mAbs in a volume of 200 mL, alone or in combinations as indicated in the figure, on days 9 and 14 (indicated by arrows). Statistics were generated using two-way ANOVA, , P <

0.05; , P < 0.01; , P < 0.001; and , P < 0.0001, when comparing groups as indicated by the vertical lines (29).

Similar results were observed in mice inoculated with H22 hepatocellular carcinoma cells or B16 melanoma cells, where 4-1BBL in combination with soluble PD-1 to inhibit the PD-L1/PD-1 pathway produced synergistic immune response compared to monotherapy with either agent (29).

Based on preclinical data, a theoretical risk for the anti-4-1BB mAb class is that treatment causes liver inflammation (8); however, significant liver toxicity has not been noted with utomilumab (17). In a preclinical study, Melero *et al*. (35) injected small doses of the antibody intratumorally as CD137 expression is strongly favored in tumor-infiltrating lymphocytes (TILs) as a result of a hypoxia-inducible factor (HIF)-1α–dependent response to hypoxia. Combined treatments of minute doses of anti-CD137 mAb given intratumorally and anti-B7-H1 mAb given systemically achieved complete regressions in 10 of 12 CT26-bearing BALB/c mice. These cured mice were immune to a rechallenge with CT26 cells 3 months later as a result of systemic immune memory. This method of administration of the agents also helped to avoid liver inflammation (35). Limitation of such liver side effects while keeping therapeutic efficacy would be a remarkable advantage.

1.3.1.2 Combination of PF-04518600 (Anti-OX40 mAb) with Avelumab

Despite the remarkable responses that have been reported in certain murine models treated with either anti-PD-1 or OX40 mAb, monotherapies are generally ineffective against poorly immunogenic tumors like ID8 ovarian cancer, signifying a need for combination therapies (36). Further, OX40 ligation enhances IFN-γ production by T cells, which induces PD-L1 expression by the cancerous cells (21). Taken together, blockade of PD-1/PD-L1 pathway is likely to compliment the therapeutic efficacy of OX40-driven effector lymphocytes within the tumor microenvironment. Existing body of evidence suggests that blockade of PD-1/PD-L1 may synergize with OX40 agonists and may be well suited for tumors that express high levels of PD-L1.

In a recent report, Guo and colleagues observed that combined anti-PD-1/OX40 mAb treatment markedly inhibited tumor outgrowth in a murine ID8 ovarian cancer model

(Figure 4) and significantly increased progression-free survival (PFS) of mice with 60% of mice tumor free 90 days after tumor inoculation (p,0.001, combined mAb compared to single or control mAb) (37). Combined anti-PD-1/OX40 mAb treatment fostered a local immunostimulatory microenvironment and tumor protection was associated with a systemic immune response with memory and antigen specificity and required CD4+ cells and CD8+ T cells. The anti-PD-1/OX40 mAb treatment increased CD4+ and CD8+ cells and decreased immunosuppressive regulatory T cells and myeloid suppressor cells (37). The combined treatment induced a specific and long-lasting anti-tumor immune response in treated mice as they were resistant to a subsequent rechallenge intraperitoneal or subcutaneously. with the same cell line (37).

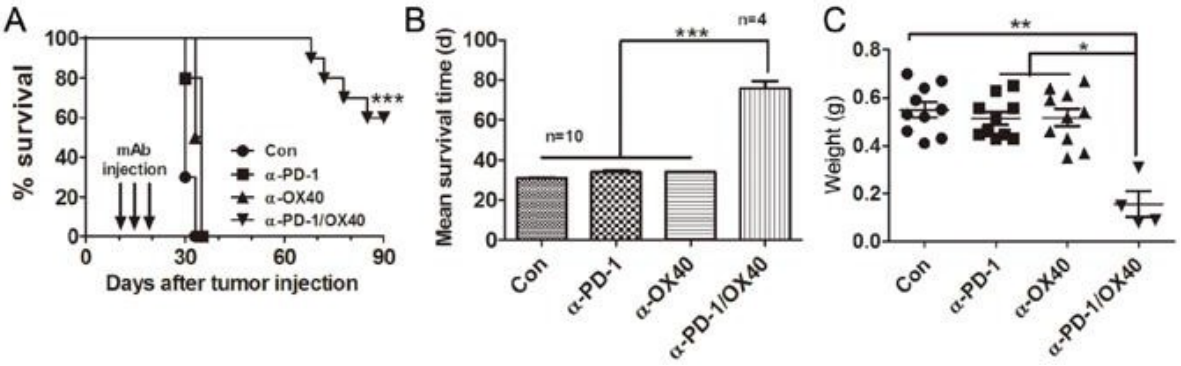

Figure 4: Treatment of combined anti-PD-1/OX40 mAb induced tumor-specific immunity against ID8 ovarian cancer. (A) Mice (10 mice per group) transplanted intraperitoneal with 16106 ID8 cells 10 day before were treated thrice with 200 mg of control, anti-PD-1, anti-OX40 and anti-PD-1/OX40 mAb at 4 days interval and overall survival of mice was recorded. **(B)** Mean survival time of mice with tumor growth was calculated. **(C)** The peritoneal tumor masses was weighed when mice were euthanized with each dot representing each mouse. ***P,0.001, combined mAb vs control or single mAb treated mice (32).

Though the combination is likely to produce increased toxicity and irAEs, synergy between anti-OX40 therapy and checkpoint blockade may yield objective responses at lower dosages than are required when each drug is used as a monotherapy (21).

1.3.1.3 Combination of Utomilumab and PF-4518600 with Avelumab

Multiple complimentary interventions enhances the possibility of effective anti-tumor immunity. One possibility is the triple combination of utomilumab (4-1BB mAb), PF-4518600 (OX40 mAb) with avelumab as all three antibodies have demonstrated signs of efficacy when administered as monotherapies (10, 21, 38) or as doublets (33, 37). Further, simultaneous dual costimulation through 4-1BB and OX40 synergistically

induced specific CD8 T cell clonal expansion in several *in vivo* models, contributing to effective tumor control in a fibrosarcoma model (39). The anti-tumor activity of this dual combination was due to enhanced effector T cell accumulation that was independent of the presence of CD4 Tcells (39), suggesting the possibility of development of an efficacious treatment under immunocompromised conditions.

In a preclinical study (40), autochthonous hepatocellular carcinoma in c-myc transgenic mice that are highly resistant to immunotherapy approaches was used to evaluate the efficacy of the combination of these 3 antibodies. Synergistic anti-tumor activity and statistically significant prolonged survival was observed in mice treated with the triple combination than any of the drugs as monotherapy (Figure 5). The mice were also selectively depleted of CD8β+ T lymphocytes or CD4+ T cells at the time of therapy instigation. It was observed that only CD8+ cells were absolutely required to prolong survival (40). Higher content of CD8+ and CD4+ T lymphocytes with brighter surface expression of CD137, OX40, and PD-1 were observed in the cell suspension from the livers of the mice treated with Combo 3. Though Tregs were also upregulated, CD8+/Treg ratios were clearly increased upon Combo3 treatment (Figure 6).

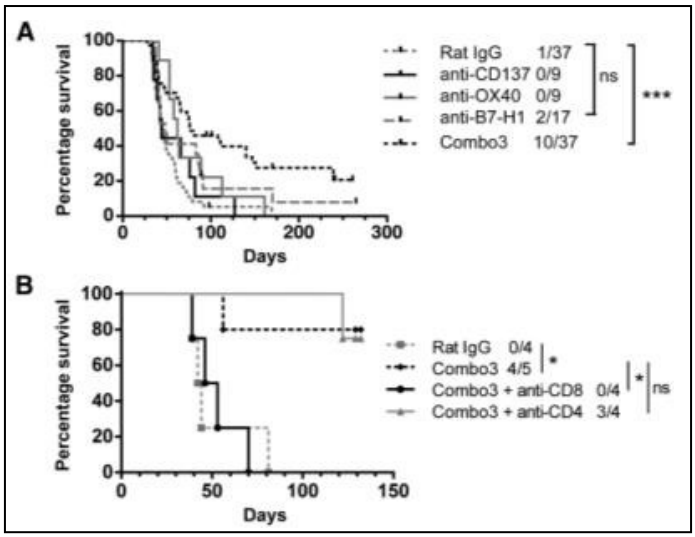

Figure 5. The triple combination is efficacious and dependent on CD8+ lymphocytes. **(A)** 100 mg of individual antibodies were dosed to the indicated groups. **(B)** Mice were depleted with anti-CD8b or anti-CD4 mAbs. Fractions of surviving mice at day 250 (A) and 150 (B) in the indicated groups are provided in the legend. P (log rank test) ns, non-significant; *P <0.05; ***, P <0.001) (34).

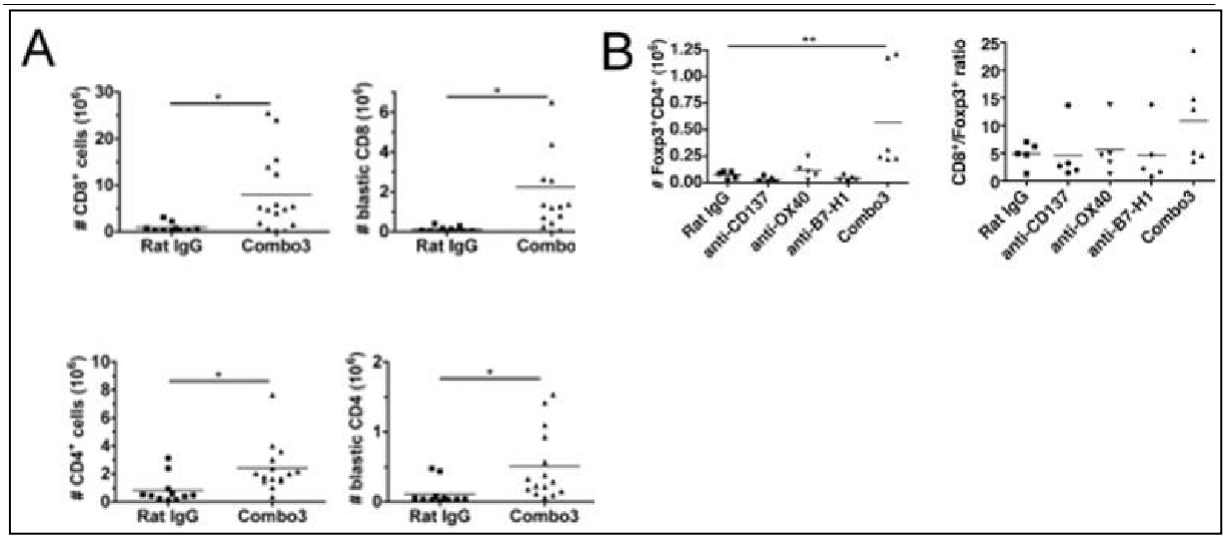

Figure 6: Combo3 treatment induces infiltrates of blastic T lymphocytes and increases the CD8/Treg ratio. (A) Absolute numbers of retrieved CD8+ and CD4+ lymphocytes for the indicated treatment groups and the number of blastic cells gated. **(B)** Absolute numbers of Foxp3+ CD4+ lymphocytes and the ratio of the absolute numbers of CD8+ lymphocytes to Foxp3+ CD4+ regulatory T cells. #, absolute number of cells. *, $P < 0.05$; **, $P < 0.01$ (34).

1.3.2 Combination of Checkpoint Agonist(s) and Radiotherapy with Avelumab

Therapies that target 4-1BB, OX40, and PD-1/PD-L1 pathway , either as single agent (10, 21, 38), doublet (33, 37, 39), or triplet (40), have exhibited anti-tumor activity in a number of model systems. Likewise, radiotherapy is known to awaken and augment dormant tumor responses (8) in non-immunogenic and weakly immunogenic tumors as radiation-induced cell death dramatically increases antigen presentation and T-cell priming in draining lymphoid tissues, leading to reduction/eradication of the primary tumor or distant metastasis in a CD8+ T cell-dependent fashion (41). But, the abscopal effect may be dampened by radiation-induced activation of immunesuppressive signals through upregulation of PD-L1 in the tumor microenvironment (42).

Nevertheless, the abscopal effect of radiation has been restored by effective suppression of immune suppresive signals through PD-L1 blockade (42). Together, immunotherapy and radiation therapy complement each other. Checkpoint agonist promotes expansion of T cells; while radiation improves antigen presentation, and primes an immune response; and, PD-L1 blockade reverses T-cell exhaustion to

alleviate depression in the CD8/Treg ratio (43). Further, radiation and immunotherapy have fundamentally different mechanisms of action, different cellular targets and non-overlapping toxicities (44). These findings support the concept that combining radiation and immunotherapy can lead to significant improvements in treatment outcomes.

1.3.2.1 Combination of PF-5082566 and Radiotherapy with Avelumab

In a preclinical study, the therapeutic efficacy of anti- 4-1BB mAbs in combination with radiation therapy was evaluated in murine lung (M109) and breast (EMT6) carcinoma models (45). 4-1BB mAbs caused modest regression of murine lung tumors, but significantly delayed the growth of breast tumors (Figure 7). However, when combined with irradiation, enhanced anti-tumor activity was observed in lung models, albeit only at the highest evaluated radiation dose. On the contrary, enhanced anti-tumor activity was observed in breast models at all radiation doses.

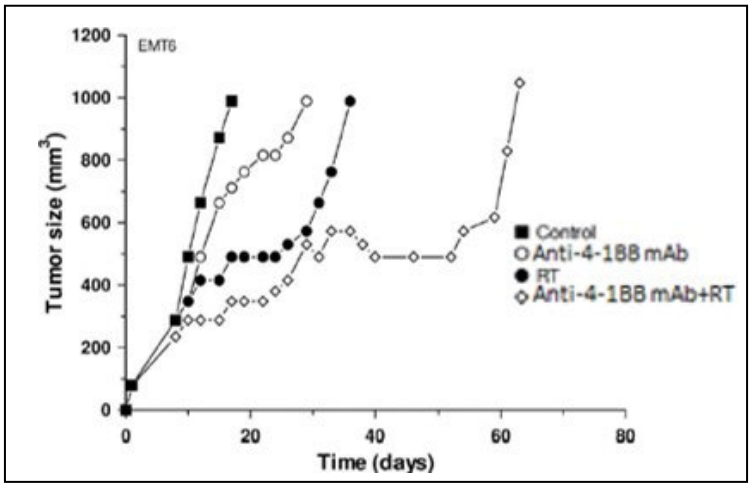

Figure 7: Median tumor response curves of EMT6 tumors exposed to 4-1BB antibodies, fractionated radiotherapy, or the combination of both treatments (39).

Though combined treatment with checkpoint agonist(s) and radiotherapy improved treatment outcomes in murine models and clinical trials (43), resistance to therapy was frequently reported as radiation-induced upregulation of PD-L1 expression in the tumor microenvironment, promotes T cell exhaustion resulting in tumor relapse after radiotherapy (46). Addition of an anti-PD-L1 was found to inhibit resistance to radiotherapy, conferring long term immunity. In a preclinical study, irradiation was combined with anti-PD-L1 antibody to treat 2 allograft tumor models, TUBO breast

cancer and MC38 colon cancer (Figure 8) (47). The combination treatment not only produced synergistic anti- tumor immunity, but also induced an abscopal effect in both tumor models, suggesting that the combination of irradiation and anti-PD-L1 antibody can potentially control both local and distal tumors.

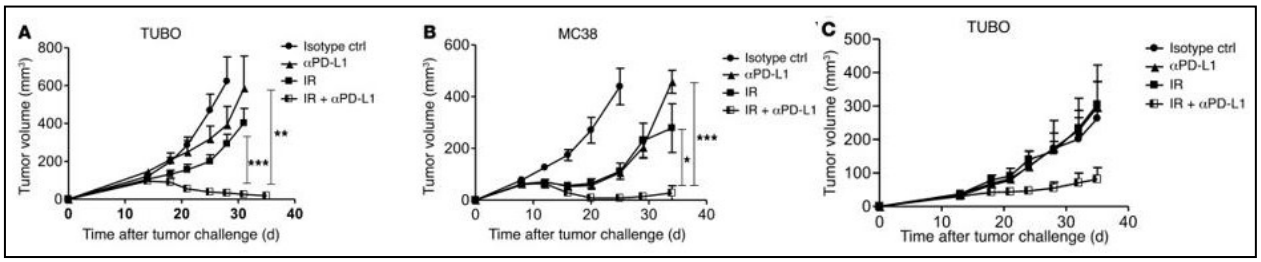

Figure 8: Irradiation (IR) and PD-L1 blockade synergistically amplify the antitumor effect. (A) Combination of anti–PD-L1 (αPD-L1) and IR significantly enhanced the inhibition of TUBO tumor growth. ***P*< 0.01; ****P*< 0.001. **(B)** Combination therapy greatly delayed MC38 tumor growth compared with single treatments. **P*< 0.05; ****P*< 0.001. **(C)** Systemic effect of combination treatment greatly reduced the growth of secondary tumors (41).

Similarly, 4-1BB combined with radiation therapy exhibited anti-tumor activity in orthotopic AT-3 triple-negative mammary tumor models (Figure 9) (48). However, enhanced growth inhibition was not possible due to PD-L1 expression by these tumors, which were largely unaffected by radiation.

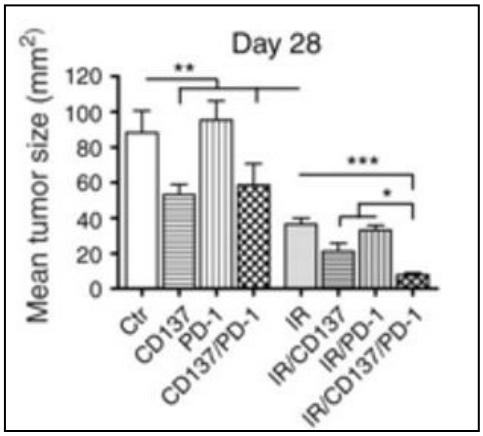

Figure 9: Rejection of established subcutaneous AT-3 tumors with radiotherapy and α-CD137/α-PD-1 mAbs. Mean tumor sizes in each group at day 28 post-tumor inoculation. *, *P* < 0.05; **, *P* < 0.01; and ***,*P*< 0.001 (42).

Surprisingly, all mice bearing established orthotopic AT-3 mammary tumors were cured when antagonistic α-PD-1 mAb was added to the combination of radiotherapy and anti-4-1BB mAb treatment (48).

Also, equally robust anti-tumor responses was reported in some of the most malignant tumor models treated with triple combination that included 4-1BB activation, CTLA-4 blockade, and focal radiation therapy (49). For example, survival significantly improved from 24 days when treated with focal radiation therapy to 67 days (p,0.05 vs. all other treatment modalities) with the triple combination in an orthotopic mouse model of glioma (Figure 10) by a CD4+ T cell dependent mechanism, with long-term survival in at least 50% of the mice (49).

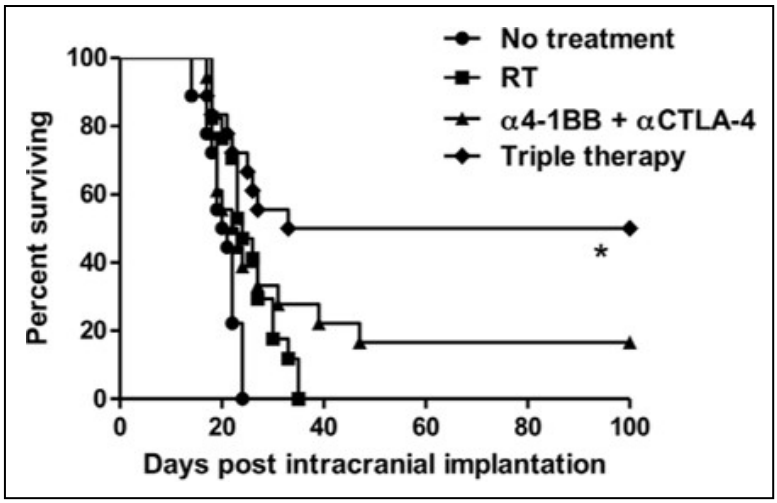

Figure 10. Kaplan Meier survival curves for double immunotherapy and triple therapy (n = 18/group). Treatment with triple therapy was superior to double immunotherapy with anti-4-1BB and anti-CTLA-4 antibodies (p,0.05), focal RT alone (p,0.01) and untreated mice (p,0.001) (43).

Together, these results forms the basis for the rational design of the combination of utomilumab (4-1BB), radiation, and avelumab.

1.3.2.2 Combination of PF-04518600 and Radiotherapy with Avelumab

In a mouse model of using lung cancer cell line 3LL (50), treatment with radiation therapy increased the median survival significantly in a CD8 dependent manner (21 day vs. 47 day $P<0.001$). Following CD8 depletion, though the median survival decreased, it was significantly better than no treatment ($P<0.005$). In order to improve the efficacy of radiation therapy, mice bearing 3LL tumors were treated with focal radiation and a single dose of OX40 or control antibody 1 day after the first radiation dose. It was reported that the combination of radiation and OX40 significantly

increased survival compared with either agent alone (Figure 11) and a significant proportion of mice were tumor free and resistant to rechallenge (50).

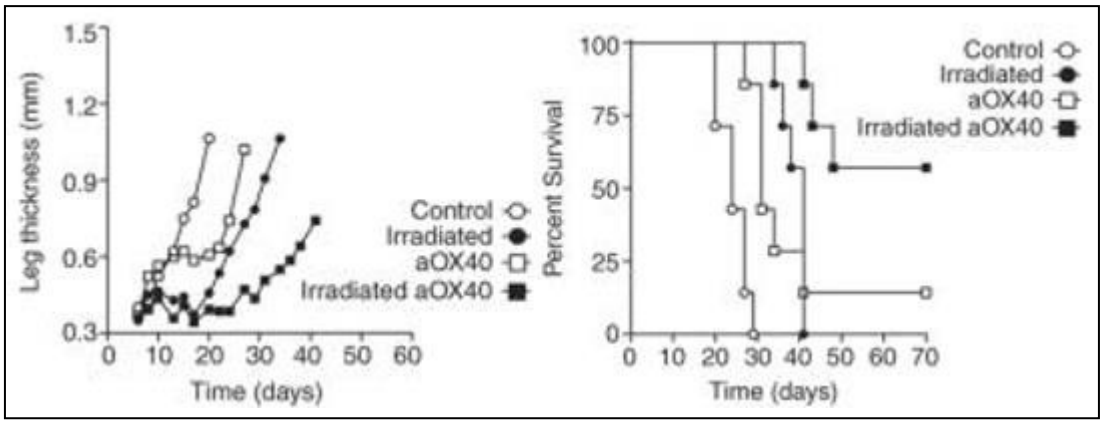

Figure 11: Response to combination of radiation and OX40 mAb in 3LL tumors. Graph shows mean leg thickness and survival of tumor-bearing mice (44).

In another murine lung cancer model, combination of anti-OX40 mAb and radiotherapy induced antigen specific cytotoxicity independent of CD4+ T cells, resulting in a high rate of CD8+ T cell-dependent complete cure rate (in 6 of 8 mice vs none) and prolonged survival compared to those treated with either radiotherapy or anti-OX40 mAb (Figure 12) (51). Irradiation enhanced the amount of OX40+ CD8+ Tcells in the draining lymph node. Further, mice treated with anti-OX40 mAb in combination with radiotherapy resisted tumor rechallenge due to development of immunological memory.

Though radiation therapy may upregulate expression of PD-L1 in tumors (46), concomitant blockade of the PD-1/PD-L1 pathway can complement treatment with OX40 mAb and radiotherapy as remarkable response has been reported with this combination in orthotopic AT-3 mammary tumors (48).

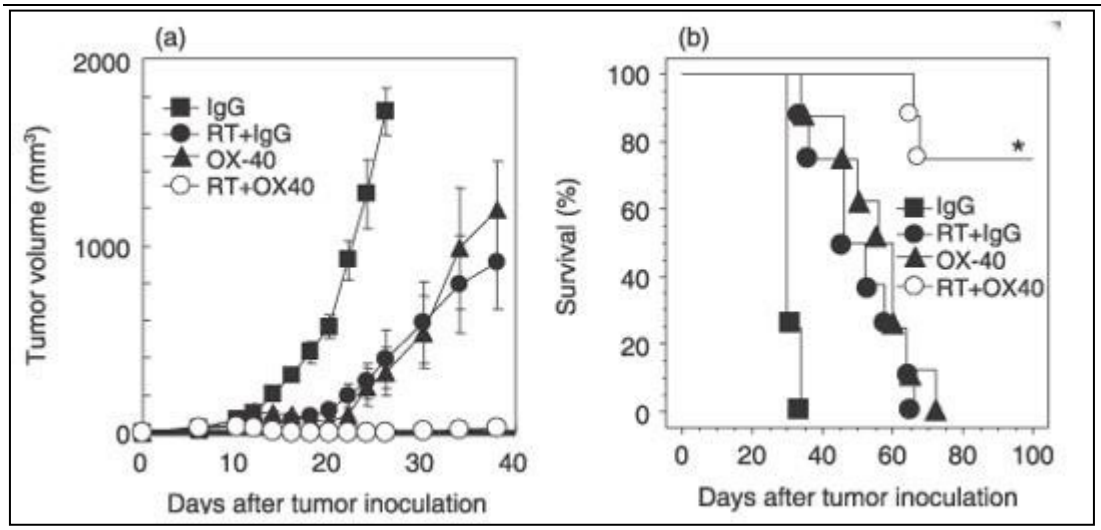

Figure 12: Anti-OX40 monoclonal antibody (mAb) in combination with radiotherapy (RT) (A) Tumor volume in mice treated with control IgG, or local radiotherapy (20 Gray (Gy)) with control IgG, anti-OX40 mAb, or radiotherapy (20 Gy) with intratumoral injection of anti-OX40 mAb. **(B)** The survival of mice following various protocols is shown. **P*=0.001 versus the anti-OX40 mAb alone group, and *P*<0.001 versus the RT+IgG group (45).

1.3.2.3 Combination of Utomilumab, PF-04518600, and Radiotherapy with Avelumab

Collectively, existing data from preclinical studies discussed above indicate that concomitant targeting of immunostimulatory and immunoinhibitory checkpoints with immunomodulatory antibodies can enhance the tumor control potential of radiotherapy. This forms the basis for the rational design of the combination of utomilumab (4-1BB), PF-04518600 (OX40), radiotherapy, and avelumab.

1.4 Potential for Overlapping Toxicities

The combination drugs used in this protocol have associated toxicities that may overlap with those of checkpoint agonists. The adverse events associated with each study drug are detailed in the respective Investigator's Brochure.

For patients in the radiation arms, radiation treatment in abdomen that could result in bowel radiation could aggravate colitis (52).

1.5 Protocol Arm Closures

In Protocol Version 07, Arm G of avelumab, radiation and cisplatin was closed due to the inability to enroll patients. Closure of Arm G was decided in the September 2018 Joint Steering Committee meeting. The protocol was revised at that time to remove all language regarding Arm G.

In Protocol Version 09, Arm E of avelumab, PF-04518600 (OX40), and radiation; and Arm F of avelumab, utomilumab (4-1BB), PF-04518600 (OX40), and radiation were closed due to emerging data, which does not support combination of two T cell agonists. Closure of Arm F was decided in the November 2019 Joint Steering Committee meeting. Closure of Arm E was decided in the January 2020 meeting between Pfizer and the PI. The protocol was revised at that time to remove all language regarding Arms E and F.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- For Arm D, to establish the safety, tolerability, and dose-limiting toxicities (DLTs) of different treatment combinations of avelumab when administered in combination with a checkpoint agonist with radiation in patients with metastatic solid tumors in order to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 dose (RP2D).
- To correlate pre- and post-treatment CD8 expression with clinical benefit (complete response [CR], partial response [PR], or stable disease [SD] for > 6 months).

2.1.2 Secondary Objectives

- To evaluate the efficacy of the different treatment combinations in patients with metastatic solid tumors by assessing objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and immune-related RECIST (irRECIST)(53).
- To evaluate the efficacy of the different treatment combinations in patients with metastatic solid tumors by assessing progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

2.1.3 Exploratory Objectives

- To understand the mechanism of action of the avelumab plus an immune modulator combination, as well as potential mechanisms of resistance.
- To characterize the effect of avelumab combinations on immune biomarkers in peripheral blood and tumor tissue obtained from subjects pre- and post-treatment.
- To compare the response in irradiated versus non-irradiated lesions in Arm D.
- To investigate immune biomarkers that are potentially predictive of response and resistance with the combination of avelumab and an immune modulator.

2.2 Endpoints

2.2.1 Primary Endpoints

- Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
- Evaluation of CD8 biomarkers from tumor and blood biospecimens.

2.2.2 Secondary and Exploratory Endpoints

- Objective response rate determined by radiographic disease assessments per RECIST v1.1 and irRECIST.
- Progression-free survival, defined as the time from Cycle 1 start date until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1 and irRECIST, or death due to any cause, if occurring sooner than progression.
- Duration of response determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1 and irRECIST, or death due to any cause, if occurring sooner than progression.
- Overall survival determined from the Cycle 1 start date until death due to any cause.
- Response data in irradiated and non-irradiated lesions.
- Evaluation of various immune biomarkers from tumor and blood biospecimens.

3.0 STUDY DESIGN

3.1 Study Overview

Currently, this is a single-center, open-label, four-arm Phase I/II study of avelumab in combination with additional therapy. In Arms A, B, and C, avelumab will be administered in combination with a checkpoint agonist(s) in patients with advanced or metastatic solid tumors. In Arm D, avelumab will be administered in combination with a checkpoint agonist with radiation in patients with advanced or metastatic solid tumors.

As of Amendment Version 09, there are 4 treatment arms in this study:

- Arm A: Avelumab + Utomilumab (4-1BB)
- Arm B: Avelumab + PF-04518600 (OX40)
- Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)
- Arm D: Avelumab + Utomilumab (4-1BB) + XRT.

Arm D will have two phases: 1) Dose De-Escalation Phase; and, 2) Maximum-Tolerated Dose (MTD) Expansion Phase. In Arm A: Avelumab + Utomilumab (4-1BB) and Arm B: Avelumab + PF-04518600 (OX40), and Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40), the known MTDs from the ongoing studies enrolling patients for treatment with utomilumab (4-1BB) and avelumab and PF-04518600 (OX40) and avelumab will be provided by Pfizer. Therefore, patients in Arms A-C will be enrolled on MTD expansion cohorts only in Phase I part of the study.

All study treatment arms will undergo a 28-day study cycle.

3.1.1 Part I: Dose Escalation or Dose De-Escalation (Part D Only)

A standard “3+3” study design will be used for this study. Patients enrolled at each dose level in Arm D will be evaluated for dose-limiting toxicity (DLT) for the purpose of determining the MTD. For Arm D, dose de-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 2 patients with DLT out of at least six patients in the cohort. Management

and dose modifications associated with adverse events are outlined in subsequent protocol sections.

Two dose levels may be examined during the dose de-escalation with a standard “3+3” design, and a total of 3-6 patients will be enrolled per dose level. The de-escalation will be conducted as shown in Table 2 to evaluate the safety, tolerability, and MTD in patients with or metastatic solid tumors.

Table 2: Dosing Pattern of Avelumab in Combination with Other Cancer Immunotherapies with or without XRT.

Categories	Treatment Arm	Treatment	De-Escalation	Fixed Dose
I. Avelumab + Checkpoint Agonist(s)	**A**	Avelumab + Utomilumab (4-1BB)	MTD from Pfizer	
	B	Avelumab + PF-04518600 (OX40)	MTD from Pfizer	
	C	Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)	MTD from Pfizer	
II. Avelumab + Checkpoint Agonist(s) + XRT	**D**	Avelumab + Utomilumab (4-1BB) + XRT	XRT**	Utomilumab (4-1BB) + Avelumab

**Dose de-escalation

Arm D will have de-escalation of radiation schedules.

3.1.2 Part II: MTD Expansion

Once the MTD is determined, an additional 14 patients will be enrolled on the MTD expansion cohort for additional characterization of safety and response, and for correlative studies to establish the recommended phase 2 dose (RP2D) for each combination.

For patients enrolled in the MTD expansions of Arms A-C, biopsies, blood samples will be collected at baseline, between Cycle 1 Day 12-15 (prior to study drug dosing), prior to Cycle 3 Day 1 study drug dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission) to evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers.

For patients enrolled in the MTD expansion of Arm D, biopsies will be collected at baseline, prior to Cycle 3 Day 1 dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission). For patients enrolled in the MTD expansion of Arm D, blood samples will be collected at baseline, prior to Cycle 1 Day 1 dosing, prior to Cycle 1 Day 15 dosing, prior to Cycle 2 Day 1 dosing, prior to Cycle 3 Day 1, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission). We will also evaluate mutation burden and immune scoring. Cell free DNA from patient's blood samples will also be analyzed.

Once the pharmacodynamic, toxicity, and efficacy data is available, the Investigational Cancer Therapeutics team will collaborate with Pfizer and disease-specific experts in each department to a) identify the most effective combination dose for these tumor types, as well as other tumor types of interest, based on toxicity, biology, and target interaction, and b) evaluate the most appropriate methods for determining progression-free survival and other clinical variables that may vary across tumor types.

3.2 Study Treatment Arms

All study treatment arms will have a 28 day cycle. Study drug administration may be delayed for toxicity according to protocol Section 5.2.4.

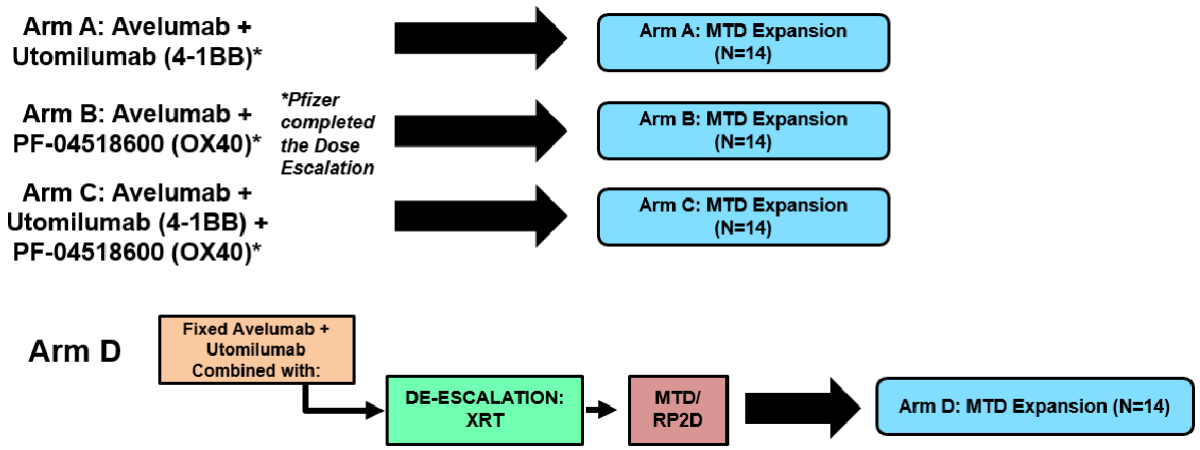

Figure 13: Study Treatment Arms

3.2.1 Arm A: Avelumab + Utomilumab (4-1BB)

In Arm A of avelumab and utomilumab, there will be no dose escalation. The escalation of avelumab and utomilumab will be performed under a previously conducted Pfizer protocol.

The Arm A MTD expansion will enroll up to 14 patients at the established safe dose for additional safety and correlative studies to establish the RP2D for this combination.

Utomilumab will be administered at the fixed flat dose of 100 milligrams (mg) intravenously (IV) on Day 1 of each 28-day cycle or every 4 weeks. Avelumab will be administered at the fixed dose of 10 mg/kg IV on Day 15 of Cycle 1 and Days 1 and Day 15 of subsequent cycles. Premedications will be administered per institutional standard.

On days when both avelumab and utomilumab are administered, avelumab will be administered first.

Patients will be restaged at the end of every two cycles and tumor response evaluation will be based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune-related RECIST (irRECIST). Patients may be allowed to continue treatment

after two cycles of avelumab combinations if there is continued clinical response or disease stabilization and patients do not have significant toxicities. A patient may continue treatment on this combination therapy until the patient experiences confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, and/or treatment is discontinued following investigator's decision to withdraw the patient, pregnancy, patient withdraws consent, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Table 3: Dosing for Arm A: Avelumab + Utomilumab (4-1BB)

Dose Level	Utomilumab (4-1BB) *IV* *Every 4 Weeks* *Starting Cycle 1 Day 1*	Avelumab IV *Every 2 Weeks* *Starting Cycle 1 Day 15*
MTD/RP2D Determined by Pfizer	100 mg	10 mg/kg

As of Amendment Version 06, the avelumab dosing for Arm A was revised; therefore, a new cohort of 14 patients was enrolled.

3.2.2 Arm B: Avelumab + PF-04518600 (OX40)

In Arm B of avelumab and PF-04518600 (OX40), there will be no dose escalation. The escalation of avelumab and PF-04518600 will be performed under a previously conducted Pfizer protocol.

The Arm B MTD expansion will enroll up to 14 patients at the established safe dose for additional safety and correlative studies to establish the RP2D for this combination.

PF-04518600 (OX40) will be administered at the fixed dose of 0.3 mg/kg IV on Days 1 and 15 of each 28-day cycle or every 2 weeks. Avelumab will be administered at the fixed dose of 10 mg/kg IV on Day 15 of Cycle 1 and Days 1 and 15 of subsequent cycles. Premedications will be administered per institutional standard.

On days when both avelumab and PF-04518600 are administered, avelumab will be administered first.

Patients will be restaged at the end of every two cycles and tumor response evaluation will be based on RECIST 1.1 and irRECIST. Patients may be allowed to continue treatment after two cycles of avelumab combinations if there is continued clinical response or disease stabilization and patients do not have significant toxicities. A patient may continue treatment on this combination therapy until the patient experiences confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, and/or treatment is discontinued following investigator's decision to withdraw the patient, pregnancy, patient withdraws consent, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Table 4: Dosing for Arm B: Avelumab + PF-04518600 (OX40)

Dose Level	PF-04518600 (OX40) IV *Every 2 Weeks Starting Cycle 1 Day 1*	Avelumab IV *Every 2 Weeks Starting Cycle 1 Day 15*
MTD/RP2D Determined by Pfizer	0.3 mg/kg	10 mg/kg

As of Amendment Version 06, the avelumab dosing for Arm B was revised; therefore, a new cohort of 14 patients was enrolled.

3.2.3 Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)

As of Amendment Version 05, in Arm C of avelumab, utomilumab (4-1BB), and PF-04518600 (OX40), there will be no dose escalation. The escalation of PF-04518600 (OX40) in combination with fixed doses of avelumab and utomilumab (4-1BB) was performed under a previously conducted Pfizer protocol.

The Arm C MTD expansion will enroll up to 14 patients at the established safe dose for additional safety and correlative studies to establish the RP2D for this combination.

PF-04518600 (OX40) will be administered at the fixed dose of 0.3 mg/kg by IV on Days 1 and 15 of each 28-day cycle or every 2 weeks. Utomilumab (4-1BB) will be administered at the fixed flat dose of 20 mg IV on Day 1 of each 28-day cycle or every 4 weeks. Avelumab will be administered at the fixed dose of 10 mg/kg IV on Day 15 of

Cycle 1 and Days 1 and 15 of subsequent cycles. Premedications will be administered per institutional standard.

On days when avelumab, utomilumab, and PF-04518600 are administered, avelumab will be administered first followed by utomilumab then PF-04518600.

Patients will be restaged at the end of every two cycles and tumor response evaluation will be based on RECIST 1.1 and irRECIST. Patients may be allowed to continue treatment after two cycles of avelumab combinations if there is continued clinical response or disease stabilization and patients do not have significant toxicities. A patient may continue treatment on this combination therapy until the patient experiences confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, and/or treatment is discontinued following investigator's decision to withdraw the patient, pregnancy, patient withdraws consent, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Table 5: Dosing for Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)

Dose Level	**PF-04518600 (OX40) IV *Every 2 Weeks Starting Cycle 1 Day 1***	**Utomilumab (4-1BB) *IV Every 4 Weeks Starting Cycle 1 Day 1***	**Avelumab IV *Every 2 Weeks Starting Cycle 1 Day 15***
MTD/RP2D Determined by Pfizer	0.3 mg/kg	20 mg	10 mg/kg

As of Amendment Version 06, the avelumab dosing for Arm C was revised; therefore, a new cohort of 14 patients was enrolled.

3.2.4 Arm D: Avelumab + Utomilumab (4-1BB) + Radiation

In the dose escalation phase, the dose of radiation will be de-escalated in combination with fixed doses of utomilumab (4-1BB) and avelumab to evaluate the safety, tolerability, and MTD in patients with advanced solid tumors.

Once the MTD or RP2D is determined, the Arm D MTD expansion will enroll up to 14 patients at the previously established safe dose for additional safety and correlative studies to establish the RP2D for this combination.

Radiation will be administered to 1-3 metastatic sites. This will be de-escalated from a total of 24 Gy to 21 Gy. The technique will be stereotactic radiation via intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT). The radiation lead-in will occur within Days -5 to -1 with a +/- 3 day window. There will be 3 fractions or days of radiation. In all cases, the radiation must initiate and end within the radiation lead-time. Cycle 1 Day 1 study drug treatment should begin within 3 days of last dose of radiation.

Utomilumab (4-1BB) will be administered at the fixed flat dose of 100 mg IV on Day 1 of each 28-day cycle or every 4 weeks. Avelumab will be administered at the fixed dose of 10 mg/kg IV on Day 15 of Cycle 1 and Days 1 and 15 of each subsequent 28-day cycle or every 2 weeks. Premedications will be administered per institutional standard.

On days when both avelumab and utomilumab are administered, avelumab will be administered first.

Patients will be restaged at the end of every two cycles and tumor response evaluation will be based on RECIST 1.1 and irRECIST. Patients may be allowed to continue treatment after two cycles of avelumab combinations if there is continued clinical response or disease stabilization and patients do not have significant toxicities. Following radiation, a patient may continue treatment on this combination therapy until the patient experiences confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, and/or treatment is discontinued following investigator’s decision to withdraw the patient, pregnancy, patient withdraws consent, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Table 6: Dosing for Arm D: Avelumab + Utomilumab (4-1BB) + Radiation

Dose Level	Radiation Days -5 to -1	Utomilumab (4-1BB) *IV Every 4 Weeks Starting Cycle 1 Day 1*	Avelumab IV *Every 2 Weeks Starting Cycle 1 Day 15*
1 (Start)	24 Gy in 8 Gy / fraction for 3 fractions	100 mg	10 mg/kg
-1	21 Gy in 7 Gy/ fraction for 3 fractions	100 mg	10 mg/kg

As of Amendment Version 09, the avelumab and radiation dosing for Arm D was revised; therefore, the dose de-escalation was re-started.

3.3 Dose-Limiting Toxicity (DLT) Definition

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose de-escalation, a DLT is defined as any of the following adverse events occurring in the first 56 days following Cycle 1 Day 1 (dosing of PF-04518600 (OX40) and/ or Utomilumab (4-1BB)) of study participation during the dose de-escalation, unless there is a clear alternative explanation (eg, related to underlying disease/ progression):

- Discontinuation of a patient due a toxicity that is at least possibly study drug(s) and/or radiation related before completing DLT period.
- Delay by more than 4 weeks (28 days) in receiving the next scheduled cycle due to persisting toxicities attributable to the study drug(s) and/or radiation.
- Non Hematologic (all will be graded according to CTCAEv4.03 criteria):
    - Grade >/= 3 nausea/vomiting or diarrhea lasting >/= 72 hours while taking optimal supportive medications;
    - Grade >/= 3 fatigue lasting >/=7 days;
    - Grade >/= 2 pneumonitis lasting >/= 7 days despite treatment with corticosteroids;
    - Grade >/=3 rash lasting >/= 7 days despite treatment;
    - Grade >/= 3 immune related toxicities lasting >/= 7 days despite treatment with corticosteroids;

- Any other Grade >/=3 non-hematological toxicity (except for electrolytes abnormalities that are reversible and asymptomatic or hair loss which is not dose-limiting);
- Grade >/= 3 AST, ALT, or total bilirubin elevation lasting >/= 7 days.

- Hematologic:
  - Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm^3] lasting >/=7 days;
  - Febrile neutropenia (ANC<1000/mm^3 with a single temperature >/= 38.3ºC or sustained temperature of >38°C for over 1 hour);
  - Grade >/=3 thrombocytopenia associated with bleeding, or grade 4 thrombocytopenia;
  - Grade 4 anemia.

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.

During the dose de-escalation portion (Arm D) of the study, patients who missed any doses during the DLT period for reasons unrelated to study drug are not evaluable for DLT and will be replaced.
For both de-escalation (up to 4 cycles) and expansion (up to 6 cycles) phases of the study, if a patient comes off study unrelated to toxicity or progression of disease (such as intercurrent disease or social reasons), the patient for that cohort will be replaced.

The expansion cohort for each arm will be stopped early if the aggregate DLT rate > 33% for that particular arm. The aggregate DLT rate for each arm will include patients that were treated at the same dose level in the dose escalation or de-escalation phase.

In rare instances, an event may fall within the definition of a DLT as defined above but the event may be considered not a DLT (eg: not clinically meaningful/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 which do not meet the definition of a DLT but are concerning to the PI, may be then considered to be DLTs.

In the event that a DLT is at least possibly related to the study drug(s) occurs, patients will halt treatment with the combination until symptoms resolve to the grade outlined in Section 5.2.4. Study drug(s) may be restarted as described in Section 5.2.4.

3.4 Maximum Tolerated Dose (MTD) Definition

In the Dose De-Escalation cohorts, patients will be assigned sequentially into cohorts of up to six patients in each cohort. Three to six patients will initially be enrolled in each cohort for DLT observation. A total of six patients will be enrolled in a cohort in the event that a DLT is observed in one of the first three 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 six patients in the cohort. Management and dose modifications associated with adverse events are outlined in subsequent protocol sections.

For all Arms, the DLT assessment window is 56 days (from Cycle 1 Day 1). In the absence of DLTs, patients continue consecutive treatment. For patients who experience a DLT, they may continue treatment with modifications if the toxicity resolves and at discretion of the attending physician and 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 combinations after the first indication of progressive disease until a confirmation 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 toxicity at the discretion of the investigator will be evaluated on a case-by-case basis upon consultation between the IND Office, Pfizer, and the principal investigator. At minimum, a review and discussion of potential delayed onset of significant toxicity will take place at each cohort 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 three patients in a cohort have completed 56 days (2 cycles) of dosing (from Cycle 1 Day 1). Prior to advancing/changing dose levels, a cohort summary will be completed and submitted to the IND Medical Monitor for review and approval.

Dose de-escalation decisions will be made in accordance with a standard “3+3” study design using the rules below:

Table 7.

Number of Patients with DLT* at a Given Dose Level (assessed independent for each of arm)	**De-Escalation Decision Rule**
0 out of 3	Enter 3 more patients at this dose level
≥2	Dose de-escalation will occur. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, then this is the maximum tolerated dose (MTD). If 1 or more of this group suffer DLT, then dose de-escalation will occur. Three additional patients will be entered at the next lowest dose level.
MTD: The highest dose at which no more than 1 of 6 evaluable patients has had a DLT. Six patients should be treated before the dose is declared the MTD.	

Dose de-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 2 patients with DLT out of at least six patients in the cohort. The recommended Phase 2 dose (RP2D) will be based on safety and preliminary efficacy data from the dose escalation and dose expansion cohorts.

All patients will be treated at the highest current dose level. All enrolled participants will be considered in the DLT analysis. If a DLT occurs in a cohort with 3 patients within first 56 days (from Cycle 1 Day 1), 3 additional patients will be enrolled in that cohort. If at any time more than or equal to one third (33%) of the participants at a dose level experience DLT, the MTD will be reassessed and the next lowest dose level for the combination therapy will be considered the MTD.

4.0 PATIENT SELECTION

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

Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study. Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for enrollment into the study:

The baseline tumor assessment must have taken place within 28 days prior to start of treatment. Under no circumstances are patients, who were once enrolled and treated in this study, permitted to be re-enrolled into the same study. If patients screenfail prior to receiving treatment, the patient may be re-enrolled if eligible.

4.1 Inclusion Criteria

To be eligible for this trial, subjects must fulfill the following criteria:

1. Subjects must be refractory to, or intolerant of, established therapy known to provide clinical benefit for their conditions, or where subjects refuse existing therapies.
2. Subjects must have measurable disease (RECIST v1.1) or patients may have bone metastatic disease evaluable by Prostate Cancer Working Group 2 (PCWG2) for subjects with metastatic castration-resistant prostate cancer (CRPC) or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated.
3. Age >/= 18 years.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
5. Adequate hematologic function defined as:

- Platelets >/= 100 x 10^9/L (For patients with hepatocellular carcinoma, Platelets >/= 70 x 10^9/L);
- Hemoglobin >/= 9 g/dL;
- Absolute Neutrophil Count (ANC) >/=1.5 x 10^9/L;
- White Blood Cell (WBC) >/= 3 x 10^9/L.

6. Adequate liver function defined as:
    - Alanine transaminase (ALT) </= 2.5 x upper normal limit (ULN) (</=5 x ULN for subjects with documented metastatic disease to the liver);
    - Aspartate aminotransferase (AST) </= 2.5 x ULN (</=5 x ULN for subjects with documented metastatic disease to the liver);
    - Alkaline phosphatase < 4 x ULN;
    - Total Bilirubin </= 1.5 x ULN (In the expansion cohort, subjects with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of </= 3 x ULN);
    - Albumin >/=3 g/dL.
7. Renal function defined serum creatinine </=2 x upper limit of normal (ULN) or estimated creatinine clearance >/=30 ml/min as calculated using the Cockroft-Gault formula.
8. Subject has recovered to Grade </= 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v4.03)[14] from the effects of recent surgery, radiotherapy, chemotherapy, hormonal therapy, or other targeted therapies, with the exception of alopecia. The exceptions for such effects are allowed lab values of </= Grade 2 specified elsewhere in these inclusion criteria.
9. Life expectancy of at least 12 weeks.
10. Negative serum pregnancy test in women of childbearing potential within 7 days of first dose of treatment and patients of child-bearing potential must agree to use effective contraception during and after 90 days post dose. A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single and women whose male sexual partners have been vasectomized or whose male sexual partners have received or are utilizing mechanical contraceptive devices.

11. Subjects must have biopsiable disease. For Arms A, B, and C, subjects must have at least two lesions amenable to biopsy and response evaluation. For Arm D subjects should have at least three lesions amenable to biopsy, response evaluation, and radiation. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. However, if patients in Arm D do not have three separate lesions, patients will be eligible if there are two lesions, in which one is > 2 centimeters (short axis) and can be used for both biopsy and response evaluation.
12. Subjects must give informed consent according to the rules and regulations of the individual participating sites.

4.2 Exclusion Criteria

Subjects with any of the following will not be eligible for the study:

1. Subjects with primary central nervous system (CNS) tumor or CNS tumor involvement. However, subjects with metastatic CNS tumors may participate in this study if the subject is:
   - >4 weeks from prior therapy completion (including radiation and/or surgery)
   - Clinically stable with respect to the CNS tumor at the time of study entry
   - Not receiving steroid therapy in treating CNS tumor or CNS tumor involvement
   - Not receiving anti-convulsive medications (that were started for brain metastases).
2. Major surgery, radiation therapy or systemic anti-cancer therapy within 4 weeks of study drug administration (6 weeks for mitomycin C or nitrosoureas). Palliative radiotherapy to a limited field is allowed after consultation with the medical monitor at any time during study participation, including during screening, unless it’s clearly indicative of disease progression.
3. Subjects with prior anti-PD-1, anti-PD-L1 treatment. For Arms A and D, subjects may not have had prior 4-1BB treatment. For Arm B, subjects may not have had prior OX40 treatment. For Arm C, subjects may not have had prior 4-1BB or OX40 treatment.

4. Diagnosis or recurrence of invasive cancer other than the present cancer within 3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated).
5. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (>/= New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
6. Active infection requiring systemic therapy.
7. Treatment with an investigational anti-cancer study drug within 4 weeks prior to study drug administration date.
8. Concurrent therapy with approved or investigational anticancer therapeutics.
9. Known prior severe hypersensitivity to investigational product(s) or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade >/= 3).
10. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses </= 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
11. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
12. Prior organ transplantation including allogenic stem-cell transplantation.
13. Known history of testing positive for HIV or known acquired immunodeficiency syndrome.
14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
15. Vaccination (live attenuated virus) within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines.

16. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade </= 2, or other Grade </= 2 not constituting a safety risk based on investigator's judgment are acceptable.
17. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
18. Medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
19. Pregnancy or lactation.
20. Men whose partner is a woman of child-bearing potential, (i.e. biologically able to conceive), and who is not employing two forms of highly effective contraception. Highly effective contraception (e.g. male condom with spermicide, diaphragm with spermicide, intra-uterine device) must be used by both sexes during the study and must be continued for 90 days after the end of study treatment. Women of child-bearing potential is defined as sexually mature women who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (e.g., who has had menses any time in the preceding 12 consecutive months).
21. A diagnosis of active scleroderma, lupus, or other rheumatologic disease which in the opinion of the treating radiation oncologist precludes safe radiation therapy.
22. Has had prior radiation therapy within the past 3 months where the high dose area of the prior radiation would overlap with the high dose area of the intended radiation based on the judgement of the treatment oncologist.

4.3 Pregnancy and Contraception

In this study, patients of childbearing potential will receive study drug(s), for which the teratogenic risks are currently unknown. Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. Female patients of child-bearing potential must have a negative serum pregnancy test at screening and agree to use reliable methods of contraception for 90 days after their last dose of medication.

Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 90 days after the last dose. The investigator, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator, at each study visit, will discuss with the patient the need to use highly effective contraception consistently and correctly and document such conversation in the patient chart. In addition, the investigator will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the patient remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

5.0 STUDY TREATMENTS

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 previous cohort's 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

Avelumab, utomilumab (4-1BB), and PF-04518600 (OX40) will be supplied for the study by Pfizer.

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

5.2.1.1 Avelumab

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

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

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

5.2.1.2 Utomilumab (4-1BB)

Utomilumab is provided as a 10 mg/mL sterile solution for injection, in a 20 mM histidine buffered solution at pH 5.5. The drug product is supplied in 2 mL Type 1 clear glass vial sealed with a coated serum stopper and aluminum seal (nominal fill volume of 2.0 mL or 10.0 mL). The labeled storage conditions for utomilumab, Injection, 10 mg/mL is 2–8°C, and it should not be frozen.

5.2.1.3 PF-04518600 (OX40)

PF-04518600 drug product, 10 mg/mL is presented as an aqueous solution compounded in histidine buffer with excipients at pH 5.5. The drug product is supplied in sterilized 10 mL Type 1 clear glass vials with 20 mm serum stoppers and 20 mm aluminum flip-off seals, with a nominal fill volume of 10 mL. The drug product should be stored refrigerated (2-8 °C) and protected from light.

5.2.2 Preparation and Dispensing

5.2.2.1 Avelumab

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques.

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size

to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

5.2.1.2 Utomilumab (4-1BB)

Refrigerated utomilumab drug product will be equilibrated to ambient temperature before preparation and administration.

5.2.1.3 PF-04518600 (OX40)

PF-04518600 10 mg/mL injection is presented as a sterile solution for intravenous administration. Each vial has a nominal volume of 10 mL, is sealed with a coated stopper and an overseal, and labeled according to local regulatory requirements. The vial is intended for single use only.

PF-04518600 will be shipped under refrigerated conditions (2-8°C) that are monitored with temperature control monitoring devices.

5.2.3 Administration, Dose Calculation and Infusion Reactions

5.2.3.1 Avelumab

Avelumab will be administered as a 1-hour (+/- 30 minutes) infusion dose of 10 mg/kg body weight administered IV once every 2 weeks starting on Cycle 1 Day 15.

Subjects are at risk of developing infusion-related reactions including drug hypersensitivity reactions, mainly mild to moderate, but which may also be life-threatening. Premedication with an antihistamine and with paracetamol (acetaminophen) (e.g., 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) is mandatory prior to each dose of avelumab.

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

Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions

5.2.3.2 Utomilumab (4-1BB)

Patients will receive doses of utomilumab IV once every four weeks (one cycle). A cycle is defined as the time from day 1 dose to the next day 1 dose. If there are no treatment delays, a cycle will be four weeks in duration.

Pre-medication is recommended for all patients, and may include an antihistamine, anti-inflammatory agent or pain reliever.

The duration of infusion is 1 hour (+/- 30 minutes). The infusion rate should be reduced or interrupted in the case of symptoms of infusion reaction, and symptomatic treatment administered. The infusion may be continued at one-half the previous rate upon improvement of symptoms. If symptoms persist or worsen, the infusion should be discontinued.

5.2.3.3 PF-04518600 (OX40)

PF-04518600 will be administered as an intravenous infusion over 1 hour (+/- 5 minutes) on Days 1 and 15 of each 28-day cycle. In previous studies, the starting dose for the monotherapy portion of the study was 0.01 mg/kg IV with escalation to subsequent dosages of 0.1, 0.3, 1.5, and 3.0 mg/kg after review of the results. The starting dose for PF-04518600 in combination with utomilumab will be 0.1 mg/kg, escalating to 0.3 mg/kg. On cycles whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered after, but no

sooner than 30 minutes after completion of the utomilumab infusion in absence of infusion reaction.

5.2.4 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 4.03. 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.

5.2.4.1 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 section Dose Delays (Section 5.2.4.2).

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 5.2.4.3), unless

expressly agreed otherwise following discussion between the Investigator and the MDACC IND Office.

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

5.2.4.2 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 (eg, proven clinical benefit).

A new cycle of treatment (or Day 15 of any cycle subject to treatment) may begin only if:

- ANC >/= 1,000/µL;
- Platelet count >/= 50,000/µL;
- Hemoglobin >/= 8 g/dL;
- 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 grade >/=3 clinically significant lab abnormality attributed to the treatment. Resume the treatment once the lab abnormality returns to grade </=1. 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, 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.

For Arm D, patients who experience:

- Grade 1 and 2 diarrhea related to radiation therapy and chemotherapy occurs in majority of patients starting around the end of the 3rd week of radiation therapy. Diarrhea prior to the 3rd week of radiation therapy is not usually associated with chemotherapy and radiation therapy and other causes need to be ruled out including C. Diff. This diarrhea lasts through the 5th week of radiation therapy and up to a week after the external beam radiation therapy is completed. This diarrhea is usually controlled with Imodium AD but sometimes Lomotil is used to control it. Grade 3 or higher diarrhea – not controlled with Imodium or Lomotil is rare – usually less than 2-3% in patients in patients receiving chemotherapy and radiation therapy.
- Grade 1 and 2 diarrhea related to radiation may continue avelumab or utomilumab (4-1BB) at the discretion of the physician,
- Grade 3 and 4 diarrhea related to radiation will hold avelumab or utomilumab (4-1BB). At the physician’s discretion, avelumab or utomilumab (4-1BB) may continue at same dose if diarrhea improves to </= Grade 1.
- In case the event of diarrhea is suspected to be immune-related and/or in the case the event of diarrhea does not respond to the measures applied for

radiotherapy-induced diarrhea and has an increase in severity, follow the toxicity management described for diarrhea/colitis in the immune-related adverse event toxicity management (Table 10).

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.

5.2.4.3 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 5.2.4.2, 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 dose escalation cohorts, 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 cohorts 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. Immunotherapy study drugs (avelumab, utomilumab, and PF-04518600) must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8-10 below. 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 one or more of the immunotherapy study drugs (avelumab, utomilumab, and PF-04518600).

For subjects whose dose was withheld due to toxicity, subjects may resume immunotherapy study drug(s) (avelumab, utomilumab, and PF-04518600) upon resolution of toxicity to Grade 0-1 or baseline.

Table 8. Adverse Drug Reactions Requiring Immunotherapy Agent Discontinuation or Modification

In the following table, immunotherapy study drugs or agents refer to avelumab, utomilumab, or PF-04518600.

Any Grade 4 Adverse Drug Reactions (ADRs) require treatment discontinuation with immunotherapy agents (avelumab, utomilumab, or PF-04518600) except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management

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

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

Any Grade 2 ADR should be managed as follows:

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

Table 9. Treatment Modification for Symptoms of Infusion-Related Reactions

In the following table, immunotherapy study drugs or agents refer to avelumab, utomilumab, or PF-04518600.

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening. The total infusion time for study drug should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Stop study drug 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 study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
- Once the **immunotherapy agents** infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. - If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment. - If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

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

Table 10. Management of Immune-mediated Adverse Reactions

In the following table, immunotherapy study drugs or agents refer to avelumab, utomilumab, or PF-04518600.

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade): Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4) Grade 3 to 4: treat with high dose corticosteroids Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines set forth in the table.		
Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue **immunotherapy agent** therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
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	Delay **immunotherapy agent** therapy Symptomatic treatment	If improves to Grade 1: Resume **immunotherapy agent** therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume **immunotherapy agent** therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue **immunotherapy agent** therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone 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 If 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 (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue **immunotherapy agent** therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay **immunotherapy agent** therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume **immunotherapy agent** therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue **immunotherapy agent** therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume **immunotherapy agent** therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of **immunotherapy agent** therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay **immunotherapy agent** therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume **immunotherapy agent** therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue **immunotherapy agent** therapy Hospitalize	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening:

	Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue **immunotherapy agent** therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay **immunotherapy agent** therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume **immunotherapy agent** therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume **immunotherapy agent** therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue **immunotherapy agent** therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue **immunotherapy agent** therapy	

	If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay **immunotherapy agent** therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume **immunotherapy agent** therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue **immunotherapy agent** therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold **immunotherapy agent** 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 appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start **immunotherapy agent** 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 **immunotherapy agent**. Guideline based supportive treatment as appropriate per cardiology consult.* Methylprednisolone 1-2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressions (e.g. azathioprine, cyclosporine A)

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

*Local guidelines, or eg. ESC or AHA guidelines

ESC guidelines website:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

5.2.5 Compliance

The Investigational Pharmacy site will complete required accountability and dosage preparation logs to be monitored by the MDACC IND Office. The existing clinical site's documentation system will capture all pertinent /required information on the preparation and administration of the dose.

5.3 Drug Storage and Drug Accountability

The study drugs will be shipped and stored at a temperature between 2° and 8 °C. 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 (eg, 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.

5.4 Concomitant Medications

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

All concomitant medications, blood products, as well as interventions (eg, paracentesis, etc.) received by patients from screening until the end of study visit will be recorded in the electronic medical record (EMR).

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.

5.4.3 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first two cycles of treatment 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): p. 3187-3205).

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

5.4.4 Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed. Systemic anti-inflammatory therapies may be used to treat SAEs potentially related to the study drug(s). However, in such cases it is suggested that Investigators consult with a specialist based on the involved organ systems before instituting treatment.

5.4.5 Corticosteroids

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

5.4.6 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.

5.4.7 Radiation Therapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

The technique of radiation will be VMAT/IMRT for all arms. For Arm D, the treatment dose will be prescribed to the planning target volume (PTV) for all treatment groups. It is required that the prescribed isodose line should cover 100% of the internal gross tumor volume (IGTV) and more than 95% of the PTV. For central lung or liver lesion close to critical structures, compromised PTV coverage is allowed in order to meet normal tissue dose constraints, pending clinical judgments regarding optimal target coverage and normal tissues sparing by the treating physician.

There is no or little aperture margin recommended. The external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, which typically ranges from 70-95%. However, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Heterogeneity correction should be applied for planning.

5.4.7.1 Radiation Technique

Patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability. Based on this evaluation, a treatment delivery technique will be selected among the following:

1. Breath-hold (with or without feedback guidance).
2. Gated treatment.
3. Free-breathing (with or without feedback guidance).
4. Abdominal compression.
5. A combination of the above techniques.

A CT scan obtained using the same method of respiratory management as intended for treatment will be required for treatment planning purposes. This includes 4-dimensional CT (4DCT) for free-breathing, gated or abdominal compression techniques or repeated breath-hold CTs for breath hold techniques. Feedback guidance, including visual and/or audio techniques, will be used for all patients who would both benefit from and respond to training with such devices.

4DCT is a fast CT scan that capable of imaging tumor position during the entire breath cycle. A CT scan is obtained with the patient in each couch position for a whole breath cycle (usually lasting 5 to 6 seconds in each position) followed by repositioning to the next couch position. Following a scan, the computer resorts all images and reconstructs the tumor positions for an entire breath cycle, i.e., a movie file is created which captures organ movement throughout the breath cycle. Radiotherapy will be designed based on the path of organ motion captured by 4DCT.

5.4.7.2 Target Volumes

1. Gross Target Volume (GTV): Gross tumor as observed on a non-contrast CT should be delineated on lung (for lung tumors) or abdominal (for liver or adrenal tumors) windows from either 4DCT or repeated breath-hold CTs (see IGTV below).

2. Internal Gross Target Volume (IGTV): IGTV is the volume containing the GTV throughout its motion during respiration or positional variability during repeated breath holds. The motion during free breathing (with or without abdominal compression) will be determined from 4DCT, the variability of tumor location during breath hold will be determined by repeated breath hold CTs obtained on the same day. One method to combine the data from the multiple CT datasets is to create a maximal intensity projection (MIP) that is used as an aid to contour the IGTV. All CT datasets will be transferred to the treatment planning system for reference.

3. Clinical Target Volume (CTV) + Planning Target Volume (PTV): GTV plus 5-10 mm margin (based on physician discretion). Due to tight PTV margin, CTV margin is not recommended to be edited except when normal tissue toxicity is concerning based on treating physician's judgment. The prescribed dose of radiation (either 50 Gy or 60 Gy) will be dosed to the PTV, we recommend 95% coverage if possible.

5.4.7.3 Daily Treatment Setup

The appropriate immobilization will be chosen for each patient. Most patients will be immobilized with arms up using a commercially available vacuum immobilization bag that extends from the patient's head to their pelvis combined with a wing board.

On-board imaging: Daily on-board imaging such as CT on-rails, cone beam CT, or 4-D cone beam CT will be conducted prior to each radiation fraction. Position adjustment and target coverage confirmation will be performed daily based on imaging study. The setup uncertainty will be kept to less than a 3 mm (2 s) variation. This value is based on the uncertainties of the couch readouts added in quadurature with ½ the voxel size of the CT. Adjustment of patient position is needed if target coverage is judged by the treating physician to be inadequate and/or critical normal tissues toxicity is concerning.

Repeated on-board CT after position adjustment is recommended if more than 5 mm shift is conducted.

5.4.7.4 Dose Volume Constraints

60 Gy in 10 fractions dose constraints (54-58):

- Spinal Cord: 40 Gy ≤1 cc
- Lung: V20 ≤20%, V10<30%, V5<50%
- Esophagus: 60 Gy ≤1 cc, 40 Gy ≤10 cc
- Trachea: 70 Gy ≤1 cc, 60 Gy ≤10 cc
- Main bronchus: 70 Gy ≤1 cc, 60 Gy ≤10 cc
- Heart: 70 Gy ≤5 cc, 50 Gy ≤10 cc
- Brachial plexus: 50 Gy ≤1 cc, 40 Gy ≤10 cc
- Major vessels: 70 Gy ≤5 cc, 60 Gy ≤10 cc
- Skin (defined as outer 0.5 cm of body surface): 60 Gy ≤1 cc, 50 Gy ≤10 cc
- Kidney: V50 ≤33%

Please note that patients on Arm D will have radiation as part of the study treatment regimen combination.

5.4.7.5 Radiation Breaks and Discontinuation

Radiation breaks will occur for radiation-related Grade ≥ 3 toxicities uncontrolled by symptom management and medications pending judgment of the treating radiation oncologist. Continual re-evaluation will occur daily while a patient is on a radiation break until which time the treating radiation oncologist re-initiates the patient on radiation or discontinues treatment. Patients will be considered evaluable on the study if the planned radiation fractions were administered with < 5 days of unplanned treatment breaks. Patients will be considered evaluable on the study if patients received 75% of radiation dose.

For Arm D, patients who experience:

- Grade 1 and 2 diarrhea related to radiation therapy and chemotherapy occurs in majority of patients starting around the end of the 3rd week of radiation therapy. Diarrhea prior to the 3rd week of radiation therapy is not usually associated with chemotherapy and radiation therapy and other causes need to be ruled out including C. Diff. This diarrhea lasts through the 5th week of radiation therapy and up to a week after the external beam radiation therapy is completed. This diarrhea is usually controlled with Imodium AD but sometimes Lomotil is used to control it. Grade 3 or higher diarrhea – not controlled with Imodium or Lomotil is rare – usually less than 2-3% in patients in patients receiving chemotherapy and radiation therapy.
- Grade 1 and 2 diarrhea related to radiation may continue avelumab or utomilumab (4-1BB) at the discretion of the physician,
- Grade 3 and 4 diarrhea related to radiation will hold avelumab or utomilumab (4-1BB). At the physician's discretion, avelumab or utomilumab (4-1BB) may continue at same dose if diarrhea improves to </= Grade 1.
- In case the event of diarrhea is suspected to be immune-related and/or in the case the event of diarrhea does not respond to the measures applied for radiotherapy-induced diarrhea and has an increase in severity, follow the toxicity management described for diarrhea/colitis in the immune-related adverse event toxicity management (Table 10).

6.0 SCHEDULE OF ASSESSMENT AND PROCEDURES

For screening, treatment period and follow-up procedures, see Schedule of Assessments.

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:

- Clinical safety lab tests – obtain prior to study drug administration.
- Blood pressure/ pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to study drug administration.
- ECGs – obtain within 30 minutes of drug administration.
- 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.

6.1 Screening Period

All patients will be screened and screening procedures performed within 28 days prior to the start of induction treatment.

The required screening assessments and laboratory tests are summarized in the Schedule of Assessments and Section 7.0 Assessments. Following completion of the screening assessments and confirmation of eligibility, patients may be 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 Schedule of Assessments.

Per the physician's discretion, a patient may continue treatment even if there is progression of disease after avelumab is added as long as the patient remains clinically stable and/or pseudoprogression is assumed.

Clinical and radiological examinations for disease status are performed every 2 cycles or 8 weeks (± 7 days) for up to 1 year. After completion of 1 year, tumor assessments will be performed every 3 cycles or 12 weeks (± 7 days) during treatment, independent of cycle delays.

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, 30 days (+/-7 days) after the last dose of study medication.

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 by using information from a chart review, patient visit, or telephone call. 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:

- Disease progression;
- Non-compliance;
- Need of treatment with medications not allowed by the study protocol;
- Patient no longer consents to participate in the study;
- Intercurrent illness that interferes with study assessments;
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient;
- Investigator discretion;

- Pregnancy;
- Termination of the study.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- 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.

7.0 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

All procedures should be followed within the allowed flexibility windows as outlined in the Schedule of Assessments.

7.1 Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, ECG (12 lead), laboratory assessments, including pregnancy tests and verification of concurrent medications.

7.1.1 Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy-once at the start of screening and once at the baseline visit (prior to initiating study drugs (Arms A-C) or radiation (Arm D), immediately before investigational product administration.

Following a negative pregnancy 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 may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle 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 the study medication and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/ Independent Ethics Committee (IECs) or if required by local regulations.

7.1.2 Adverse Events

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. 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 4.03) timing, seriousness, and relatedness.

AEs that occur during the study, including baseline signs and symptoms, will be recorded on the AEs CRF page. 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, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 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.

Table 11: Recommended Adverse Event Recording Guidelines

Recommended Adverse Event Recording Guidelines

Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.1.3 Laboratory Safety Assessments

Hematology, serum chemistry, and thyroid function labs will be drawn at the time points described in the Schedule of Assessments and analyzed at local laboratories. All laboratory safety assessments conducted on Cycle 1 Day 1 (C1D1) for Arms A-C or prior to radiation for Arm D must be completed prior to dosing; hematology and chemistry results must be reviewed by an advance practice provider or a physician prior to dosing.

Assessments performed on dosing days in each subsequent cycle should be performed within 48 hours prior to dosing. Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following AEs.

For Arms A-C, there is no need to repeat C1D1 laboratory assessments if baseline assessment is performed within 2 days prior to that date. For Arm D, there is no need to repeat initial laboratory assessments if baseline assessment is performed within 3 days prior to initiation of radiation.

Hematology	Chemistry	Endocrine Monitoring	Coagulation	Urinalysis	Pregnancy Test	Hepatitis Screening	Cardiac Enzyme Monitoring
Hemoglobin	ALT	TSH	PT or INR	Urine dipstick for urine protein: If positive(≥ 2+), collect 24-hr urine or collect spot urine) and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine	Hepatitis B surface antigen and core antibody; anti-hepatitis C antibody.	Troponin T and NT-proBNP
Platelets	AST	Free T4	PTT				
WBC	Alkaline Phosphatase	Total T3					
Absolute Neutrophils	Sodium						
	Potassium						
Absolute Monocytes	Magnesium			Urine dipstick for urine blood: If positive and clinically indicated collect a microscopic (Reflex Testing)			
Absolute Eosinophils	Chloride						
Absolute Basophils	Total Calcium						
	Total Bilirubin Direct Bilirubin Indirect Bilirubin						
	Blood urea nitrogen (BUN) or Urea						
	Creatinine						
	Uric Acid						
	Glucose (non-fasted)						
	Albumin						

Hematology	Chemistry	Endocrine Monitoring	Coagulation	Urinalysis	Pregnancy Test	Hepatitis Screening	Cardiac Enzyme Monitoring
	Phosphorous or Phosphate						
	Total protein						
	Amylase						
	Lipase						
	Creatine kinase						
	Lactate dehydrogenase (LDH)						
	Bicarbonate						

7.1.4 Vital Signs and Physical Examination

Patients will have a physical exam to include weight, vital signs, assessment of ECOG status and height.

A complete physical examination (PE) will be performed at Screening, Days 1 and 15 of each cycle, and the End of Treatment visit for each patient 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.

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

Vital signs will include measurements of blood pressure, pulse rate and temperature (oral, tympanic, temporal or axillary). Sitting blood pressure (BP) will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg after approximately 5 minutes of rest. 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 same arm (preferably the dominant arm) will be used throughout the trial. 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.

7.1.5 ECG Assessments

Electrocardiogram (ECG): Single 12-lead (with a 10-second rhythm strip) tracing in the supine position will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Single ECGs will be performed Day 1 of every cycle.

If the QTc is prolonged (>500 msec by any correction method, ie, CTCAE Grade 3), then the ECG should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECG should be immediately performed hourly for at least 3 hours until the QTc interval resolves to Grade 1 or less.

If QTc interval reverts to less than 500 msec, and in the judgment of Investigator(s) and the MDACC IND Office is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the study drug will be held until the QTc interval decreases to Grade 1 or less. Patients will then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to <500 msec after 2 weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

7.1.6 Echocardiogram/ Multigated Acquisition Assessments

For patients with prior history of anthracycline treatment that are enrolled on the PF-04518600 (OX40) Arms B or C, an echocardiogram (ECHO) or multigated acquisition (MUGA) scan will be performed at screening, every 3 cycles (starting at Cycle 4 Day 1), and End of Treatment (if not performed within 3 months of discontinuation).

7.1.7 Cardiac Enzyme Monitoring

For patients with prior history of anthracycline treatment that are enrolled on the PF-04518600 (OX40) Arms B or C, cardiac ezyme monitoring will be performed at screening, Day 1 of every cycle, and End of Treatment.

Troponin T and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) will be evaluated in patients with previous history of anthracycline treatment. Assessments must be performed prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if the screening assessment is performed within 2 days prior to that date. Assessments performed on Cycle 2 Day 1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. Assessments should also be performed when clinically indicated.

7.2 Tumor Response Assessments

Objective response will be evaluated based on RECIST criteria Version 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.

For Arm D (radiation), radiated target lesions will be evaluated with a modified version of the international criteria proposed by the RECIST Committee, version 1.1.

The exact technique used for measurement of lesions (i.e., either CT or 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 accepted 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) during treatment, 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.

7.3 Biopsy Analyses

For patients in the MTD expansion cohorts of Arms A-C, tumor tissue will be obtained pre- treatment (baseline), between Cycle 1 Day 12-15 (prior to study drug dosing), prior to Cycle 3 Day 1 study drug dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.

For patients in the escalation cohorts of Arm C (patients enrolled prior to Version 05), tumor tissue will be obtained pre- treatment (baseline), prior to Cycle 2 Day 1 dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.

For patients in the de-escalation and MTD Expansion cohort of Arm D, tumor tissue will be obtained pre- treatment (baseline), prior to Cycle 3 Day 1 dosing, and at progression (if achieved stable disease ≥6 months, partial response, or complete remission) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.

Correlative studies for biomarker analyses will be performed during this study.

A fresh core needle biopsy (CNB) will be obtained solely with the purpose of research studies (pre-treatment samples) and sent to the Institutional Tissue Bank (ITB) immediately after collection. Up to 5 cores will be obtained from the CNB procedure. The number of cores obtained will be affected by the patient clinical condition at the time of biopsy and determined by the radiologist who is performing the procedure. It is important to note that in some of these trials, the biopsy sample will also be required for clinical diagnosis. In such case, the first specimen will be prioritized for clinical specimen processing. In most instances, a rapid on site evaluation (ROSE) is available locally to evaluate the adequacy of clinical sample, thus additional biopsies may be procured for this research project. Nevertheless, the amount tissue available for correlative studies can be variable. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected.

For Arms A, B, and C, subjects must have at least two lesions amenable to biopsy and response evaluation. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Every effort will be made to biopsy the same lesion at each time point.

For Arm D, subjects should have at least three lesions amenable to biopsy, response evaluation, and radiation. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Every effort will be made to biopsy the same lesion at each time point. In addition, the radiated lesion will also be biopsied at each time point. However, if patients in Arm D do not have three separate lesions, patients will be eligible if there are two lesions, in which one is > 2 centimeters (short axis) and can be used for both biopsy and response evaluation.

7.4 Biomarker Analyses

Biomarker analyses will be performed to investigate biomarkers that are potentially predictive of response with the combination of avelumab and an immune modulator. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the avelumab plus the study treatments, as well as potential mechanisms of resistance.

For the MTD Expansion cohorts of Arms A-C, blood samples will be collected at baseline, between Cycle 1 Day 12-15 (prior to study drug dosing), prior to Cycle 3 Day 1 study drug dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission) to evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers. Cell free DNA from patient’s blood samples will also be analyzed.

For the escalation cohorts of Arm C (patients enrolled prior to Version 05), blood samples will be collected at baseline, prior to Cycle 2 Day 1 dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission) to evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers. Cell free DNA from patient's blood samples will also be analyzed.

For the de-escalation and MTD Expansion cohort of Arm D, blood samples will be collected at baseline, prior to Cycle 1 Day 1, prior to Cycle 1 Day 15, prior to Cycle 2 Day 1 dosing, prior to Cycle 3 Day 1 dosing, and at the time of progression (if patient had an initial response of stable disease ≥6 months, partial response, or complete remission). Cell free DNA from patient's blood samples will also be analyzed.

The plan for biomarker analyses in Arms A-D is the following:

Immunohistochemistry (IHC): The samples collected will be analyzed by IHC analysis of tumors for markers that may include, but are not limited to, PD-L1, CD3, CD4, Foxp3, CD25, CD8, CD68, CD56, CD20, CD45RO and granzyme B. We may also include PD-L2, B7-H3, B7-x/H4, galectin 9, HVEM and CD48 to measure in tumors and PD-1, 2B4, LAG-3, Tim-3 and BTLA in TILs.

Multiplex IF Analysis: Up to 10 immune markers, 2 panels may be utilized. Currently, there are 2 Vectra panels optimized: Panel#1, CD3, CD8, CD68, PD-L1, PD-1 pan-cytokeratin and DAPI; Panel #2, CD20, CD45RO, FOXP3, Granzyme B, CD57, pan-cytokeratin and DAPI. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. Additional markers will be selected according the results of the gene expression analysis and may include other immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).

Molecular Analyses (in Tissue and Blood): Using FFPE tumor tissues and blood samples, Immuno-oncology (IO) gene panels will be examined using the Nanostring technology (nCounter). This assay will be used to measure expression levels of drug targets, tumor infiltrate composition, and total immune cell composition using a single section of FFPE tumor tissue. Next Generation Sequencing (NGS) analysis: To study tumor molecular abnormalities, fresh, and alternatively, FFPE tumor tissues and blood samples before and after treatment will be examined for targeted gene panel NGS (analysis of mutations, copy number, indels, and translocations), whole exome sequencing (WES) and RNA sequencing (Illumina Hi-seq platform).

Flow Cytometry of Blood: Collected blood will be analyzed by flow cytometry for lymphocyte subsets in PBMCs. This flow cytometry panel includes: (1) FACS phenotyping for CD4+ and CD8+ naïve (TN), central memory (TCM), effector-memory (TEM) and terminally differentiated effector (TTDE) cells; (2) Staining for suppressor cells such as CD4+ T-regulatory cell and myeloid derived suppressor cells (MDSC) subsets; (3) Phenotyping of NK cells and (4) Identification of APC subsets (pDC, mDC, B cells, macrophages). To detect and enumerate these populations we have developed FACS cell surface and intracellular staining panels on samples that are analyzed using a FACScanto II flow cytometer (BD Biosciences). These staining panels include antibodies against pan-leukocytes (CD45), T cells (CD4, CD8, CD25, CD27, CD28, CD45RA, CD45RO, CD62L, CD69, OX40, 41BB, CCR7, GB, PFN), CD4+ T-reg cells (CD4, CD25, Foxp3, CD127, CD27, CD62L, CTLA-4, GARP, ICOS, CD39, and LAP), B cells (CD19 CD20), pDC and mDC (CD11c, CD11b, BDCA2, CD123, CD86, CD80, CD83, HLA class II), monocyte/macrophages (CD14, CD11b, CD13), MDSCs (CD33, CD11b, CD14, CD15, HLA-DR, S100A9) and NK cells (CD16, CD56, CD69, NKG2D).

Flow cytometry of freshly disaggregated tumor tissue: Fresh tissue will be available for flow cytometry analysis on larger tumor samples only using Core 3. This will include assessment of the proportion of various immune cells by gating on the pan immune marker CD45 and sub-gating on cell specific markers defining T cell, MDSC, macrophage, DC or NK cell subsets. The expression of checkpoints or their ligands can be explored on each of those cell subsets. In addition, for tissue samples, live

cells can be sub-gated on the CD45-negative fraction to exclude immune cells. EPCAM will be used as a marker of tumor cells and CD90 as a fibroblast marker. The expression of CD80, CD86, GITR-L, ICOS-L, MIC A/B, B7-H3, B7-H4, CD73, PD-L2 and OX40L can all be assessed.

Serum Cytokine Analyses: Cytokines (IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, and TNF-α) will be measured in the serum using the Meso Scale Discovery Platform (Rockville, MD). 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 up to 1000 fold 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.

Liquid Biopsy Analyses: For cfDNA, both ultra-deep next-generation sequencing (NGS) mutation analysis of a panel of 50 genes (CMS50) (Ion Torrent PGM and Ion Proton), as well as uniplex or multiplex digital droplet PCR (ddPCR, BioRad and Raindance) are available using 40-50 ng of DNA extracted from 4-5 ml of plasma (blood, purple top).

7.5 Co-Enrollment on Additional Studies

Patients enrolled on this study will be approached for co-enrollment on PA15-0315 prospective study to assess immune-related adverse events when receiving immunotherapy at the University of Texas MD Anderson Cancer Center (Aung Naing, MD). All samples and scans will be collected using procedures characterized in this protocol, and all patients will be consented for procedures done under this protocol separately.

Patients enrolled on this study will be approached for co-enrollment on the 2014-0938, APOLLO (Adaptive Patient-Oriented Longitudinal Learning and Optimization)

protocol, which is an MD Anderson Moon Shot platform. All samples will be collected using procedures characterized in this protocol, and all patients will be consented for procedures done under this protocol separately.

8.0 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 Pfizer or its designated representative. 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 seriousness 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 30 calendar days after the last administration of the investigational product.

8.2 Definition of Adverse Event

An adverse event is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice 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 can 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:

- Death
- 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, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 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 judgment, 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 Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. 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, 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 30 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 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

8.4 Reporting to FDA

Serious adverse events will be forwarded to 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 serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

8.5 Investigator Communications with Pfizer

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent through 30 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to Pfizer 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 are to be reported to Pfizer.

AEs (serious and non-serious) should be recorded 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 primary responsibilities in the safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to IRB, IND Office, and Pfizer, as required by local regulations (for regulatory reporting) and Investigator-Initiated Research (IIR) agreement (for reporting to Pfizer).

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

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)

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

Contact information for submission of reportable events to Pfizer:

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

Or

- **E-mail: USA.AEReporting@pfizer.com , specifying:**
  PROTOCOL:
  SUBJECT:
  SITE/PI:
  SAE/ONSET:

The MDACC SAE form will be submitted to Pfizer. The following detailed information must be recorded for each serious adverse event in the SAE report form:

- A description of the AE in medical terms according to NCI-CTC Version 4.03, not as reported by the subject.
- The severity grade as assessed by the investigator according to the definitions in NCI-CTC Version 4.03.
- The date of becoming serious and the date of becoming known (if different).
- The reason for seriousness.
- The outcome of the SAE at the time of the report.
- Information on administration of the study drug and chemotherapy and any action taken.
- 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 subjects are properly recorded in the subjects' medical records and the electronic case report form.

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

- Adverse event term according to the NCI-CTC criteria Version 4.03;
- Severity grade according to the NCI-CTC criteria Version 4.03;
- Start date and stop date (or date of last assessment);
- Outcome;
- Causality to study drug and chemotherapy (to be assessed as either related or unrelated);
- Any action taken.

Adverse events will be followed until they resolve to baseline or considered stable. It will be left to the investigator's clinical judgment to determine whether an adverse event 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 cease or the condition becomes stable.

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if the meet the criteria described in Section 8.3.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. If an adverse event occurs which is not described in the CTCAE version 4.03, 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: Represents 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:

1) Accompanied by clinical symptoms;
2) Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation);
3) Requiring a change in concomitant therapy (e.g. addition of, interruption of, 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 (SAE) 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 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 must be withdrawn from the study. Pregnancies occurring up to 6 months after the 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 Pfizer. 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 Pfizer. The partner should be counseled and followed as described above.

8.6.2 Adverse Drug Reactions with Concomitant Medication

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.

9.0 DATA ANALYSIS/ STATISTICAL METHODS

Dr. Juhee Song (Department of Biostatistics at MD Anderson) will perform all statistical analyses. Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented below.

9.1 Analysis Sets

1) Safety Analysis Set

The safety analysis set includes all enrolled patients who receive at least one dose of each study medication in the assigned treatment combination. Patients in Arms A and D must receive at least one dose of avelumab and utomilumab each. Patients in Arm B must receive at least one dose of avelumab and PF-04518600 (OX40) each. Patients in Arm C must receive at least one dose of avelumab, utomilumab, and PF-04518600 (OX40) each. Subjects who have not received at least one dose of each study medication in the assigned treatment combination will be replaced.

2) Full Analysis Set

The full analysis set includes all enrolled patients.

3) Per Protocol Analysis Set

All enrolled patients who are eligible, receive study treatment and who either experience DLT during the first 56 days (following Cycle 1 Day 1) of study treatment or complete the 56-day treatment without DLT will be included. Patients who are lost to follow-up due to reasons unrelated to treatment related AEs are not evaluable for DLT.

The per-protocol population will consist of all patients who are compliant with study assessments and who have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy. This population will be used for primary inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the treated population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of

further studies.

4) Response Analysis Set

All enrolled patients who are eligible, receive study treatment, have baseline assessments and at least 1 on-study tumor assessment will be considered evaluable for response. Patients who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures.

9.2 Statistical Methods and Properties

As of Amendment Version 09, this study will be conducted in 4 arms. Arms A, B, and C will each enroll an MTD expansion cohort. Arm D will have a dose de-escalation and MTD.

In Arm D, standard 3 +3 dose de-escalation and MTD will be applied for dose level 1 and -1 with standard MTD and DLTs rule. We will use CTCAE criteria to capture adverse events related to the study drugs. If cohort 1 is not tolerable, there will be de-escalation to cohort -1.

Each study treatment arm will have an MTD expansion cohort of up to 14 patients each. The expansion cohort for each arm will be stopped early if the aggregate DLT rate > 33% for that particular arm. The aggregate DLT rate for each arm will include patients that were treated at the same dose level in the dose escalation or de-escalation phase. If the trial does not stop early, we will estimate the disease control rate and the response rate separately for each cohort with appropriate 95% confidence intervals. We will also estimate the progression free survival (PFS) and overall survival (OS) distributions using the Kaplan-Meier product limit method and report summary measures such as the median value and probabilities at selected times (again with appropriate 95% confidence intervals).

9.3 Sample Size Determination

During the course of the study, two to three dose levels were to be examined in each combination arm during the dose escalation/de-escalation with a standard “3+3” design, and a total of 3-6 patients will be enrolled per dose level. After each escalation or MTD determination by Pfizer, there will be an MTD expansion cohort of up to 14 patients each.

Prior to Amendment Version 05, Arm C was designed to have an escalation and 4 patients were enrolled; however, Pfizer provided recommendations for the MTD and requested that the MTD expansion commence. As of Amendment Version 06, the avelumab dosing for Arms A-C was revised; therefore, a new cohort of 14 patients each are expected to be enrolled for the MTD expansions of Arms A-C. As of Amendment Version 07, the original Arm G escalation and expansion (N= 32 total patients) cohorts have been removed from the study due to inability to accrue patients. Prior to Amendment Version 06, there was a total of 31 patients treated in the MTD expansions on the previous avelumab dosing schedule (Arm A: 8; Arm B: 12; Arm C: 11).

As of Amendment Version 08, the dosing schedules for Arms D-F were revised; therefore, Arms D, E, and F were re-initiated with the new schedule. Prior to Amendment Version 08, there were 11 patients enrolled on Arms D-F (Arm D: 4; Arm E: 3; Arm D: 4).

As of Amendment Version 09, the dosing schedule for Arm D was revised; therefore, Arm D dose de-escalation was to be re-initiated with the new schedule (2 dose levels of up to 6 patients each, or up to 12 patients total). Arms E and F were discontinued. Prior to Amendment Version 09, there were 20 patients enrolled on Arms D-F (Arm D prior to Amendment Version 08: 4 and Arm D on Version 08: 3; Arm E prior to Amendment Version 08: 3 and Arm E on Version 08: 3; and Arm F prior to Amendment Version 08: 4 and Arm F on Version 08: 3).

Thus, the planned maximum number of patients for the dose escalation/ de-escalation phase is 36 patients as indicated in Table 12. The planned maximum number of patients for the MTD expansion phase is 92 as indicated in Table 12. Therefore, the planned total maximum accrual in this study will be 128 patients (Escalation 36 + MTD

Expansions 92). Due to screen failures and replacement of inevaluable patients, up to 250 patients may be consented to this trial.

For the objective of describing the toxicity profile, descriptive statistics will be provided on the grade and type of toxicity by dose level. Clinical efficacy will be measured by objective tumor response per RECIST criteria. The clinical response is defined as a CR or PR or at least 6 months SD. A 95% confidence interval of response rate will be estimated based on a binomial distribution.

Table 12: Total Planned Accrual for Each Treatment Arm

Treatment Arm	Dose Escalation	MTD Expansion	Total Enrollment
Arm A: Avelumab + Utomilumab (4-1BB)	NA (Escalation at Pfizer)	N=8 (Prior to Amendment Version 06) N=16 (As of Amendment Version 06)	24
Arm B: Avelumab + PF-04518600 (OX40)	NA (Escalation at Pfizer)	N=12 (Prior to Amendment Version 06) N=14 (As of Amendment Version 06) *Treated 16 after replacing 2 patients with IND Office Approval	28
Arm C: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40)	N=4 NA (Escalation at Pfizer)	N=11 (Prior to Amendment Version 06) N=14 (As of Amendment Version 06) *Treated 17 after replacing 3 patients with IND Office Approval	32
Arm D: Avelumab + Utomilumab (4-1BB) + XRT	N=4 (Prior to Amendment Version 08) N=3 (On Amendment 08)	N=14	33

Treatment Arm	Dose Escalation	MTD Expansion	Total Enrollment
	N=12 (As of Amendment 09)		
Arm E: Avelumab + PF-04518600 (OX40) + XRT	N=3 (Prior to Amendment Version 08)	Closed per Amendment Version 09	6
	N=3 (On Amendment 08)		
Arm F: Avelumab + Utomilumab (4-1BB) + PF-04518600 (OX40) + XRT	N=4 (Prior to Amendment Version 08)	Closed per Amendment Version 09	7
	N=3 (On Amendment 08)		
Total	**36**	**92**	**128**

MDACC Investigational New Drug (IND) Office, Medical Affairs and Safety Group will review safety and efficacy data with Principal Investigator (and statistician if needed), at a predetermined interval as indicated next:

PHASE I

The first analysis will occur after the first 3 evaluable subjects per arm (Arm D), are treated for 56 days from Cycle 1 Day 1 and prior to advancing/changing dose levels; and every 3 evaluable subjects thereafter.

PHASE II

Efficacy/toxicity analysis will occur every 7 evaluable subjects per arm when treated for 6 months after the first study therapy dose. Assess toxicity at the end of the first 56 days following Cycle 1 Day 1, and response after 6 months of treatment. On every report submission, the information from previous reported patients will need to be updated for response.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Evaluation of toxicity based on the duration of radiation therapy:
if after 7 patients, 3 or more have a duration of radiation therapy greater than 8 weeks then the treatment should be considered excessively toxic in this cohort.
This will allow for identification of toxicity causing a delay in radiation which will translate to worse outcomes. Let p = true probability of duration of radiation therapy being > 8 weeks. Let q = probability of seeing 3 or more patients with excessive radiation duration out of 7 patients. Table 13 is a table of p and q.

Table 13: Probability

p	q
0.2	3%
0.3	13%
0.4	29%
0.5	50%
0.6	71%
0.7	87%
0.8	97%

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 adverse events (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.

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 treated population will consist of all patients who receive at least one dose of each study medication and have post-baseline efficacy follow-up information. This population will be used for primary analyses of efficacy.

9.5.1 Efficacy Evaluation

Clinical efficacy will be measured by objective tumor response per RECIST 1.1 criteria. The clinical response is defined as a CR or PR or SD. A 95% confidence interval of response rate will be estimated based on a binomial distribution.

9.6 Safety Analysis

The safety population will consist of all patients who have received any amount of study medication.

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 (4.03) dictionary and displayed for all study patients combined. 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 30 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 for all study patients combined. 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, for all study patients combined. 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 Biomarker Analysis

For the primary objective, we will analyze changes in CD8 expression before and after treatment using a paired t-test if the data are Normally distributed, and a Wilcoxon signed rank test if not. With 14 patients in each cohort, we will have 90% power (assuming 2-sided 5% alpha) to detect a 0.94*s mean difference where “s” is the standard deviation of the differences. With all 7 cohorts combined, we will have 98 patients, which yields 90% power to detect a 0.33*s mean difference. We will correlate CD8 expression with clinical benefit (CR/PR/SD>6m) using ROC curve analysis. With 98 patients, we would have 90% power to detect and area under the ROC curve of 0.69 (vs. 0.5 which is the null value) assuming 5% alpha and half the patients showing clinical benefit.

For the exploratory objective, we will conduct similar analyses on additional unspecified biomarkers.

9.8 Final Analysis

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

10.0 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.

11.0 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 Platform (MOCLIP).

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, ethics committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities (if applicable), drug records, staff curriculum vitae and authorisation 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.

11.3 Audits and Inspections

This study may be audited by the IND sponsor, any person authorized by the IND sponsor, or the competent health authority in order to determine the authenticity of the recorded data and compliance with the study protocol.

The investigator must be aware that source documents for this trial should be made available to appropriately qualified personnel working on behalf of the authority inspectors after appropriate notification for the purposes of source data verification and proper review of the study progress. The verification of the case report form data must be done via direct inspection of the source documents. The investigator agrees to comply with the IND sponsor and regulatory authority requirements regarding the auditing of the study.

All materials used in clinical studies are subjected to quality control.

12.0 DEFINITION OF END OF TRIAL

End of Trial is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Study Application (CTA)). Poor recruitment (recruiting less than the anticipated number in the CTA) is not a reason for premature termination but is considered a normal conclusion.

End of Trial is defined as Last Patient Last Visit.

13.0 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the MDACC IND Office. In addition, Pfizer retains the right to discontinue development of avelumab, utomilumab, PF-04518600 at any time.

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

14.0 APPENDICES

Appendix 1: Adverse Event Categories for Determining Relationship to Test Drug

Appendix 2: ECOG Performance Status

Appendix 1 – Adverse Event Categories for Determining Relationship to Test Drug

(a) Related (must have one of them)

This category applies to those adverse events that are considered to be related to the test drug. An adverse event may be considered related if:

1. It follows a reasonable temporal sequence from administration of the drug
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists: e.g. (1) bone marrow depression, (2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug
5. It reappears upon rechallenge

(b) Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under related.

Appendix 2 – ECOG Performance Status

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

15.0 REFERENCES

1. Hadrup S, Donia M, Thor Straten P. Effector CD4 and CD8 T cells and their role in the tumor microenvironment. Cancer microenvironment : official journal of the International Cancer Microenvironment Society. 2013 Aug;6(2):123-33.

2. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. The New England journal of medicine. 2003 Jan 16;348(3):203-13.

3. Aspeslagh S, Postel-Vinay S, Rusakiewicz S, Soria JC, Zitvogel L, Marabelle A. Rationale for anti-OX40 cancer immunotherapy. Eur J Cancer. 2016 Jan;52:50-66.

4. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Dec 20;29(36):4828-36.

5. Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, et al. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab. Proceedings of the National Academy of Sciences of the United States of America. 2011 Oct 4;108(40):16723-8.

6. Di Giacomo AM, Calabro L, Danielli R, Fonsatti E, Bertocci E, Pesce I, et al. Long-term survival and immunological parameters in metastatic melanoma patients who responded to ipilimumab 10 mg/kg within an expanded access programme. Cancer Immunol Immun. 2013 Jun;62(6):1021-8.

7. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. British journal of cancer. 2011 Jun 28;105(1):93-103.

8. Bartkowiak T, Curran MA. 4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity. Front Oncol. 2015;5:117.

9. Gelao L, Criscitiello C, Esposito A, Goldhirsch A, Curigliano G. Immune Checkpoint Blockade in Cancer Treatment: A Double-Edged Sword Cross-Targeting the Host as an "Innocent Bystander". Toxins. 2014 Mar;6(3):914-33.

10. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. 2012 Jun 28;366(26):2455-65.

11. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med. 2012 Mar 28;4(127):127ra37.

12. Pfizer. Avelumab (MSB0010718C). Investigator's Brochure. 2016;5.

13. Beatty S, O'Neill L. FDA Accepts the Biologics License Application for Avelumab for the Treatment of Metastatic Urothelial Carcinoma for Priority Review. 2017.

14. Beatty S, O'Neill L. FDA Grants Approval for BAVENCIO®(avelumab), the First Immunotherapy Approved for Metastatic Merkel Cell Carcinoma. 2017.

15. Lynch DH. The promise of 4-1BB (CD137)-mediated immunomodulation and the immunotherapy of cancer. Immunological reviews. 2008 Apr;222:277-86.

16. Curran MA, Geiger TL, Montalvo W, Kim M, Reiner SL, Al-Shamkhani A, et al. Systemic 4-1BB activation induces a novel T cell phenotype driven by high expression of Eomesodermin. The Journal of experimental medicine. 2013 Apr 8;210(4):743-55.

17. Pfizer. PF-05082566. Investigator's Brochure, 2015.

18. Croft M. Control of Immunity by the TNFR-Related Molecule OX40 (CD134). Annual Review of Immunology, Vol 28. 2010;28:57-78.

19. Vu MD, Xiao X, Gao W, Degauque N, Chen M, Kroemer A, et al. OX40 costimulation turns off Foxp3+ Tregs. Blood. 2007 Oct 1;110(7):2501-10.

20. Weinberg AD, Morris NP, Kovacsovics-Bankowski M, Urba WJ, Curti BD. Science gone translational: the OX40 agonist story. Immunological reviews. 2011 Nov;244(1):218-31.

21. Linch SN, McNamara MJ, Redmond WL. OX40 Agonists and Combination Immunotherapy: Putting the Pedal to the Metal. Front Oncol. 2015;5:34.

22. Weinberg AD, Rivera MM, Prell R, Morris A, Ramstad T, Vetto JT, et al. Engagement of the OX-40 receptor in vivo enhances antitumor immunity. J Immunol. 2000 Feb 15;164(4):2160-9.

23. Morris A, Vetto JT, Ramstad T, Funatake CJ, Choolun E, Entwisle C, et al. Induction of anti-mammary cancer immunity by engaging the OX-40 receptor in vivo. Breast cancer research and treatment. 2001 May;67(1):71-80.

24. Goulding J, Tahiliani V, Salek-Ardakani S. OX40:OX40L axis: emerging targets for improving poxvirus-based CD8(+) T-cell vaccines against respiratory viruses. Immunological reviews. 2011 Nov;244(1):149-68.

25. Curti BD, Kovacsovics-Bankowski M, Morris N, Walker E, Chisholm L, Floyd K, et al. OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients. Cancer research. 2013 Dec 15;73(24):7189-98.

26. Pfizer. PF-04518600. Investigator's Brochure. 2016.

27. Diab A, El-Khoueiry A, Eskens F, Ros W, Thompson J, Konto C, et al. A first-in-human (FIH) study of PF-04518600 (PF-8600) OX40 agonist in adult patients (pts) with select advanced malignancies. Annals of Oncology. 2016;27(suppl 6):1053PD.

28. Wang C, Lin GH, McPherson AJ, Watts TH. Immune regulation by 4-1BB and 4-1BBL: complexities and challenges. Immunological reviews. 2009 May;229(1):192-215.

29. Xiao H, Huang B, Yuan Y, Li D, Han LF, Liu Y, et al. Soluble PD-1 facilitates 4-1BBL-triggered antitumor immunity against murine H22 hepatocarcinoma in vivo. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007 Mar 15;13(6):1823-30.

30. Ai M, Curran MA. Immune checkpoint combinations from mouse to man. Cancer Immunol Immunother. 2015 Jul;64(7):885-92.

31. Zhang Y, Kang S, Shen J, He J, Jiang L, Wang W, et al. Prognostic significance of programmed cell death 1 (PD-1) or PD-1 ligand 1 (PD-L1) Expression in epithelial-originated cancer: a meta-analysis. Medicine (Baltimore). 2015 Feb;94(6):e515.

32. Duraiswamy J, Freeman GJ, Coukos G. Therapeutic PD-1 pathway blockade augments with other modalities of immunotherapy T-cell function to prevent immune decline in ovarian cancer. Cancer research. 2013 Dec 1;73(23):6900-12.

33. Wei HF, Zhao LK, Li W, Fan KX, Qian WZ, Hou S, et al. Combinatorial PD-1 Blockade and CD137 Activation Has Therapeutic Efficacy in Murine Cancer Models and Synergizes with Cisplatin. PloS one. 2013 Dec 19;8(12).

34. Chen S, Lee LF, Fisher TS, Jessen B, Elliott M, Evering W, et al. Combination of 4-1BB agonist and PD-1 antagonist promotes antitumor effector/memory CD8 T cells in a poorly immunogenic tumor model. Cancer immunology research. 2015 Feb;3(2):149-60.

35. Palazon A, Martinez-Forero I, Teijeira A, Morales-Kastresana A, Alfaro C, Sanmamed MF, et al. The HIF-1alpha hypoxia response in tumor-infiltrating T

lymphocytes induces functional CD137 (4-1BB) for immunotherapy. Cancer Discov. 2012 Jul;2(7):608-23.

36. Dai M, Wei H, Yip YY, Feng Q, He K, Popov V, et al. Long-lasting complete regression of established mouse tumors by counteracting Th2 inflammation. J Immunother. 2013 May;36(4):248-57.

37. Guo ZQ, Wang X, Cheng DL, Xia ZJ, Luan M, Zhang SL. PD-1 Blockade and OX40 Triggering Synergistically Protects against Tumor Growth in a Murine Model of Ovarian Cancer. PloS one. 2014 Feb 27;9(2).

38. Ascierto PA, Simeone E, Sznol M, Fu YX, Melero I. Clinical experiences with anti-CD137 and anti-PD1 therapeutic antibodies. Seminars in oncology. 2010 Oct;37(5):508-16.

39. Lee SJ, Myers L, Muralimohan G, Dai J, Qiao Y, Li Z, et al. 4-1BB and OX40 dual costimulation synergistically stimulate primary specific CD8 T cells for robust effector function. J Immunol. 2004 Sep 1;173(5):3002-12.

40. Morales-Kastresana A, Sanmamed MF, Rodriguez I, Palazon A, Martinez-Forero I, Labiano S, et al. Combined Immunostimulatory Monoclonal Antibodies Extend Survival in an Aggressive Transgenic Hepatocellular Carcinoma Mouse Model. Clinical Cancer Research. 2013 Nov 15;19(22):6151-62.

41. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009 Jul 16;114(3):589-95.

42. Seyedin SN, Schoenhals JE, Lee DA, Cortez MA, Wang X, Niknam S, et al. Strategies for combining immunotherapy with radiation for anticancer therapy. Immunotherapy. 2015;7(9):967-80.

43. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015 Apr 16;520(7547):373-7.

44. Koski GK, Czerniecki BJ. Combining innate immunity with radiation therapy for cancer treatment. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005 Jan 1;11(1):7-11.

45. Shi W, Siemann DW. Augmented antitumor effects of radiation therapy by 4-1BB antibody (BMS-469492) treatment. Anticancer research. 2006 Sep-Oct;26(5A):3445-53.

46. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. The Journal of clinical investigation. 2014 Feb;124(2):687-95.

47. Deng L, Liang H, Burnette B, Weicheslbaum RR, Fu YX. Radiation and anti-PD-L1 antibody combinatorial therapy induces T cell-mediated depletion of myeloid-derived suppressor cells and tumor regression. Oncoimmunology. 2014;3:e28499.

48. Verbrugge I, Hagekyriakou J, Sharp LL, Galli M, West A, McLaughlin NM, et al. Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. Cancer research. 2012 Jul 1;72(13):3163-74.

49. Belcaid Z, Phallen JA, Zeng J, See AP, Mathios D, Gottschalk C, et al. Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model. PloS one. 2014;9(7):e101764.

50. Gough MJ, Crittenden MR, Sarff M, Pang P, Seung SK, Vetto JT, et al. Adjuvant Therapy With Agonistic Antibodies to CD134 (OX40) Increases Local Control After Surgical or Radiation Therapy of Cancer in Mice. Journal of Immunotherapy. 2010 Oct;33(8):798-809.

51. Yokouchi H, Yamazaki K, Chamoto K, Kikuchi E, Shinagawa N, Oizumi S, et al. Anti-OX40 monoclonal antibody therapy in combination with radiotherapy results in therapeutic antitumor immunity to murine lung cancer. Cancer science. 2008 Feb;99(2):361-7.

52. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiation research. 2007;167(4):396-416.

53. Bohnsack O, Hoos A, Ludajic K. Adaptation and modification of the immune related response criteria (IRRC): IrRECIST. American Society of Clinical Oncology, 2014.

54. Chang JY, Balter PA, Dong L, Yang Q, Liao Z, Jeter M, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non–small-cell lung cancer. International Journal of Radiation Oncology* Biology* Physics. 2008;72(4):967-71.

55. Kelly P, Balter PA, Rebueno N, Sharp HJ, Liao Z, Komaki R, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. International Journal of Radiation Oncology* Biology* Physics. 2010;78(5):1387-93.

56. Welsh J, Thomas J, Shah D, Allen PK, Wei X, Mitchell K, et al. Obesity increases the risk of chest wall pain from thoracic stereotactic body radiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2011;81(1):91-6.

57. Chang JY, Liu H, Balter P, Komaki R, Liao Z, Welsh J, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiation Oncology. 2012;7(1):152.

58. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. Journal of Clinical Oncology. 2009;27(10):1572-8.