A PHASE 1B/2 OPEN-LABEL STUDY TO EVALUATE SAFETY, CLINICAL ACTIVITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AVELUMAB (MSB0010718C) IN COMBINATION WITH OTHER CANCER IMMUNOTHERAPIES IN PATIENTS WITH ADVANCED MALIGNANCIES

JAVELIN MEDLEY

Compounds:	MSB0010718C PF-05082566 PF-04518600 PD 0360324 CMP-001
Compound Name:	Avelumab (MSB0010718C) Utomilumab (PF-05082566)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2015-002552-27
Protocol Number:	B9991004
Phase:	1b/2

Document History

Document	Version Date	Summary of Changes
Original Protocol	09 June 2015	Not applicable (N/A)
Protocol Amendment 1	31 August 2015	The following are FDA directed changes to the original Protocol: Table 2 of the Schedule of Activities was revised to include 2 additional PK blood samples for PF-05082566 and avelumab on Cycle 1 Day 8 and Cycle 1 Day 15. Protocol Section 1.2.2.3 was revised to include safety data from patients receiving 10 mg/kg of PF-05082566. Protocol Summary, Protocol Sections 3.1.3, Figure 3, Section 9.2 and Table 9, the wording for stopping a dose level cohort based on the number of DLTs in the Phase 1b portion of the study was changed from 3 out of 6 patients to 2 out of 6 patients with DLTs. In Protocol Section 3.2, the definition of Grade 3 diarrhea was revised to place a restriction on the time before it is considered a DLT. The definition of DLT for liver function tests was revised to reflect Hy's Law. In Protocol Section 4.1, inclusion criterion 1 was revised so that patients with ALK-rearranged or EGFR-mutated NSCLC have received and are refractory to or intolerant of standard treatment options. Protocol Section 5.3.5.3 was revised to require investigators to re-consent patients who will continue on therapy after initial progression of disease. Table 5 in Protocol Section 5.3.7.2 was revised to remove "single value out of normal range that are likely related to treatment as assessed by the Investigator" under "Exceptions to permanent discontinuation". In addition, compound number MSB0010718C has been corrected throughout the document, Section 1.2.2 heading was revised to "anti-4-1BB", and Section 3.1.2 was revised to remove wording not required per protocol template and was redundant with Section 3.1.3.

Document	Version Date	Summary of Changes
Protocol Amendment 2	29 February 2016	Amendment 2 is 1) adding a triple-negative breast cancer (TNBC) cohort to Combination A (avelumab and PF-05082566), and 2) adding a new combination to the study (Combination B; avelumab and PF-04518600). Changes to specific sections of the protocol are listed below. Schedule of Activities for Combination A (avelumab and PF-05082566) and Section 7.1.4 updated to remove ANA, ANCA, and RF tests. Schedule of Activities for Combination A (avelumab and PF-05082566): physical examination, hematology, blood chemistry, and vital signs have been removed from Day 8 and Day 22 of Cycles ≥3. Schedule of Activities for Combination A: Contraceptive check added to Day 1 of each cycle, to EOT, and end of contraception requirement period. Concomitant treatment collection added to Follow-Up. Schedule of Activities for Combination A: TCR Analysis added. Schedule of Activities for Combination A: Footnote 22 replaced with wording from Section 8.2 to clarify previous inconsistencies. Schedule of Activities for Combination A: Footnotes 28 and 29 revised to clarify requirements for archival and *de novo* biopsies. Schedule of Activities for Combination B (avelumab and PF-04518600) added. Section 1: Triple-negative breast cancer (TNBC) and colorectal cancer tumor types and description of Combination B (avelumab and PF-04518600) were added. Section 1.2.2.3: Section on pre-clinical combination studies moved in front of clinical safety and efficacy to improve readability.

Document	Version Date	Summary of Changes
		Section 1.2.2.4: Clinical Efficacy of PF-05082566 was updated. Section 1.2.3: Background of PF-04518600 (anti-OX40) added. Section 1.2.4: Study rationale for Combination B added. Section 1.2.5: Title changed to Rationale for Investigational Product Doses. Section 1.2.5.3: Rationale for PF-04518600 doses added. Section 1.3: Added information about PF-04518600 to Summary of Benefit/Risk Assessment. Section 1.4: Biomarker rationale added. Section 2: Study objectives and endpoints updated to include TNBC and CRC tumor types, added OR as a secondary endpoint for Phase 1b, CCI [redacted] Section 3: Phase 2 study design for Combination A updated to include TNBC cohort. Phase 1b dose-escalation lead-in and Phase 2 for Combination B added to study design. Collection of MSI status for CRC patients and HPV status for SCCHN patients added. Section 3.3: Added MTD definition. Section 3.4: Added MAD definition. Section 4.1: Inclusion criterion 1 updated to include specifications for Combination A and Combination B. Inclusion criterion 8 updated to remove investigator judgment. Inclusion criterion 10 revised for clarity. Section 4.2: Exclusion criterion 1 revised to exclude use of mAb therapy within 28 days prior to study entry and small molecule-based therapy (targeted or chemotherapy) within 14 days prior to study entry. Exclusion criterion 10 revised to no longer exclude deep vein thrombosis within 6 months of study entry.

Document	Version Date	Summary of Changes
		Section 4.3: Lifestyle guidelines revised to include details for Combination B. Section 5: Updated throughout to include information on PF-04518600. Section 5:1: Updated to include information for allocation to treatment for Combination B. Section 5.3.3: Added supplies of PF-04518600. Section 5.3.4.3: Added formulation and packaging of PF-04528600. Section 5.3.5.3: Added preparation of PF-04518600. Section 5.3.6: Updated wording for premedication for infusions for clarity. Section 5.3.6.1: Updated to include a +20 minute time window, if needed, in between infusions of avelumab and PF-05082566 or PF-04518600. Section 5.3.6.3: Added details of administration of PF-04518600. Section 6.1.1: Text revised for clarification of requirements for archival and *de novo* biopsies. Section 7.2.3: Added PK analysis of PF-04518600. Section 7.3.3: Added immunogenicity assessment of PF-04518600. Section 7.4: Updated to include a table of biomarker collections and analyses. Section 7.5.1: Revised to include specifics for Combination B. Section 7.6: Updated to include blood samples for carcinoembryonic antigen (CEA) testing in CRC patients in Combination B when tumor assessments are performed. MRI added as an option for bone imaging.

Document	Version Date	Summary of Changes
		Section 9: Updated throughout to include specific details for Combination B. Section 9.1: Analysis sets updated to include those for Combination B. Section 9.2.2: Added with statistical methods for Combination B. Section 9.3: Updated to include sample size determination for the TNBC cohort for Combination A and sample size determination for Combination B. Section 9.4: Updated to include Combination B in efficacy analysis. Section 9.5.1.1: Revised analysis of biomarker endpoints. Section 16: Updated references 22 and 27. Added references 34-49 related to anti-OX40 and the addition of Combination B. Appendix 1: The RECIST v1.1 appendix was re-formatted to maintain consistency across avelumab studies. The content and meaning of this appendix has not changed. Appendix 4: The irRECIST appendix was revised to reflect the most recent publication from Nishino, et al. There are 3 differences from the original Appendix 4: up to 2 new target lesions per organ are allowed instead of up to 5 new target lesions per organ; up to 5 target lesions total are allowed instead of up to 10 target lesions total; and lymph nodes are measured on the short axis and must be ≥15 mm. Other administrative changes have been incorporated throughout the document.

Document	Version Date	Summary of Changes
Protocol Amendment 3	22 April 2016	Section 3.1.5: Table 8 regarding the decision rules of the mTPI design was revised to reflect a target DLT rate change from 30% to 25% per FDA request. Section 3.3: The definition of MTD for PF-04518600 in combination with avelumab was revised to clarify that MTD decision making is dependent on the higher dose of PF-04518600 tested in combination with 10 mg/kg avelumab. Section 4.1: Inclusion criterion #1 for Combination A Phase 2 was revised to not include patients with PD-1 or PD-L1 refractory disease (best response of PD). Section 9.2.2: The target probability rate was changed from 0.3 to 0.25, and the DLT interval was changed to (0.16, 0.33) per FDA request.
Protocol Amendment 4	11 August 2016	Section 3.1.5: Wording added to allow flexibility in the timing and the number of patients in dose escalation cohorts.
Protocol Amendment 5	30 September 2016	Major changes to the protocol included the following: • "PF-05082566" replaced with the proposed International Nonproprietary Name (INN), "utomilumab", throughout the protocol. • Avelumab and utomilumab clinical experience data (safety, PK, and immunogenicity) updated in the Introduction section. • Combination A (avelumab plus utomilumab): cohorts of patients with SCLC (n=20) and first-line NSCLC (n=20) added to the Phase 2 part. In addition, the sample size for the TNBC cohort was reduced to 20, and sample size justifications for the tumor-specific cohorts were added or modified, as applicable. • Combination B: patient population modified to specify that the Phase 2 tumor-specific cohorts to be evaluated will include a total of 25 patients each, including at least 20 anti-PD-1/PD-L1 treatment-naïve patients and up to 5 patients who have previously received anti-PD-1/PD-L1 therapy.

Document	Version Date	Summary of Changes
		• Two new combinations of avelumab plus other cancer immunotherapies were added: 1) Combination C (avelumab plus PD 0360324) and 2) Combination D (avelumab plus utomilumab plus PF-04518600). Due to the addition of these new combinations, several sections of the protocol were modified. A high-level summary of the major changes made by section are as follows: • Protocol Summary updated; • Schedule of Activities (SOAs) updated; • New SOA Tables 5 – 8 added; • Section 1, Introduction, updated; • Background information for the new combination agent (PD 0360324) added; • Study rationale for Combinations C and D added. • Section 2, Study Objectives and Endpoints, updated to include objectives and endpoints specific to Combinations C and D; • Section 3, Study Design, updated to include details specific to Combinations C and D. In addition, the Study Design section was revised to minimize redundancies across the various combinations included in the study; • Section 4, Patient Selection, updated to include details specific to Combinations C and D; • Section 5, Study Treatments, updated to include investigational product details (appearance/packaging, preparation, administration) for PD 0360324 (Combination C). In addition, dose modification guidelines for PD 0360324 and considerations specific to Combination D were added;

Document	Version Date	Summary of Changes
		• Section 7, Assessments, updated to include details regarding PK, immunogenicity, and biomarker/pharmacodynamic (PD) sample collections for Combinations C and D; • Section 9, Data Analysis/Statistical Methods, updated to describe sample size determinations for Combinations C and D; • Appendix 3, Abbreviations and Definition of Terms, updated. • In addition, several changes were made to the overall protocol structure to reduce redundancies and other administrative changes made to improve clarity.
Protocol Amendment 6	16 May 2017	The primary purpose of Protocol Amendment 6 was to add a new combination treatment of avelumab plus PF-06840003 for evaluation in patients with advanced solid tumors (Combination E). A high-level summary of changes made to the protocol specific to Combination E by section is as follows: • Protocol Summary updated; • Schedule of Activities (SOA) updated (Tables 9 and 10 added); • Section 1, Introduction, updated; • Background information for the new combination agent (PF-06840003) added; • Study rationale for Combination E added. • Section 3, Study Design, updated to include details specific to Combination E; • Section 4, Patient Selection, updated to include details specific to Combination E; • Section 5, Study Treatments, updated to include investigational product details for PF-06840003;

Document	Version Date	Summary of Changes

		• Section 7, Assessments, updated to include details regarding PK, immunogenicity, ECG, and biomarker assessments specific to Combination E;
		
		• Section 9, Data Analysis/Statistical Methods, updated to describe statistical methods specific to Combination E.
		
		In addition to Combination E, the following changes were also made as part of Protocol Amendment 6:
		
		Added two new cohorts (Cohort A9 and Cohort A10) of patients with 1st-line NSCLC to Combination A to evaluate sequenced administration of avelumab and utomilumab.
		
		Modified specific tumor-type inclusion criteria for each of the Combinations to improve overall clarity, and ensure homogenous patient population enrollment.
		
		Allowed Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS) patients in combination C.
		
		Instructions for treatment modifications for drug-related toxicities and management of immune-related adverse events were updated as per latest avelumab Investigator's Brochure (IB) and reorganized for clarity.
		
		An overview of these and other additional changes by section are as follows:
		
		• Schedule of Activities, Tables 1 and 2 (SOA for Combination A) modified to include evaluations specific to new Cohorts A9 and A10.
		
		• Section 1, Introduction, updated;
		
		  • Current clinical experience data (safety, PK, immunogenicity, and preliminary efficacy) updated for avelumab, PF-04518600, and utolimumab;
		
		  • Study rationale specific to Cohorts A9 and A10 added;

Document	Version Date	Summary of Changes
		• Advanced/metastatic CRC has been removed as a specified tumor type across the study for strategic reasons. • Section 3, Study Design, updated to include details specific to Cohorts A9 and A10. • Section 4, Patient Selection, Inclusion Criterion 1 modified to improve clarity and improve homogeneity of tumor-related criteria for all Combinations. • Section 5, Study Treatments, Table 18 (Investigational Product Treatment Modifications for Drug-Related Toxicity) condensed, Table 20 (Management of Immune-Related Adverse Events) modified per current avelumab program standards, and Figure 15 (Assessment and Initial Management of Tumor Lysis Syndrome [TLS]) deleted. • Section 6, Study Procedures, instructions for tumor biospecimens revised for consistency with changes made to Section 4, Patient Selection; requirements regarding assessments during the follow-up period revised for consistency. • CCI [redacted] • Section 8, Adverse Event Reporting, language updated to comply with current safety reporting standards. • Section 9, Data Analysis/Statistical Methods, sample size methodology for Combinations A and B updated; additional details regarding the planned PK and ECG analyses added. Other minor administrative and/or editorial changes were also incorporated to improve overall document clarity and accuracy.

Document	Version Date	Summary of Changes

Protocol Amendment 7	18 Sep 2017	The primary purpose of Protocol Amendment 7 was to remove a new combination treatment of avelumab plus PF-06840003 for evaluation in patients with advanced solid tumors (Combination E) sections. A high-level summary of changes made to remove the Combination E by section is as follows:
		• Protocol Summary;
		• Schedule of Activities (SOA) updated (Tables 9 and 10 has been removed);
		• Section 1, Introduction, has been updated and all information pertaining to Combination E has been removed including;
		  • Background information for the new combination agent (PF-06840003);
		  • Study rationale for Combination E.
		• Section 3, Study Design, updated to remove details specific to Combination E;
		• Section 4, Patient Selection, updated to remove details specific to Combination E;
		• Section 5, Study Treatments, updated to remove investigational product details for PF-06840003;
		• Section 7, Assessments, updated to remove details regarding PK, ECG, and biomarker assessments specific to Combination E;
		• Section 9, Data Analysis/Statistical Methods, updated to remove section on statistical methods specific to Combination E.
		Other minor administrative and/or editorial changes were also incorporated to improve overall document clarity and accuracy.

Protocol Amendment 8	27 Feb 2019	The primary purpose of Protocol Amendment 8 was to add new combination treatments for evaluation in patients with SCCHN: Cohort F1, avelumab plus CMP-001; Cohort F2, avelumab plus CMP-001 and

Document	Version Date	Summary of Changes

		utomilumab; Cohort F3, avelumab plus CMP-001 and PF-04518600. In addition the current status of Combinations A, B and C is updated and certain procedures applicable to all combinations are updated. The amendment will be submitted in all countries and will be applicable to all study centers upon approval. However, the avelumab plus CMP-001 combination (Combination F) will only enroll patients at centers in the United States (US). A high-level summary of changes made to the protocol, by section, is as follows:
		
		• Protocol Summary updated;
		
		• Schedule of Activities (SOA) updated (Tables 3, 5, 7, 9 for Combination A to D) to remove the requirement of onsite Day 60 and Day 90 follow up visits and safety lab assessments;
		
		• SOA updated (Tables 6, 8, 10 for Combination B to D) to remove the requirement of biomarker assessments on Cycles 7, 13 and Day 30 follow up visit;
		
		• SOA added for Combination F (Tables 11 and 12);
		
		• Section 1, Introduction, updated;
		
		  • Background information for the new combination agent (CMP-001) added;
		
		  • Study rationale for Combination F added.
		
		• Section 2, Study Objectives and Endpoints;
		
		  • Original Primary endpoint language updated to clarify that it refers to Combinations A, B, C, and D;
		
		  • Specific Primary endpoint for Combination F added;
		
		  • CCI [redacted]

Document	Version Date	Summary of Changes

		CCI
		• Section 3, Study Design, updated;
		  • Study Design, updated to include details specific to Combination F;
		  • The frequency of tumor assessments updated for visits after 24 months from randomization;
		  • Current status of combination A, B and C updated.
		• Section 4, Patient Selection;
		  • Added selection criteria specific to Combination F;
		  • Updated the requirements regarding lifestyle/contraceptive requirement guidance.
		• Section 5, Study Treatments;
		  • Added investigational product details for CMP-001, edits to text pertaining to the management of infusion-related reactions, and addition of information pertaining to management of cytokine release syndrome and injection site reactions;
		  • Updated premedication and observation period-related requirements for avelumab infusion.
		• Section 6, Study Procedures;
		  • Updated to include details of an on-treatment biopsy specific to Combination F;
		  • Updated to specify the maximum duration of study treatment;
		  • Updated the follow-up visit procedures and laboratory tests included in the standard safety

Document	Version Date	Summary of Changes

		laboratory assessments for all combinations.
		
		• Section 7, Assessments;
		
		  • Updated to include details regarding PK, immunogenicity, ECG, and biomarker assessments specific to Combination F;
		
		  • The requirement to collect and store images by an independent third-party laboratory removed;
		
		• Section 9, Data Analysis/Statistical Methods, updated to describe statistical methods specific to Combination F;
		
		• Appendix 3, Abbreviations and Definition of Terms, updated;
		
		• Appendix 4, Immune Related Response Criteria removed and added text to clarify CMP-001 study drug administration.
		
		The following changes were made as a result of protocol administrative change letters (PACLs) dated 29 June 2018 and 28 September 2018:
		
		<u>PACL dated 29 June 2018:</u>
		
		• CCI [redacted]
		
		• Section 7.4, Biomarker and Pharmacodynamic Assessments, modification of text pertaining to the handling of biospecimens remaining at the close of the study;
		
		• CCI [redacted]
		
		<u>PACL dated 28 September 2018</u>:
		
		• Edits made to the SOA tables (Tables 3, 5, 7, and 9) to modify the frequency of assessments for patients

Document	Version Date	Summary of Changes
		who participate in the study for more than 2 years. Other minor administrative and/or editorial changes were also incorporated to improve overall document clarity and accuracy. The following changes were made as a result of program level protocol deviation alert letter (PDAL dated 09 August 2018): • Section 7.1.4, Laboratory Safety Assessments, addition of text describing the requirement to review laboratory test results prior to study drug administration

Protocol Amendment 9	13 Dec 2019	The primary purpose of Protocol Amendment 9 was to modify the inclusion criteria for Combination F and to update the current status of Combination D. A high-level summary of changes made to the protocol, by section, is as follows:
		
		• SOA updated for Combination F (Tables 11 and 12).
		
		• Section 4, Patient Selection:
		
		  • Modified inclusion criterion specific to prior immunotherapy in Combination F;
		
		  • Modified inclusion criterion specific to eligibility for intralesional administration in Combination F;
		
		  • Modified exclusion criterion specific to prior radiotherapy.
		
		• Section 5, Study Treatments:
		
		  • Addition of Section 5.3.3.2.5 detailing CMP-001 diluent;
		
		  • Updated Section 5.3.5.2 Timing of Investigational Product Administration to allow investigational product administration to be spread over two consecutive days for Combination F;

Document	Version Date	Summary of Changes
		• Premedication guidance for Combination F updated for when dosing is spread over 2 days; • Stress dose steroids prophylaxis for patients who have experienced CRS updated to align with dose modification requirement to discontinue study treatment for CRS of Grade 3 lasting >24 hours and CRS ≥Grade 4. • Appendix 4, CMP-administration: • Details on tumor lesion selection criteria for injectable lesions added. Other minor administrative and/or editorial changes were also incorporated to improve overall document clarity and accuracy. The following changes were made as a result of PACLs dated 8 April 2019, 30 July 2019, and 26 September 2019: <u>PACL dated 8 April 2019:</u> • SOA updated Combination A, B, C and D Footnote(s) 15 & Combination F Footnote 14 and Section 7.1.6 to clarify single ECG requirement at End of Treatment Visit; • SOA updated Combination D Footnote 16 & Combination F Footnote 15 to clarify hepatitis B blood tests requirements; • SOA Combination F Footnote 1 updated to clarify screening period definition; • Sections 5.3.2 Other Immune Modulators and Section 5.3.3 Formulation Dosage/Forms and Packaging updated to add CMP-001 diluent; • Section 5.3.5.2 Combination F observation period updated to correct typo error; • Section 13 Definition of End of Trial duplicate

Document	Version Date	Summary of Changes
		paragraph deleted. <u>PACL dated 30 July 2019:</u> • Protocol Summary updated and Section 3, Study Design updated to document current status of Combination D. <u>PACL dated 26 September 2019:</u> • SOA updated (Tables 6, 8, and 10, Combination B to D) to remove the requirement of immune cell phenotyping at the End of Treatment/Withdrawal Visit; • SOA updated (Tables 5 and 9, Combination B and D) to clarify PF-04518600 administration on Day 15 of Cycles ≥24; • SOA table formatting corrected (Tables 3, 5, 7, 9 and 11) to show Cycles ≥24 visits in On Treatment column.

These amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SUMMARY

Indication

Avelumab is a fully human anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype that is currently being investigated in combination with other cancer immunotherapies to enhance anti-tumor activity over that expected by avelumab alone in patients with locally advanced or metastatic solid tumors. Avelumab is expected to increase the effectiveness of anti-tumor T cells by preventing inhibition of T cell activation. This effect is expected to be enhanced by agents that promote anti-tumor immunity by complementary mechanisms such as promotion of T cell survival or removal of inhibitory myeloid cells.

Background

This is a Phase 1b/2 dose-finding study to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of avelumab (MSB0010718C), a PD-L1 mAb, in combination with other cancer immunotherapies in patients with locally advanced or metastatic solid tumors. Avelumab reversal of T cell inhibition via PD-L1 blockade is only one potential mechanism which can augment anti-tumor immunity. However, in many patients, blocking this single resistance pathway is insufficient to trigger a robust anti-tumor response. As will be detailed in this protocol, mouse tumor modeling suggests that combining avelumab with 4-1BB or OX40 (CD134) agonist mAbs as doublets leads to increased anti-tumor activity compared with mice treated with any of the single agents. In addition, macrophage-colony stimulating factor (M-CSF) blocking antibodies when combined with 4-1BB agonist mAbs and avelumab as a triplet, in models where myeloid suppressive cells may be important, exhibits greater anti-tumor activity than the respective doublets. Furthermore, triplet combinations of 4-1BB and OX40 agonist mAbs or 4-1BB agonist showed a marked increase in anti-tumor activity in these models compared with the respective doublets. It is thought that triplets may be more effective compared with doublets as it is likely that doublet therapies, while potentially effective, do not address resistance mechanisms tied to immune homeostasis as well as select triplets. Therefore, after the evaluation of respective doublets in this study for safety and preliminary clinical activity, triplet combinations may be explored in specific clinical settings where these combinations might be more effective.

While the above combinations address mechanisms thought to be active in tumors harboring a pre-existing immune response, they do not address the growing unmet medical need of patients who progress on PD-1/PD-L1 therapy due to absent or inactive immune responses. Preclinical studies detailed in this protocol suggest a Toll-like Receptor 9 (TLR9) receptor agonist may initiate immune responses that could be further enhanced by a PD-L1 pathway inhibitor in settings where single agent inhibition of the PD-L1 pathway is less effective. These preclinical studies also support the hypothesis that 4-1BB and OX40 agonist mAbs may further enhance T cell responses activated by the TLR9/PD-L1 combination.

The primary purpose of this study is to assess the safety and early signs of activity of the above mentioned avelumab doublet and triplet combinations. The proposed combinations are as follows:

- Combination A: avelumab plus utomilumab (PF-05082566), a fully human Ig G2 mAb agonist of 4-1BB (CD137, TNFRSF9) that promotes survival and function of T cells, especially CD8+ T cells.

- Combination B: avelumab plus PF-04518600, a fully human IgG2 mAb agonist of OX 40 (CD134) that promotes survival and function of T cells, especially CD4+ T cells.

- Combination C: avelumab plus PD 0360324, a fully human IgG2 mAb directed against M-CSF that may inhibit tumor infiltration by immunosuppressive macrophages. (Sites in the United Kingdom [UK] will not participate in this combination).

- Combination D: avelumab plus utomilumab and PF-04518600 that is expected to provide complementary support for CD8+ and CD4+ T cells.

- Combination F: avelumab plus CMP-001, an encapsulated TLR9 agonist that is expected to activate tumor-infiltrating plasmacytoid dendritic cells (pDCs) leading to activation and recruitment of anti-tumor T-cells to the tumor microenvironment. CMP-001 is expected to elicit T cell priming and infiltration into the tumor microenvironment, whereas avelumab is expected to block T cell inhibition by PD-L1 that is induced by CMP-001. Utomilumab or PF-04518600 will be evaluated in combination with avelumab and CMP-001 for the promotion of survival and function of T-cells activated by the combination. (Only sites in the United States [US] will participate in this combination).

Study Objectives and Endpoints:

Primary Objectives

- Phase 1b lead-in: To assess safety and tolerability of a single dose level of avelumab in combination with increasing dose levels of other immune modulators in patients with locally advanced or metastatic solid tumors in order to select the Recommended Phase 2 Dose(s) (RP2D)/schedule for the combination.

- Phase 2: To assess objective response (OR) of avelumab in combination with other immune modulators in patients with locally advanced or metastatic solid tumors.

Secondary Objectives

- To assess the overall safety and tolerability of avelumab and other immune modulators when given in combination;

- To characterize the PK of avelumab and other immune modulators when given in combination;
- To evaluate the immunogenicity of avelumab and other immune modulators when given in combination;
- To assess the antitumor activity of avelumab and other immune modulators when given in combination in patients with locally advanced or metastatic solid tumors;
- To assess the correlation of antitumor activity of avelumab and other immune modulators with immune biomarkers in baseline tumor tissue.

Exploratory Objectives

- CCI [redacted]
- CCI [redacted]

Primary Endpoints

- Phase 1b lead-in:
  - First 2 Cycles Dose Limiting Toxicity (DLT) for Combination A, B, C and D;
  - First Cycle DLT(s) for Combination F only.
- Phase 2: Confirmed OR, as assessed by the Investigator using RECIST v1.1.

Secondary Endpoints

- Adverse events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness, and relationship to study treatments;
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;
- PK parameters (C_{max} and C_{trough});
- Anti-drug antibody (ADA) levels;

- Time-to-event endpoints including time to tumor response (TTR), duration of response (DR), progression-free survival (PFS) as assessed by the Investigator using RECIST v1.1, and overall survival (OS);

- Confirmed OR during Phase 1b, as assessed by the investigator using RECIST v1.1;

- Biomarkers such as PD-L1 expression and tumor infiltrating CD8+ T lymphocytes in baseline tumor tissue.

Exploratory Endpoints

- CCI [redacted]

- CCI [redacted]

Study Design and Sample Size:

This is a Phase 1b/2, open-label, multi-center, multiple-dose, safety, clinical activity, PK, and PD study of avelumab in combination with other immune modulators in adult patients with locally advanced or metastatic solid tumors (eg, non-small cell lung cancer [NSCLC], melanoma, squamous cell carcinoma of the head and neck [SCCHN], triple-negative breast cancer [TNBC], gastric cancer, ovarian cancer, bladder cancer, or small cell lung cancer [SCLC]). In Phase 1b and Phase 2, enrollment criteria vary by tumor type and are described in detail in Section 4.1. Incorporation of the other immune modulators into this study is based on preclinical and clinical data supportive of single-agent tolerability and potential clinical benefit, as well as non-clinical data suggesting safety, tolerability and clinical benefit of the agent(s) in combination with avelumab. Combinations of avelumab plus other immune modulator(s) to be evaluated are as follows:

- Combination A: avelumab plus utomilumab (4-1BB agonist mAb);

- Combination B: avelumab plus PF-04518600 (OX40 agonist mAb);

- Combination C: avelumab plus PD 0360324 (M-CSF mAb);

- Combination D: avelumab plus utomilumab plus PF-04518600.

- Combination F: avelumab plus CMP-001 (TLR9 agonist) and utomilumab or PF-04518600:
  - Cohort F1: avelumab plus CMP-001;
  - Cohort F2: avelumab plus CMP-001 and utomilumab;
  - Cohort F3: avelumab plus CMP-001 and PF-04518600.

For Phase 1b dose escalation and Phase 2 expansion cohorts, patients may be enrolled into different combinations in parallel. In non-randomized cohorts, slot assignments will be managed by the study team and sites will be notified in advance of cohort initiations. Patients are not allowed to crossover between the different combinations evaluated in this study.

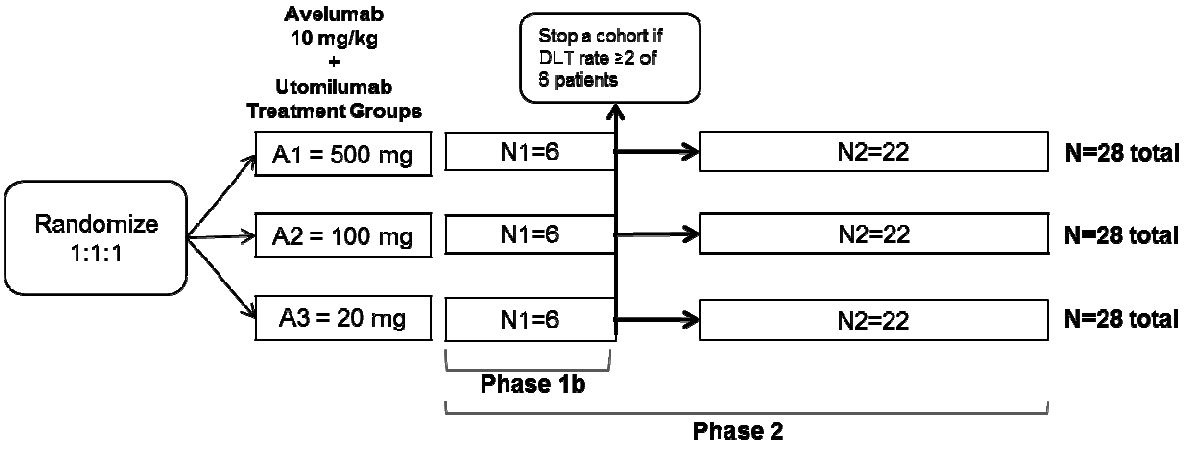
Each combination will be studied individually in 2 study parts: 1) a Phase 1b Lead-in part to evaluate safety, and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and RP2D (if applicable), of the combination, and 2) a Phase 2 part to evaluate efficacy and further evaluate safety of the selected dose from the Phase 1b portion in prespecified patient populations. Enrollment of patients in different combinations may be staged in order of combination alphabetical order and by tumor type. Therefore, in Phase 1b dose escalation cohorts and Phase 2 expansion cohorts, staging of patient recruitment will be communicated to clinical sites in advance of the opening of new cohorts. Study design details for each combination are provided below.

Additional combinations of avelumab with other immune modulators may be added to this protocol based on emerging preclinical and clinical data.

Combination A (Avelumab plus Utomilumab)

Combination A includes a Phase 1b lead-in part and a Phase 2 part (Figure 1 and Figure 2). During Phase 1b, up to 18 NSCLC patients will be randomized 1:1:1 to 1 of 3 cohorts (6 patients each) to receive utomilumab at 500 mg (Cohort A1), 100 mg (Cohort A2), or 20 mg (Cohort A3) administered intravenously (IV) every 4 weeks (Q4W) in combination with 10 mg/kg of avelumab administered IV every 2 weeks (Q2W) for 2 cycles (ie, 8 weeks). If a DLT is observed in at least 2 of 6 DLT-evaluable patients treated within a cohort, further evaluation of the cohort will be stopped (DLT definitions are provided in Section 3.3). Patients treated in Phase 1b who are not considered DLT evaluable will be replaced for the assessment of the DLT rate in the cohort to which they were randomized.

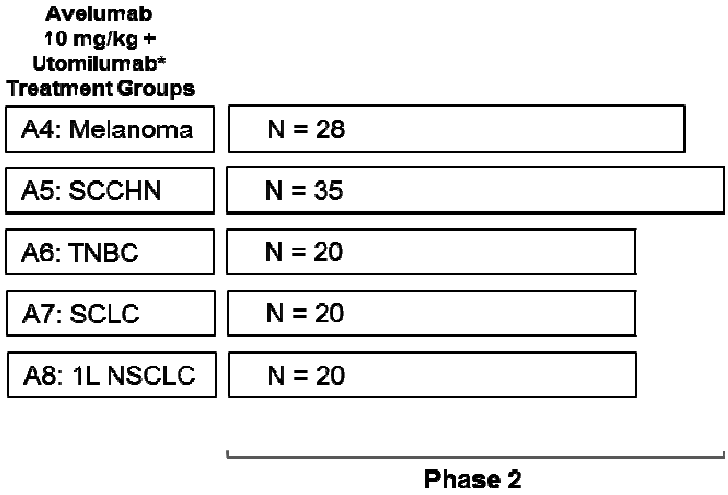
Figure 1. Combination A Phase 1b and Phase 2 Study Design Schema - NSCLC Only (Cohorts A1, A2, A3)



For each utomilumab dose level that is tolerated (ie, not meeting the DLT criteria) in the Phase 1b lead-in, the corresponding dose level cohort(s) will continue enrollment in Phase 2 with up to 22 additional patients each. Therefore, all 3 cohorts could potentially enroll additional patients.

In addition to potential expansion of enrollment of patients with NSCLC to Cohorts A1, A2, or A3, Phase 2 will also enroll patients with melanoma (Cohort A4; N=28), SCCHN (Cohort A5; N=35), TNBC (Cohort A6; N=20), SCLC (Cohort A7; N=20), and first-line (1L) advanced NSCLC (Cohort A8; N=20, up to 26 patients will be enrolled to achieve a minimum of 20 PD-L1-positive patients).

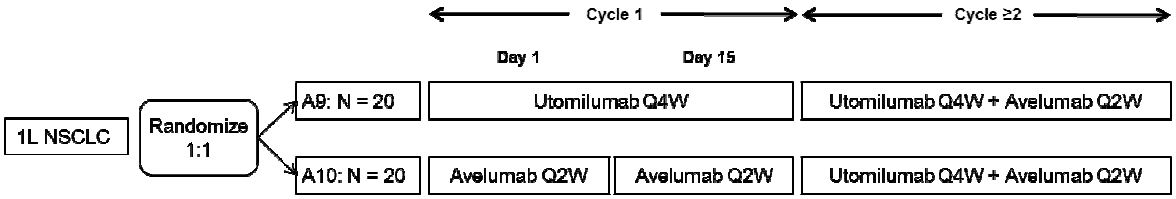
Figure 2. Combination A Phase 2 Study Design Schema - Melanoma (Cohort A4), SCCHN (Cohort A5), TNBC (Cohort A6), SCLC (Cohort A7), and First-Line NSCLC (Cohort A8)



* Utomilumab dose = 100 mg (may be modified based on emerging data).

Sequenced administration of single agent avelumab or utomilumab for 1 cycle followed by administration of combination (avelumab plus utomilumab) will be evaluated in 2 additional cohorts. Both cohorts will enroll 20 patients each with PD-L1 positive, first-line advanced NSCLC. Cohort A9 will evaluate utomilumab single-agent administration, one month prior to initiation of combination treatment on Cycle 2 Day 1 (28 days after start of the single-agent treatment). Cohort A10 will evaluate avelumab single-agent administration, one month prior to initiation of combination treatment on Cycle 2 Day 1 (28 days after start of the single-agent treatment). Enrollment into Cohorts A9 and A10 will be randomized 1:1.

Figure 3. Combination A Phase 2 Study Design Schema – Sequenced Administration in Patients with First-Line NSCLC (Cohort A9 and Cohort A10)



In Phase 2, efficacy and safety will be assessed separately for each cohort of utomilumab plus avelumab in the NSCLC Cohorts A1, A2, and A3, as well as for Cohorts A4 (melanoma), A5 (SCCHN), A6 (TNBC), A7 (SCLC), and A8–A10 (first-line NSCLC).

Originally, approximately 253 patients with solid tumors were planned to be enrolled in Combination A across all cohorts. Enrollment of patients into Cohorts A1 to A6 and A8 were completed as planned. In Cohort A7, 10 SCLC patients were enrolled. However, the level of clinical activity observed in Cohort A7 does not support further clinical development and further enrollment in this cohort is not planned. In addition, due to recent improvements in the standard of care for 1L NSCLC patients, the level of clinical activity observed in Cohort A10 does not support further development. Given that Cohort A9 and A10 use 1:1 randomization for enrollment, further enrollment in Cohort A9 alone would not conform with the study design. Therefore, further enrollment in Cohorts A7, A9, and A10 is not planned.

Combination B (Avelumab plus PF-04518600)

Combination B includes a Phase 1b dose-escalation part and Phase 2 part. In the Phase 1b part for Combination B, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus PF-04518600 using the modified toxicity probability interval (mTPI) design. Patients will receive PF-04518600 IV Q2W in combination with 10 mg/kg avelumab Q2W for 2 cycles (8 weeks).

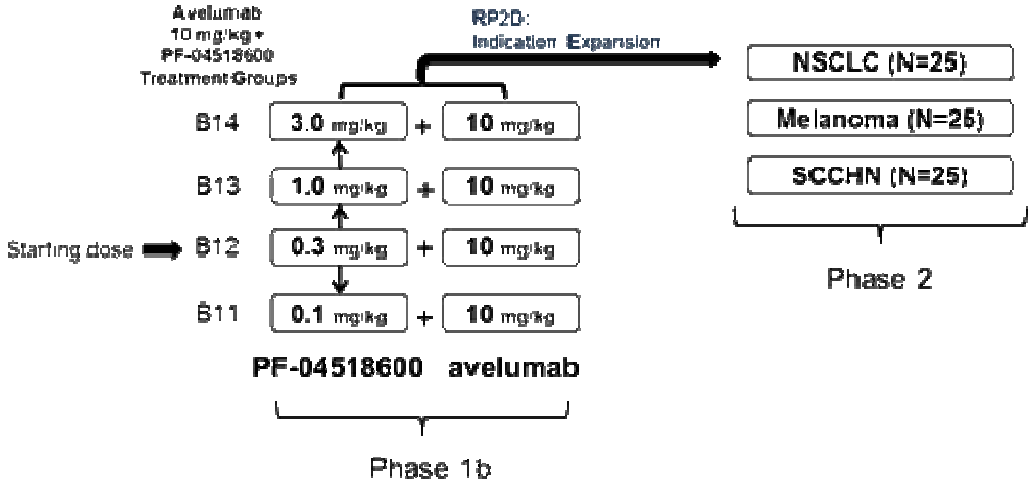
The starting dose level (B12) for Combination B is 0.3 mg/kg PF-04518600 Q2W plus 10 mg/kg avelumab Q2W. Initially 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. If recommended by the mTPI design, the dose level can be a) expanded in cohorts of up to 3 patients and then up to an additional 6 patients, b) escalated

to the next dose level, or c) de-escalated to a lower dose level. A total of 12 patients will be treated at the RP2D. If at any point the mTPI requires a de-escalation, the next 3 patients will be enrolled at the lower dose level. Dose escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

Following the 8-week DLT observation period, if no patients experience DLTs, the next higher dose level cohort may be initiated. Initially 3 patients will be assigned to a new open dose level. Up to 3 patients can be added at the same dose level if no DLTs are observed after 4 weeks of observation. After the first 3 patients enrolled in a dose escalation cohort have completed the 8-week DLT period, additional cohorts of up to 6 patients each may be enrolled into any dose level that has been deemed safe (if recommended by the mTPI design) for a total of 12 patients to obtain additional safety and PD data. See the subsection for all combinations in Inclusion Criterion 1 (Section 4.1) for biopsy requirements.

Once the Phase 1b part is completed and the MTD or MAD is determined, the Phase 2 portion of Combination B will be initiated. During Phase 2, patients with NSCLC, melanoma, SCCHN will be enrolled into 3 separate cohorts of 25 patients each to evaluate safety and efficacy at the RP2D determined during Phase 1b for those tumor types. Each cohort will provide preliminary estimates for objective response rate (ORR) to help inform future trials. The overall study schema for Combination B, including study treatments to be evaluated during Phase 1b, is presented in Figure 4).

Figure 4. Combination B Phase 1b and Phase 2 Study Design Schema



Originally, approximately 105 patients were planned to be enrolled in Combination B. Enrollment in Phase 1 was completed and enrollment in the Phase 2 SCCHN cohort was also completed. The safety profile of this combination was acceptable and there was evidence of pharmacodynamic activity. However, the observed clinical activity does not support further development. Therefore, the completion of patient enrollment into the Phase 2 NSCLC cohort and the initiation of enrollment into the Phase 2 melanoma cohort are not planned.

Combination C (Avelumab plus PD 0360324)

Combination C includes a Phase 1b sequential dose-escalation lead-in part and Phase 2 part. In the Phase 1b lead-in part for Combination C, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus PD 0360324 using the mTPI design. Patients will receive PD 0360324 IV Q2W in combination with 10 mg/kg avelumab Q2W for 2 cycles (8 weeks).

If recommended by the mTPI design, a dose level may be a) expanded in cohorts of up to 3 patients and then up to an additional 4 patients, b) escalated to the next dose level, or c) de-escalated to a lower dose level.

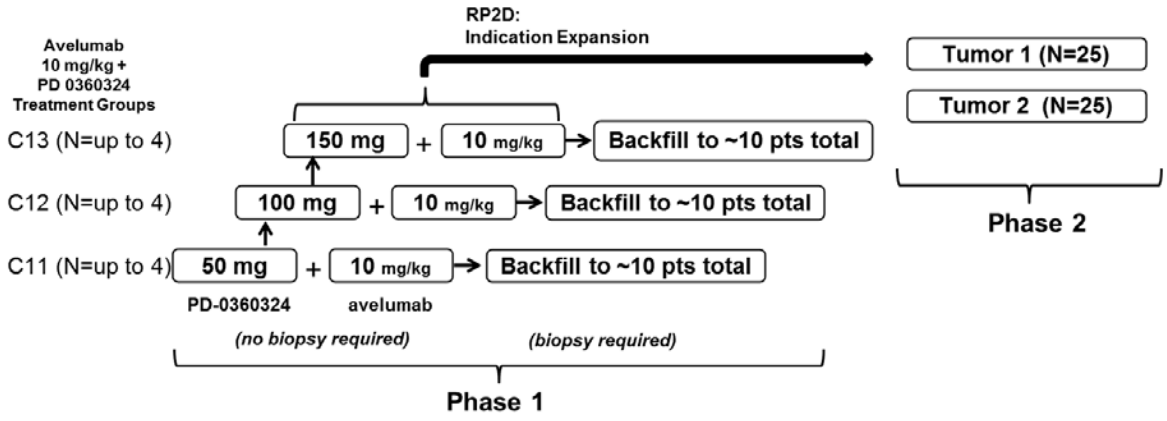
The starting dose level (C11) of Combination C is 50 mg PD 0360324 Q2W plus 10 mg/kg avelumab Q2W. Starting with dose level C11, 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. Fresh biopsies will not be required for the first 3 patients enrolled in each dose level. If at any point the mTPI requires a de-escalation, the next 3 patients will be enrolled at the lower dose level. Dose escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

In addition, if a DLT is observed in a lower dose level previously determined to be safe per mTPI, enrollment of additional patients in the higher dose levels will be delayed until the safety of the lower dose is reconfirmed per mTPI design.

During Phase 1b, if allowed by the mTPI design, a cohort may be expanded to approximately 10 patients total to collect additional safety, clinical activity, and biomarker related data.

Once the Phase 1b is completed and the MTD or MAD is determined, the Phase 2 portion of Combination C will be initiated to evaluate safety and efficacy at the RP2D determined during Phase 1b. Up to 2 tumor types among the following will be selected for evaluation: ovarian cancer, SCCHN, NSCLC, or gastric cancer. The overall study schema for Combination C, including study treatments to be evaluated during Phase 1b, is presented in Figure 5.

Figure 5. Combination C Phase 1b and Phase 2 Study Design Schema



Originally, approximately 80 patients were planned to be enrolled in Combination C. However, the level of clinical activity observed in cohorts C11, C12, and C13, did not support development beyond Phase 1b. Therefore, Phase 2 is not planned.

Combination D (Avelumab plus Utomilumab plus PF-04518600)

Combination D includes a Phase 1b sequential dose escalation part and a Phase 2 part. In the Phase 1b part for Combination D, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus utomilumab plus PF-04518600 using the mTPI design. Patients will receive utomilumab plus PF-04518600 in combination with avelumab Q2W for 2 cycles (8 weeks) and be evaluated for DLT.

The starting dose level (D11) for Combination D is 20 mg utomilumab Q4W plus 0.1 mg/kg PF-04518600 Q2W plus 10 mg/kg avelumab Q2W. The initiation of patient recruitment at D11 is dependent upon the observation of no more than 1 DLT out of 6 patients treated in Phase 1b Combinations A and B at 500 mg utomilumab and 1 mg/kg PF-04518600, respectively. As of 30 September 2016, this study has completed the Phase 1b part of Combination A with no DLTs observed and, for the Phase 1b part of Combination B, no DLTs have been observed at the starting dose level of 0.3 mg/kg PF-04518600 (B12) with evaluation of the 1 mg/kg PF-04158600 dose level ongoing. Since no DLTs were observed during Phase 1b of Combination A, Combination D will be initiated once the safety of the 1 mg/kg PF-04518600 dose level of Combination B is confirmed (eg, dose is acceptable per mTPI design following treatment of at least 6 patients treated at that dose or higher).

If recommended by the mTPI design, a dose level may be a) expanded in cohorts of up to 3 patients and then up to an additional 4 patients, b) escalated to the next dose level, or c) de-escalated to a lower dose level.

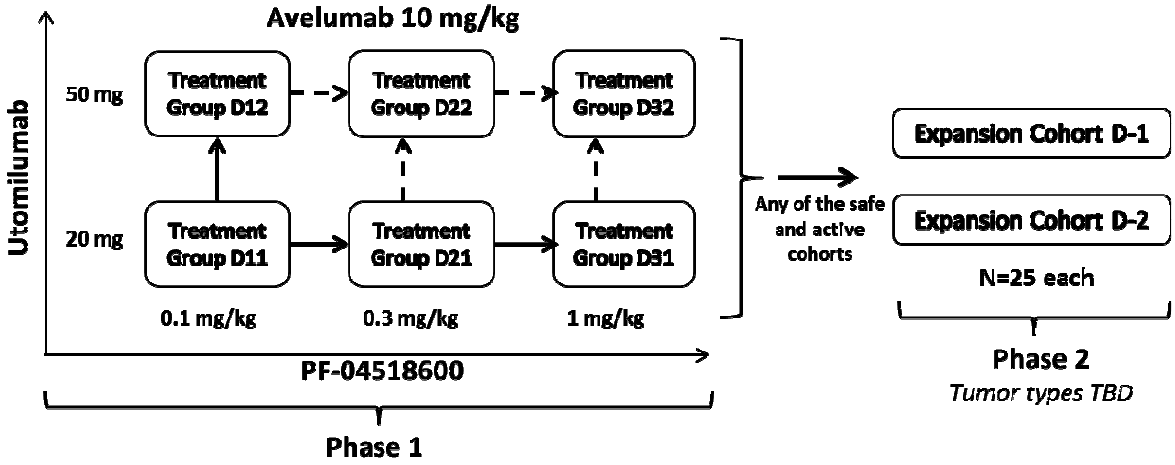
Starting with dose level D11, 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. Fresh biopsies will not be required for the first 3 patients enrolled in each dose level. If at any point mTPI requires de-escalation, the next 3 patients will be enrolled at the lower dose level. Dose escalation will be allowed as long as the dose level satisfies the mTPI criteria.

In addition, if a DLT is observed in a lower dose level previously determined to be safe per mTPI, enrollment of additional patients in the higher dose levels will be delayed until the safety of the lower dose is re-confirmed per mTPI design. During Phase 1b, if allowed by the mTPI design, a cohort may be expanded to approximately 10 patients total to collect additional safety, clinical activity, and biomarker related data.

Once the Phase 1b lead-in is completed and the MTD or MAD is determined, the Phase 2 portion of Combination D may be initiated to evaluate the safety and efficacy at the RP2D (one or more dose levels) determined during Phase 1b, if the safety and clinical activity are supportive of further development. Up to 2 tumor types among the following may be selected for evaluation: NSCLC, melanoma, SCCHN, or bladder cancer. The overall

study schema for Combination D, including study treatments to be evaluated during Phase 1b, is presented in Figure 6.

Figure 6. Combination D Phase 1b and Phase 2 Study Design Schema*



* A solid arrow to a dose level implies that only the dose level from which the arrow is originating needs to be safe (escalate per mTPI design) for that dose level to be opened. For example, D21 may be opened if D11 is safe, and D31 may be opened if D21 is safe. A dashed arrow to a dose level implies that more than 1 dose level is required to be safe (escalate per mTPI design for more than 1 dose level) for that dose level to be opened. For example, D12 and D21 both need to be safe (escalate per mTPI design for both) for D22 to be opened, and D31 and D22 both need to be safe for D32 to be opened. Cohorts D12 and D21 and Cohorts D22 and D31 may be opened and enroll patients in parallel since only either utomilumab or PF-04518600 is escalated at a time.

Originally, approximately 122 patients were planned to be enrolled into Combination D. However, the level of clinical activity observed in cohorts D11 to D32 did not support development beyond Phase 1b. Therefore, Phase 2 is not planned. Overall 71 patients were enrolled for Combination D treatment.

Combination F (Avelumab plus CMP-001 with or without Utomilumab or PF-04518600)

Combination F includes a Phase 1b safety lead-in part and a Phase 2 part. Eligible patients will have recurrent or metastatic SCCHN, will have been previously treated with an anti-PD-1 or anti-PD-L1 containing therapy, and will have experienced disease progression prior to study entry (see Inclusion Criteria in Section 4.1).

In the Phase 1b safety lead-in part, patients will initially be randomized 1:1:1 into each of Cohorts F1, F2, and F3. Six DLT evaluable patients are needed to assess safety in each cohort. Patient who are not evaluable for DLTs, might be replaced by enrolling a patient without randomization.

Up to 12 patients will be randomized into each cohort in the Phase 1b safety lead-in and evaluated for DLT during the first treatment cycle (4 weeks) as follows:

- If ≤1 of 6 patients experience DLT, the cohort will be expanded to enroll up to 14 additional patients in the Phase 2 cohort expansion.
- If 2 of 6 patients experience DLT, the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b lead-in part of the study:
  - If ≤3 of 12 patients experience DLT, the cohort will be expanded to enroll up to 8 additional patients in the Phase 2 cohort expansion;
  - If ≥4 of up to 12 patients experience DLT, enrollment in the specific cohort will be discontinued.
- If ≥3 of up to 6 patients experience DLT, enrollment in the specific cohort will be discontinued.

If one cohort is discontinued, patients will be randomized to the remaining cohorts in a 1:1 ratio. Therefore, the total number of possible enrolled patients per cohort may be approximately 20 patients for cohorts that do not meet the DLT stopping criteria and the total number of patients enrolled for this combination may be approximately 60 patients.

In addition to the rules for the continuation of a cohort based on DLTs, the Sponsor will monitor DLTs across the cohorts and may elect to pause or discontinue patient enrollment at any time based on emerging safety and efficacy data from the current study or other studies with CMP-001.

The following 3 cohorts will be evaluated (see Figure 7):

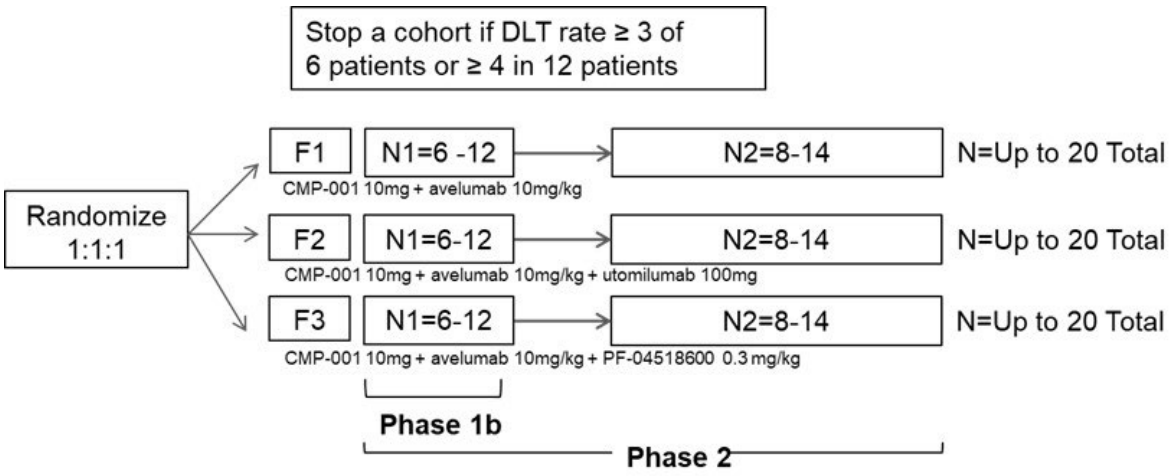
- Cohort F1: avelumab plus CMP-001;
- Cohort F2: avelumab plus CMP-001 and utomilumab;
- Cohort F3: avelumab plus CMP-001 and PF-04518600.

The following doses of study drugs will be administered:

- CMP-001 at 10 mg for an initial 7 doses (2 subcutaneous [SC] administrations at weekly intervals, followed by 5 intratumoral administrations [IT] at weekly intervals) and then IT administration every 2 weeks (Q2W) (all cohorts).
- Avelumab at 10 mg/kg administered IV every 2 weeks (Q2W) (All cohorts);
- Utomilumab at 100 mg administered IV every 4 weeks (Q4W) (F2);
- PF-04518600 at 0.3 mg/kg administered IV every 2 weeks (Q2W) (F3).

The overall study schema for Combination F, including study treatments to be evaluated, is presented in Figure 7.

Figure 7. Combination F Phase 1b and Phase 2 Study Design Schema



The dose levels of the study treatments to be evaluated during Combination F are presented in Table 1.

Table 1. Combination F (Avelumab Plus CMP-001 and Utomilumab or PF-04518600) Study Treatments

Cohort	CMP-001 (SC and IT)	Utomilumab Dose (IV)	PF-04518600 Dose (IV)	Avelumab Dose (IV)
F1	10 mg	NA	NA	10 mg/kg Q2W
F2	10 mg	100 mg Q4W	NA	10 mg/kg Q2W
F3	10 mg	NA	0.3 mg/kg Q2W	10 mg/kg Q2W

IV=intravenous; SC=subcutaneous; NA=not applicable; IT=intratumoral.

Study Design Elements Common to All Combinations

For all combinations, treatment with investigational products will continue until disease progression is confirmed by the Investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.

Patients who stop avelumab or the other immune modulator(s) may continue on treatment with the investigational product(s) that is/are not considered to be responsible for any severe adverse event (AE) in consultation with the Sponsor's Medical Monitor.

It is recommended that patients who have experienced a confirmed complete response (CR) should continue to be treated with investigational products at the discretion of the Investigator after discussion with the Sponsor.

Patients who stop treatment for reasons other than toxicity and experience radiologic disease progression shortly thereafter will be eligible for re-treatment with either avelumab or the other immune modulator(s) at the discretion of the Investigator and after discussion with the Sponsor.

Tumor Assessment: Anti-tumor activity will be assessed by radiological tumor assessments at 8-week intervals using RECIST v1.1. In case partial response (PR), CR, or progressive disease (PD) is observed according to RECIST v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. After 1 year from randomization in the study (randomized cohorts) or the first dose (non-randomized cohorts), tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the End of Treatment/Withdrawal (if not done in the previous 4 weeks and prior response is other than confirmed PD). Details of the treatment after initial evidence of radiological disease progression are provided in Section 5.3.5.3.

Further specific guidance on tumor imaging is provided in Section 7.6.

Safety Assessments: Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as described in the Schedule of Activities and described in Section 7.1. The hematology, blood chemistry, and pregnancy test (if applicable) results must be available and reviewed by the treating physician prior to study treatment administration. Further details are presented in Section 5.3.7.

PK/Immunogenicity Assessments: PK/immunogenicity blood sampling will be collected as described in the Schedule of Activities for each combination and described in Section 7.2.

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

Biomarker Assessments: A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and other immune modulator(s). In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the combinations of avelumab plus other immune modulator(s), as well as potential mechanisms of resistance. Biomarkers that correlate with pharmacodynamic effects may be considered when prioritizing dose levels for further exploration. Biomarker assessments are described in Section 7.4.

Investigational Products:

All investigational products will be administered at the investigational site on an outpatient basis. After Cycle 1, investigational products may be administered up to 2 days before or after the scheduled treatment day of each cycle for administrative reasons. However, if the administration is given 2 days before or after the scheduled treatment day, and multiple

investigational products are to be administered, all scheduled investigational products should be given on the same day.

Avelumab will be administered at 10 mg/kg as a 1-hour IV infusion Q2W on Day 1 and Day 15 of each cycle.

Utomilumab (Combination A, Combination D, and Combination F) will be administered as a 1-hour IV infusion Q4W on Day 1 of each cycle.

PF-04518600 (Combination B, Combination D, and Combination F) will be administered as a 1-hour IV infusion, Q2W on Day 1 and Day 15 of each cycle.

PD 0360324 (Combination C) will be administered as a 30-minute IV infusion Q2W on Day 1 and Day 15 of each cycle.

For Combination D, on days when 3 investigational products are to be administered, utomilumab will be administered first, followed at least 30 minutes (+20-minute time window, if needed) later by the PF-04518600 infusion (second), followed at least 30 minutes (+20-minute time window, if needed) later by the avelumab infusion (third). On days when only avelumab and PF-04518600 are administered, PF-04518600 will be administered first, followed by the avelumab infusion at least 30 minutes (+20-minute time window, if needed) after the end of the PF-04518600 infusion.

CMP-001 will be administered initially as 2 weekly SC doses, followed by IT dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 will be administered IT every 2 weeks (Q2W) (all cohorts). From C2D1, if IT is not feasible then CMP-001 should be administered in the peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh or anterior abdominal wall) administration should be implemented. For Combination F, on days when 3 investigational products are to be administered, either utomilumab (Cohort F2) or PF-04518600 (Cohort F3) will be administered first, followed by avelumab and then followed by CMP-001. CMP-001 administration and requirements are summarized in Table 2.

Table 2. CMP-001 Administration and Requirements

Visit/Dose	CMP-001 Administration[a]		Premedications	Post injection Observation Period
C1D1 and C1D8	SC (either arm, thigh or anterior abdominal wall)	Weekly	Mandated	Required (4 hrs)
C1D15, C1D22, C2D1, C2D8	IT[b]	Weekly	Mandated	Required (4 hrs)
C2D15 onwards	IT[b]	Every 2 weeks	Recommended	Required (can be reduced up to 1 hr based on reactions to prior injections and clinical judgement).

C=cycle; D=day; hr=hour; IT=intratumoral; SC=subcutaneous.
a. CMP-001 will be administered initially as 2 weekly SC doses, followed by IT dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 will be administered IT every 2 weeks (Q2W) (all cohorts).
b. From C2D1, if IT is not feasible then CMP-001 should be administered in peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh or anterior abdominal wall) should be implemented.

Detailed instructions for CMP-001 administration, including tumor lesion selection and dose splitting, are provided in Appendix 4 and in the Injection Manual.

Statistical Analyses

DLT is the primary endpoint for Phase 1b lead-in. The DLT-evaluable data set includes all enrolled patients in Phase 1b who are eligible for the study, receive at least 1 dose of study treatment, and either experience DLT or complete the DLT observation period. For Combinations A, B, C, and D, the DLT observation period is the first 2 cycles (8 weeks) of treatment. For Combination F, the DLT observation period will be 4 weeks including the first two weekly SC injections and the subsequent two weekly IT administrations.

Patients without DLTs who withdraw from study treatment before receiving at least 75% of the prescribed doses for all investigational products in the combination for reasons other than treatment-related toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

Analyses of DLT are based on the DLT-evaluable set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed per cohort for patients in the Phase 1b lead-in (Combination A and Combination F) and summarized and listed for all patients in the Phase 1b lead-in (Combinations B, C, and D).

OR is the primary endpoint for Phase 2. OR is defined as CR or PR per RECIST v1.1 from the randomization in the study (randomized cohorts) or first dose (non-randomized cohorts) until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Objective response rate (ORR) is defined as the proportion of patients with a confirmed CR or PR per Investigator's assessment according to RECIST v.1.1. The two-sided exact 90% CIs for ORR will be calculated.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section 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 in the Schedule of Activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 3. Schedule of Activities: Combination A (Avelumab and Utomilumab) - Safety and Efficacy Assessments (Phase 1b and Phase 2)

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to Randomization/ First dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [38]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[39]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3
Informed Consent[2]	X																
Tumor History[3]	X																
Medical History[4]	X																
Physical Examination[5]	X	X	X	X	X	X	X	X	X	X		X		As clinically indicated		X	X (Day 30)
Baseline Signs & Symptoms[6]		X															
ECOG PS[7]	X	X				X				X						X	X (Day 30)
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Contraceptive Check[9]	X	X				X				X				X		X	X (Day 90)
Safety Labs/Measurements																	
Hematology[10]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Coagulation[12]	X	X								As clinically indicated							
Urinalysis[13]	X									As clinically indicated							
Serum/Urine Pregnancy Test[14]	X	X		X		X		X		X		X		X	X	X	X (Day 30)
12-Lead ECG [15]	X	X				X										X	
HBV, HCV tests[16]	X																
ACTH and Thyroid Function Tests[17]	X									C3 then every 12 wks.						X	X (Day 30)
Registration and Treatment																	
Randomization/ Enrollment[18]		X															

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to Randomization/ First dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal[38]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[39]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Avelumab Administration[19]		X[19] (Except cohort A9)		X (Except cohort A9)		X		X		X		X		X	X		
Utomilumab Administration[20]		X[20] (Except cohort A10)				X				X				X			
		Tumor Assessments															
CT or MRI Scan[21]	X	Every 8 weeks (±7 days), After 1 year from randomization, for Cohorts A1-A3 and A9 and A10 or first dose for Cohorts A4-A8, every 12 weeks; After 2 years from randomization, for Cohorts A1-A3 and A9 and A10 or first dose for Cohorts A4-A8, every 16 weeks (±7 days)														X	
		Other Clinical Assessments															
Adverse Events[22]	X	Monitored and recorded continually															X
Concomitant Treatments[23]	X	Monitored and recorded continually															X
Subsequent Anti-Cancer Treatment[24]		NA															X
Survival[25]		NA															X

Table 4. Schedule of Activities: Combination A (avelumab and Utomilumab) - Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)										Post Treatment	
	≤28 days prior to Randomization/ First dose	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10, 12	End of Treatment /Withdrawal [38]	Follow Up (Day 30, 60, 90) [39]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		
Visit Window			(±) 2	(±) 2	(±) 2	(±) 2		(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Blood for utomilumab PK[26]		X (Except Cohort A10)	X	X				X		X	X (C8 and C12 only)		
Blood for Avelumab PK[27]		X (Except Cohort A9)	X	X		X			X		X (C6 and C10 only)		
Archival FFPE Tumor Tissue Block[28]	X												
De Novo Tumor Biopsy [29]	X					X		As clinically indicated				X	
TCR Analysis[30]	X	X		X		X	X	X		X		X	
Whole Blood for DNA Analysis[31]		X				X		X		X		X	
Serum for pharmacogenomic/ proteomic/metabolomic analysis[32]		X				X		X		X		X	
Plasma for pharmacogenomic/ proteomic/metabolomic analysis[33]	X	X				X		X				X	
PAXGene whole blood collection optimized for RNA analysis[34]		X				X		X		X		X	
Banked Biospecimens[35]		X											
Blood for utomilumab Immunogenicity (ADA) testing[36]		X (Except Cohort A10)						X		X	X (C8 and C12 only)		
Blood for Avelumab Immunogenicity (ADA) testing[37]		X (Except Cohort A9)				X			X		X (C6 and C10 only)		

Footnotes for Schedule of Activities (Combination A)

1. **Screening:** To be obtained within 28 days prior to randomization for the non-small cell lung cancer (NSCLC) cohorts or first dose for the melanoma, squamous cell carcinoma of the head and neck (SCCHN), and triple-negative breast cancer (TNBC) cohorts.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day screening period.
3. **Tumor History:** To be collected within 28 days prior to randomization for the NSCLC cohorts or first dose for the melanoma, SCCHN, SCLC, and TNBC cohorts. Includes oncology history, information on prior regimens (including dosing and duration of administration, best response observed, and recurrence date), surgery, and radiation therapy.
4. **Medical History:** To be collected within 28 days prior to randomization for the NSCLC cohorts or first dose for the melanoma, SCCHN, SCLC, and TNBC cohorts. Includes history of other diseases (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only. Starting on C24D1, on-treatment physical examination to be performed only when clinically indicated.
6. **Baseline Signs/Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry (Study entry is randomization date for randomized cohorts and first dose date for non-randomized cohorts) and recorded on the Medical History case report form (CRF) page. During treatment any new or worsening conditions since baseline should be reported on the Adverse Event (AE) CRF.
7. **ECOG PS:** ECOG performance scale is available as Appendix 2.
8. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
9. **Contraceptive Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.3).
10. **Hematology:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. If, during the first 2 cycles of treatment, a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as dose-limiting toxicity (DLT). See Section 7.1.4 for the list of the required Laboratory Tests.
11. **Blood Chemistry:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. Results should be available for review prior to infusion of investigational products. See Section 7.1.4 for the list of the required Laboratory Tests.
12. **Coagulation:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, starting on C3D1, coagulation test to be performed when clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
13. **Urinalysis:** During the treatment period to be performed when clinically indicated. If protein ≥2+ by semi-quantitative method (eg, urine dipstick), protein will be quantified by 24-hour urine collection. Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
14. **Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and assayed in a certified laboratory on two occasions prior to starting study treatments, once at the start of screening and once at the baseline visit immediately before investigational products administration. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of study therapy, during follow-up (up to 90 days after last study treatment), 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 (See Section 7.1.1).

15. **12-Lead ECG**: All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2, before and at the end of utomilumab infusion and at the end of avelumab infusion. For Cohorts A9 and A10, triplicate ECG measurements are not required and may be performed as clinically indicated. At each time point, three (3) consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood sample draws for PK, the ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
16. **Hepatitis B and C Virus Tests:** Conduct tests for hepatitis B surface antigen, core antibody, and anti-hepatitis C. Reflexive testing and other supporting tests may be conducted per standard practice to confirm an active hepatitis infection.
17. **ACTH and Thyroid Function Tests:** Thyroid function tests (ACTH, free T4 [FT4], thyroid stimulating hormone [TSH]) will be performed at Screening, Cycle 3 Day 1 and every 12 weeks thereafter, End of Treatment (EOT) visit, and 30 days after last investigational product administration, and if clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
18. **Randomization/Enrollment:** Patient number and dose level allocation via interactive response technology (IRT) operated by Pfizer Inc. Investigational product administration should begin within 7 days after randomization/enrollment.
19. **Avelumab Administration:** Treatment will be administered every 2 weeks in 4-week cycles (ie, 28-day cycles). Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks (eg, on Days 1, 15 of a cycle). For all cohorts except Cohort A9, avelumab administration will start on Cycle 1 Day 1. For patients randomized to Cohort A9, avelumab administration will begin on Cycle 2 Day 1. Avelumab infusion will start at least 30 minutes (+20 minute time window, if needed) after completion of utomilumab infusion. On days when PK samples are taken, avelumab infusion will start after the post- utomilumab and pre-avelumab pharmacokinetic blood samples are drawn. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
20. **Utomilumab Administration:** Treatment will be administered in a 4-week cycle (ie, 28-day cycle). Utomilumab will be administered as a 1-hour intravenous infusion on Day 1 of a cycle. For all cohorts except Cohort A10, utomilumab administration will start on Cycle 1 Day 1. For patients randomized to Cohort A10, utomilumab administration will begin on Cycle 2 Day 1. When both utomilumab-and avelumab are administered, utomilumab will be administered first, followed by the avelumab infusion at least 30 minutes (+20 minute time window, if needed) after the end of the utomilumab infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
21. **Tumor Assessments:** The decision for body areas to be scanned will depend on disease under study and extent of disease. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (or CT/^{18}F-FDG-PET/MRI for bone imaging). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The minimum recommended body areas to be scanned depending on malignancy are detailed in the Imaging Manual. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anticancer therapy. The allowable time window for disease assessments is ±7 days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). In case partial response (PR), complete response (CR), or Progressive Disease (PD) is observed according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. Tumor assessments should be repeated at End of Treatment/Withdrawal if not done in the previous 4 weeks and prior response is other than confirmed PD. Timing should follow calendar days and should not be adjusted for delays in cycle starts. After 1 year from randomization in the study (randomized Cohorts A1-A3, A9 and A10) or first dose (non-randomized Cohorts A4-A8), tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. Bone scans (or CT/^{18}F-FDG-PET/MRI) are required at baseline only if bone metastases are known or suspected outside the body areas scanned, then every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1 (see Section 7.6, Appendix 1).

22. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor. AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF. 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 study treatment, irrespective of any intervening treatment (See Section 8.2).
23. **Concomitant Treatments:** Concomitant treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.
24. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up.
25. **Survival:** Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after randomization of the last patient in the randomized cohorts and for at least 2 years after first dose of the last patient for the non-randomized cohorts unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anti-cancer treatment.
26. **Blood for Utomilumab Pharmacokinetics:** Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour (ie, at the end of infusion) on Day 1 of Cycles 1, 3, 5, 8, and Cycle 12. A sample will also be collected on Days 8 and 15 of Cycle 1 (non-dosing visit). For patients randomized to Cohort A9, PK samples will begin on Cycle 1 Day 1. For patients randomized to Cohort A10, PK samples will begin on Cycle 3 Day 1.
27. **Blood for Avelumab Pharmacokinetics**: Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit). For patients randomized to Cohort A9, PK samples will begin on Cycle 2 Day 1. For patients randomized to Cohort A10, PK samples will begin on Cycle 1 Day 1.
28. **Archival FFPE Tumor Tissue Block:** Patients in Phase 1b should provide archival FFPE tumor tissue if available. Patients in Phase 2 must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within one year of start of study treatment, with no intervening systemic anti-cancer therapy; if such tissue is not available then a de novo biopsy prior to study entry is required. The requirement for archival tissue may be waived if a de novo biopsy will be collected. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples.
29. **De Novo Tumor Biopsy:** A mandatory baseline de novo tumor biopsy from a locally recurrent or metastatic tumor site must be obtained for all patients except for the first 3 patients (including replacements) enrolled in each dose level in Phase 1b, if archival tissue meeting the specifications in footnote 28 and Section 6.1.1 is not available. On treatment biopsies are required except in instances where the procedure poses unacceptable risks per investigator documentation. See Inclusion Criteria (Section 4.1) for biopsy requirements. At end of treatment, if a patient discontinues due to disease progression, a de novo tumor sample is required except in instances where the procedure poses unacceptable risks per investigator documentation. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples. The Cycle 2 Day 1 de novo biopsy should be performed at any time between 21 days after first dose of study drug(s) ± 4 days BEFORE dosing on Cycle 2 Day 1.
30. **TCR Analysis from Peripheral Blood:** A 6 mL sample of whole blood will be collected at screening, Day 1 (pre-dose) and Day 15 (pre-dose) of Cycles 1 and 2; Day 1 (pre-dose) of Cycles 3 and 5; and at End of Treatment/Withdrawal.
31. **Whole Blood for DNA Analysis:** A 4 mL blood biospecimen will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5 and at End of Treatment/Withdrawal. See Section 7.4 for details.
32. **Serum for** pharmacogenomic**/proteomic/metabolomic analysis:** A 10 mL blood biospecimen will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5 and at End of Treatment/Withdrawal. See Section 7.4 for details.

33. **Plasma for pharmacogenomic/proteomic/metabolomic analysis:** A 20 mL blood biospecimen will be collected at screening, prior to dosing on Day 1 of Cycles 1, 2, 3, and at End of Treatment/Withdrawal. See Section 7.4 for details.
34. **PAXGene whole blood collection optimized for RNA analysis:** A 2.5 mL blood biospecimen will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5 and at End of Treatment/Withdrawal. See Section 7.4 for details.
35. **Banked Biospecimens:** A 4 mL blood biospecimen Prep D1 (K_2 ethylenediaminetetraacetic acid [EDTA] whole blood collection optimized for DNA analysis) will be collected on Day 1 of Cycle 1 prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the IRB or EC (see also Section 7.5 of the protocol).
36. **Blood for Utomilumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected on Cycles 1, 3, 5,8, and 12 on Day 1 at pre-dose. For patients randomized to Cohort A9, ADA samples will begin on Cycle 1 Day 1. For patients randomized to Cohort A10, ADA samples will begin on Cycle 3 Day 1.
37. **Blood for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose. For patients randomized to Cohort A9, ADA samples will begin on Cycle 2 Day 1. For patients randomized to Cohort A10, ADA samples will begin on Cycle 1 Day 1.
38. **End of Treatment:** Obtain these assessments if not completed during the previous week on study, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks. The EOT visit should occur within 7 days after discontinuation criteria are met.
39. **Follow-Up:** Patients should be evaluated for safety up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational products. See Section 6.3. Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the time of study treatment discontinuation will enter into disease follow-up. (For tumor assessment). Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADA = anti-drug antibodies; AE = adverse event; C=Cycle; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus;
HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; TCR = T cell receptor.

Table 5. Schedule of Activities: Combination B (Avelumab and PF-04518600) – Safety and Efficacy Assessments (Phase 1b and Phase 2)

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal[38]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[39]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3
Informed Consent[2]	X																
Tumor History[3]	X																
Medical History[4]	X																
Physical Examination[5]	X	X	X	X	X	X	X	X	X	X		X		As clinically indicated		X	X (Day 30)
Baseline Signs & Symptoms[6]		X															
ECOG PS[7]	X	X				X				X						X	X (Day 30)
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Contraceptive Check[9]	X	X				X				X				X		X	X (Day 90)
Safety Labs/Measurements																	
Hematology[10]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Coagulation[12]	X	X				X				X	As clinically indicated						
Urinalysis[13]	X	As clinically indicated															
Serum/Urine Pregnancy Test[14]	X	X		X		X		X		X		X		X	X	X	X (Day 30)
12-Lead ECG [15]	X	X				X										X	
HBV, HCV tests[16]	X																
ACTH and Thyroid Function Tests[17]	X									C3 then every 12 wks.						X	X (Day 30)
Registration and Treatment																	
Enrollment[18]		X															
Avelumab Administration[19]		X		X		X		X		X		X		X	X		
PF-04518600 (anti-OX40) Administration[20]		X		X		X		X		X		X		X	X		
		Tumor Assessments															

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [38]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[39]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
CT or MRI Scan[21]	X	Every 8 weeks (±7 days) After 1 year from first dose, every 12 weeks(±7 days) After 2 years from first dose, every 16 weeks (±7 days)														X	
		Other Clinical Assessments															
Adverse Events[22]	X	Monitored and recorded continually														X	X
Concomitant Treatments[23]	X	Monitored and recorded continually														X	X
Subsequent Anti-Cancer Treatment[24]																	X
Survival[25]																	X

Table 6. Schedule of Activities: Combination B (Avelumab and PF-04518600) - Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)											Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5		Cycles 6, 7, 10, 13	End of Treatment /Withdrawal [38]	Follow Up (Day 30, 60, 90)[39]
	≤28 days prior to First Dose	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 15	Day 1		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Blood for PF-04518600 PK[26]		X	X	X		X			X			X (C6 and C10 only)		
Blood for Avelumab PK[27]		X	X	X		X			X			X (C6 and C10 only)		
Archival FFPE Tumor Tissue Block[28]	X													
De Novo Tumor Biopsy [29]	X					X		X As clinically indicated for newly appearing lesions, unless clinically contraindicated.					X	
Banked Biospecimens[30]		X												
Immune Cell Phenotyping [31]	X	X	X	X	X	X	X		X					
TCR Analysis [32]	X	X		X		X			X				X	
Plasma for pharmacogenomic/ proteomic/metabolomic analysis[33]	X												X	
RNA Profiling [34]	X	X	X	X		X	X		X				X	
Cytokines / Chemokines / Soluble Receptors [35]		X	X	X	X	X	X		X				X	
Blood for PF-04518600 Immunogenicity (ADA) testing[36]		X				X			X			X (C6 and C10 only)		
Blood for Avelumab Immunogenicity (ADA) testing[37]		X				X			X			X (C6 and C10 only)		

Footnotes for Schedule of Activities (Combination B)

1. **Screening:** To be obtained within 28 days prior to study entry (first dose).
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day screening period.
3. **Tumor History:** To be collected within 28 days prior to start of treatment. Includes oncology history, information on prior regimens (including dosing and duration of administration, best response observed, and recurrence date), surgery, and radiation therapy. Human papilloma virus (HPV) status will be collected for patients with squamous cell carcinoma of the head and neck (SCCHN).
4. **Medical History:** To be collected within 28 days prior to study entry. Includes history of other diseases (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only. Starting on C24D1, on-treatment physical examination to be performed only when clinically indicated.
6. **Baseline Signs/Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry and recorded on the Medical History case report form (CRF) page. During treatment any new or worsening conditions since baseline should be reported on the Adverse Event (AE) CRF.
7. **ECOG PS:** ECOG performance scale is available as Appendix 2.
8. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
9. **Contraceptive Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner (See Section 4.3).
10. **Hematology:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. If, during the first 2 cycles of treatment, a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as dose-limiting toxicity (DLT). See Protocol Section 7.1.4 for the list of the required Laboratory Tests.
11. **Blood Chemistry:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. Results should be available for review prior to infusion of investigational products. See Section 7.1.4 for the list of the required Laboratory Tests.
12. **Coagulation:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, starting on C3D1 coagulation test to be performed when clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
13. **Urinalysis:** During the treatment period to be performed when clinically indicated. If protein ≥2+ by semi-quantitative method (eg, urine dipstick), protein will be quantified by 24-hour urine collection. Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
14. **Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and assayed in a certified laboratory on two occasions prior to starting study treatments, once at the start of screening and once at the baseline visit immediately before investigational products administration. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of study therapy, during follow-up (up to 90 days after last study treatment), 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 (See Section 7.1.1).
15. **12-Lead ECG**: All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2, before PF-04518600 infusion and at the end of avelumab infusion. At each time point, three (3) consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When the ECG coincides with blood sample draws for PK, the PK sample should be taken as close as possible to the end of infusion time for the investigational product with an allowance of ±10 minutes. The ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
16. **Hepatitis B and C Virus Tests:** Conduct tests for hepatitis B surface antigen, core antibody, and anti-hepatitis C. Other tests may be conducted per standard practice to confirm an active hepatitis infection.

17. **ACTH and Thyroid Function Tests:** Thyroid function tests (ACTH, free T4 [FT4], thyroid stimulating hormone [TSH]) will be performed at Screening, Cycle 3 Day 1 and every 12 weeks thereafter, End of Treatment (EOT) visit, and 30 days after last investigational product administration, and if clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
18. **Enrollment:** Patient number and allocation to treatment groups will be done via interactive response technology (IRT) operated by Pfizer Inc. Investigational product administration should begin within 7 days after enrollment.
19. **Avelumab Administration:** Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. Avelumab infusion will be administered at least 30 minutes (+20 minute time window, if needed) after the PF-04518600 infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Protocol Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
20. **PF-04518600 Administration:** PF-04518600 will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. PF-04518600 will be administered first, followed by the avelumab infusion at least 30 minutes (+20 minute time window, if needed) after the end of the PF-04518600 infusion. On days when PK samples are taken, avelumab infusion will start after the post-PF-04518600 and pre-avelumab PK blood samples are drawn. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
21. **Tumor Assessments:** The decision for body areas to be scanned will depend on disease under study and extent of disease. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (or CT/^{18}F-FDG-PET /MRI for bone imaging). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The minimum recommended body areas to be scanned depending on malignancy are detailed in the Imaging Manual. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is ±7 days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). In case partial response (PR), complete response (CR), or Progressive Disease (PD) is observed according to Response Evaluation Criteria for Solid Tumors (RECIST) v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. Tumor assessments should be repeated at End of Treatment/Withdrawal if not done in the previous 4 weeks and prior response is other than confirmed PD. Timing should follow calendar days and should not be adjusted for delays in cycle starts. After 1 year from first dose, tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. Bone scans (or CT/^{18}F-FDG-PET/MRI) are required at baseline only if bone metastases are known or suspected outside the body areas scanned, then every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1 (See Section 7.6, Appendix 1).
22. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor. AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF. 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 study treatment, irrespective of any intervening treatment (see Section 8.2).
23. **Concomitant Treatments:** Concomitant treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.
24. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up.

25. **Survival:** Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after enrollment of the last patient unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anti-cancer treatment.
26. **Blood for PF-04518600 Pharmacokinetics:** Blood samples (5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
27. **Blood for Avelumab Pharmacokinetics**: Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-infusion (ie., at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
28. **Archival FFPE Tumor Tissue Block:** Patients in Phase 1b should provide archival FFPE tumor tissue if available. Patients in Phase 2 must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within one year of start of study treatment, with no intervening systemic anti-cancer therapy; if such tissue is not available then a de novo biopsy prior to study entry is required. The requirement for archival tissue may be waived if a de novo biopsy will be collected. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples.
29. **De Novo Tumor Biopsy:** A mandatory baseline de novo tumor biopsy from a locally recurrent or metastatic tumor site must be obtained for all patients except for the first 3 patients (including replacements) enrolled in each dose level in Phase 1b, if archival tissue meeting the specifications in footnote 28 and Section 6.1.1 is not available. On-treatment biopsies are required except in instances where the procedure poses unacceptable risks per investigator documentation. See Inclusion Criteria (Section 4.1) for biopsy requirements. At end of treatment, if a patient discontinues due to disease progression, a de novo tumor sample is required except in instances where the procedure poses unacceptable risks per investigator documentation. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue. See Section 6.1.1 of the protocol and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples. The Cycle 2 Day 1 de novo biopsy should be performed at any time between 21 days after first dose of study drug(s) ±4 days BEFORE dosing on Cycle 2 Day 1.
30. **Banked Biospecimens:** A 4-mL blood sample will be collected on Day 1 of Cycle 1 prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the institutional review board or ethics committee (see also Section 7.5 of the protocol).
31. **Immune Cell Phenotyping:** A 6 mL whole blood sample will be collected at screening, Day 1 (pre-dose), Day 8, Day 15, and Day 22 of Cycle 1, Day 1 and Day 15 of Cycle 2 and Day 1 of Cycle 4. Immune cell phenotypes associated with anti-tumor immunity and immune regulation will be measured by flow cytometry.
32. **TCR Analysis from Peripheral Blood:** A 6 mL whole blood sample will be collected into a tube optimized for deoxyribonucleic acid (DNA) preservation at screening, Day 1 pre-dose and Day 15 of Cycle 1, Day 1 of Cycles 2 and 4, and at End of Treatment/Withdrawal. DNA will be submitted to TCR sequencing analysis.
33. **Plasma for pharmacogenomic/proteomic/metabolomic analysis:** A 20 mL blood biospecimen will be collected at screening and at End of Treatment/Withdrawal. See Section 7.4 for details.
34. **RNA Profiling of Peripheral Blood:** Two 2.5 mL whole blood samples will be collected into PAXgene (RNA) tubes at screening, Day 1 (pre-dose) and end of infusion (EOI) of the last investigational product (IP) administered and Day 8, and 15 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4 and at End of Treatment/Withdrawal. RNA will be analyzed for expression profile of immune- and tumor-related transcripts.
35. **Cytokine, Chemokine and Soluble Receptor:** A 4 mL blood sample will be collected into plasma collection tubes at Day 1 (pre-dose) and EOI, Day 8, 15 and 22 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4 and at End of Treatment/Withdrawal. Samples be will be analyzed for soluble factors associated with immune activation, regulation and potential pharmacodynamics activity of avelumab.
36. **Blood for PF-04518600 Immunogenicity (ADA) Testing:** Blood samples (5 mL whole blood at each time point) for PF-04518600 immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
37. **Blood for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
38. **End of Treatment:** Obtain these assessments if not completed during the previous week on study, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.

39. Follow-Up: Patients should be evaluated for safety up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational products (see Section 6.3). Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the time of study treatment discontinuation will enter into disease follow-up (for tumor assessment). Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADA = anti-drug antibodies; AE = adverse event; C=Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetics RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; TCR=T-cell receptor.

Table 7. Schedule of Activities: Combination C (Avelumab + PD 0360324) – Safety and Efficacy Assessments (Phase 1b and Phase 2)

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [37]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[38]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3
Informed Consent[2]	X																
Tumor History[3]	X																
Medical History[4]	X																
Physical Examination[5]	X	X	X	X	X	X	X	X	X	X		X		As clinically indicated		X	X (Day 30)
Baseline Signs & Symptoms[6]		X															
ECOG PS[7]	X	X				X				X						X	X (Day 30)
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Contraceptive Check[9]	X	X				X				X				X		X	X (Day 90)
Safety Labs/Measurements																	
Hematology[10]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Coagulation[12]	X	X				X				As clinically indicated							
Urinalysis[13]	X	As clinically indicated															
Serum/Urine Pregnancy Test[14]	X	X		X		X		X		X		X		X	X	X	X (Day 30)
12-Lead ECG [15]	X	X				X										X	
HBV, HCV tests[16]	X																
ACTH and Thyroid Function Tests[17]	X									C3 then every 12 wks.						X	X (Day 30)
Registration and Treatment																	
Enrollment[18]		X															
Avelumab Administration[19]		X		X		X		X		X		X		X	X		
PD 0360324 (anti-M-CSF) Administration[20]		X		X		X		X		X		X		X			

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [37]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[38]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Tumor Assessments																	
CT or MRI Scan[21]	X	Every 8 weeks (±7 days) After 1 year from first dose, every 12 weeks (±7 days) After 2 years from first dose, every 16 weeks (±7 days)														X	
Other Clinical Assessments																	
Adverse Events[22]	X	Monitored and recorded continually														X	X
Concomitant Treatments[23]	X	Monitored and recorded continually														X	X
Subsequent Anti-Cancer Treatment[24]																	X
Survival[25]																	X

Table 8. Schedule of Activities: Combination C (Avelumab and PD 0360324) - Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)											Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5		Cycles 6, 7, 10, 13	End of Treatment /Withdrawal [37]	Follow Up (Day 30, 60, 90)[38]
	≤28 days prior to First Dose	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 15	Day 1		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Blood for PD 0360324 PK[26]		X	X	X		X			X			X (C6 and C10 only)		
Blood for Avelumab PK[27]		X	X	X		X			X			X (C6 and C10 only)		
Archival FFPE Tumor Tissue Block[28]	X													
De Novo Tumor Biopsy [29]	X					X		X As clinically indicated for newly appearing lesions, unless clinically contraindicated.					X	
Banked Biospecimens[30]		X												
Immune Cell Phenotyping [31]	X	X	X	X	X	X	X		X					
TCR Analysis [32]	X	X		X		X			X				X	
RNA Profiling [33]	X	X	X	X		X	X		X				X	
Cytokines/Chemokines/Soluble Receptors [34]	X	X	X	X	X	X	X		X				X	
Blood for PD 0360324 Immunogenicity (ADA) testing[35]		X				X			X			X (C6 and C10 only)		
Blood for Avelumab Immunogenicity (ADA) testing[36]		X				X			X			X (C6 and C10 only)		

Footnotes for Schedule of Activities (Combination C)

1. **Screening:** To be obtained within 28 days prior to study entry (first dose).
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day screening period.
3. **Tumor History:** To be collected within 28 days prior to start of treatment. Includes oncology history, information on prior regimens (including dosing and duration of administration, best response observed, and recurrence date), surgery, and radiation therapy.
4. **Medical History:** To be collected within 28 days prior to study entry. Includes history of other diseases (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only. Starting on C24D1, on-treatment physical examination to be performed only when clinically indicated.
6. **Baseline Signs/Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry and recorded on the Medical History case report form (CRF) page. During treatment any new or worsening conditions since baseline should be reported on the Adverse Event (AE) CRF.
7. **ECOG PS:** ECOG performance scale is available as Appendix 2.
8. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
9. **Contraceptive Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner (See Section 4.3).
10. **Hematology:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. If, during the first 2 cycles of treatment, a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as dose-limiting toxicity (DLT). See Protocol Section 7.1.4 for the list of the required Laboratory Tests.
11. **Blood Chemistry:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. Results should be available for review prior to infusion of investigational products. See Section 7.1.4 for the list of the required Laboratory Tests.
12. **Coagulation:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, starting on C3D1, coagulation test to be performed when clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
13. **Urinalysis:** During the treatment period to be performed when clinically indicated. If protein ≥2+ by semi-quantitative method (eg, urine dipstick), protein will be quantified by 24-hour urine collection. Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
14. **Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and assayed in a certified laboratory on two occasions prior to starting study treatments, once at the start of screening and once at the baseline visit immediately before investigational products administration. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of study therapy, during follow-up (up to 90 days after last study treatment), 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 (See Section 7.1.1).
15. **12-Lead ECG**: All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2, before PD 0360324 infusion and at the end of avelumab infusion. At each time point, three (3) consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When the ECG measurements coincide with blood sample draws for PK, the PK sample should be taken as close as possible to the end of infusion time for the investigational product, with an allowance of ±10 minutes. ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
16. **Hepatitis B and C Virus Tests:** Conduct tests for hepatitis B surface antigen, core antibody, and anti-hepatitis C. Other tests may be conducted per standard practice to confirm an active hepatitis infection.

17. **ACTH and Thyroid Function Tests:** Thyroid function tests (ACTH, Free T4 [FT4], thyroid stimulating hormone [TSH]) will be performed at Screening, Cycle 3 Day 1 and every 12 weeks thereafter, End of Treatment (EOT) visit, and 30 days after last investigational product administration, and if clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
18. **Enrollment:** Patient number and allocation to treatment groups will be done via interactive response technology (IRT) operated by Pfizer Inc. Investigational product administration should begin within 7 days after enrollment.
19. **Avelumab Administration:** Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. Avelumab infusion will be administered at least 30 minutes (+20 minute time window, if needed) after the PD 0360324 infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Protocol Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
20. **PD 0360324 Administration:** PD 0360324 will be administered as a 30 minute intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. PD 0360324 will be administered first, followed by the avelumab infusion at least 30 minutes (+20 minute time window, if needed) after the end of the PD 0360324 infusion. On days when PK samples are taken, avelumab infusion will start after the post- PD 0360324 and pre-avelumab PK blood samples are drawn. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
21. **Tumor Assessments:** The decision for body areas to be scanned will depend on disease under study and extent of disease. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (or CT/^{18}F-FDG-PET /MRI for bone imaging). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The minimum recommended body areas to be scanned depending on malignancy are detailed in the Imaging Manual. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is ±7 days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). In case partial response (PR), complete response (CR), or Progressive Disease (PD) is observed according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. Tumor assessments should be repeated at End of Treatment/Withdrawal if not done in the previous 4 weeks and prior response is other than confirmed PD. Timing should follow calendar days and should not be adjusted for delays in cycle starts. After 1 year from first dose, tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. Bone scans (or CT/^{18}F-FDG-PET/MRI) are required at baseline only if bone metastases are known or suspected outside the body areas scanned, then every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1 (See Section 7.6, Appendix 1). For patients with ovarian cancer and ascites, a 50 mL aliquot of ascites fluid will be collected to evaluate the effect of PD 0360324 on the macrophage content of tumor-associated ascites fluid during the course of clinical management.
22. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor. AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF. 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 study treatment, irrespective of any intervening treatment (see Section 8.2).
23. **Concomitant Treatments:** Concomitant treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.

24. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up.
25. **Survival:** Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after enrollment of the last patient unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anti-cancer treatment.
26. **Blood for PD 0360324 Pharmacokinetics:** Blood samples (3 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 30 min post-infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
27. **Blood for Avelumab Pharmacokinetics**: Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
28. **Archival FFPE Tumor Tissue Block:** Patients in Phase 1b should provide archival FFPE tumor tissue if available. Patients in Phase 2 and additional patients enrolled during expansion of dose levels(s) determined to be safe during Phase 1b must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within one year of start of study treatment, with no intervening systemic anti-cancer therapy; if such tissue is not available then a de novo biopsy prior to study entry is required. The requirement for archival tissue may be waived if a de novo biopsy will be collected. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples.
29. **De Novo Tumor Biopsy:** A mandatory baseline de novo tumor biopsy from a locally recurrent or metastatic tumor site must be obtained for all patients except for the first 3 patients (including replacements) enrolled in each dose level in Phase 1b, if archival tissue meeting the specifications in footnote 28 and Section 6.1.1 is not available. On-treatment biopsies are required except in instances where the procedure poses unacceptable risks per investigator documentation. At end of treatment, if a patient discontinues due to disease progression, a de novo tumor sample is required except in instances where the procedure poses unacceptable risks per investigator documentation. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue. The Cycle 2 Day 1 de novo biopsy should be performed at any time between 21 days after first dose of study drug(s) ± 4 days BEFORE dosing on Cycle 2 Day 1.
30. **Banked Biospecimens:** A 4-mL blood sample will be collected on Day 1 of Cycle 1 prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the IRB or EC (see also Section 7.5 of the protocol).
31. **Immune Cell Phenotyping:** A 6 mL whole blood sample will be collected at screening, Day 1 (pre-dose), Day 8, Day 15, and Day 22 of Cycle 1, Day 1 and Day 15 of Cycle 2 and Day 1 of Cycle 4. Immune cell phenotypes associated with anti-tumor immunity and immune regulation will be measured by flow cytometry.
32. **TCR Analysis from Peripheral Blood:** A 6 mL whole blood sample will be collected into a tube optimized for deoxyribonucleic acid (DNA) preservation at screening, Day 1 pre-dose and Day 15 of Cycle 1, Day 1 of Cycles 2 and 4, and at End of Treatment/Withdrawal. DNA will be submitted to TCR sequencing analysis.
33. **RNA Profiling of Peripheral Blood:** Two 2.5 mL whole blood samples will be collected into PAXgene (RNA) tubes at screening, Day 1 (pre-dose) and end of infusion (EOI) and Day 8, and 15 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4, and at End of Treatment/Withdrawal. RNA will be analyzed for expression profile of immune- and tumor-related transcripts.
34. **Cytokine, Chemokine and Soluble Receptor:** A 4 mL blood sample will be collected into plasma collection tubes at screening, Day 1 (pre-dose) and end of infusion (EOI), Day 8, 15 and 22 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4 and at End of Treatment /Withdrawal. Samples be will be analyzed for soluble factors associated with immune activation, regulation and potential pharmacodynamics activity of avelumab.
35. **Blood for PD 0360324 Immunogenicity (ADA) Testing:** Blood samples (5 mL whole blood at each time point) for PD 0360324 immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
36. **Blood for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
37. **End of Treatment:** Obtain these assessments if not completed during the previous week on study, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.

38. **Follow-Up:** Patients should be evaluated for safety up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational products. See Section 6.3. Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the time of study treatment discontinuation will enter into disease follow-up. (For tumor assessment). Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADA = anti-drug antibodies; AE = adverse event; C=Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; M-CSF = macrophage-colony stimulating factor; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; TCR=T-cell receptor.

Table 9. Schedule of Activities: Combination D (Avelumab, Utomilumab, and PF-04518600) – Safety and Efficacy Assessments

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [41]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[42]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3
Informed Consent[2]	X																
Tumor History[3]	X																
Medical History[4]	X																
Physical Examination[5]	X	X	X	X	X	X	X	X	X	X		X		As clinically indicated		X	X (Day 30)
Baseline Signs & Symptoms[6]		X															
ECOG PS[7]	X	X				X				X						X	X (Day 30)
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X
Contraceptive Check[9]	X	X				X				X				X		X	X (Day 90)
Safety Labs/Measurements																	
Hematology[10]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X(Day 30)
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X (Day 30)
Coagulation[12]	X	X				X				As clinically indicated							
Urinalysis[13]	X	As clinically indicated															
Serum/Urine Pregnancy Test[14]	X	X		X		X		X		X		X		X	X	X	X (Day 30)
12-Lead ECG [15]	X	X				X										X	
HBV, HCV tests[16]	X																
ACTH and Thyroid Function Tests[17]	X									C3 then every 12 wks.						X	X (Day 30)
Registration and Treatment																	
Enrollment[18]		X															

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 Days)														Post Treatment	
	≤28 Days prior to First Dose	CYCLE 1				CYCLE 2				CYCLES 3-23				CYCLES ≥24		End of Treatment /Withdrawal [41]	Follow-Up 90 days after last dose (Day 30, Day 60, Day 90)[42]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Avelumab Administration[19]		X		X		X		X		X		X		X	X		
Utomilumab (anti-4-1BB) Administration[20]		X				X				X				X			
PF-04518600 (anti-OX40) Administration[21]		X		X		X		X		X		X		X	X		
Tumor Assessments																	
CT or MRI Scan[22]	X	Every 8 weeks (±7 days) After 1 year from first dose, every 12 weeks(±7 days) After 2 years from first dose, every 16 weeks (±7 days)														X	
Other Clinical Assessments																	
Adverse Events[23]	X	Monitored and recorded continually														X	X
Concomitant Treatments[24]	X	Monitored and recorded continually														X	X
Subsequent Anti-Cancer Treatment[25]																	X
Survival[26]																	X

Table 10. Schedule of Activities: Combination D (Avelumab, Utomilumab, and PF-04518600) - Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)											Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5		Cycles 6, 7, 8, 10, 12, 13	End of Treatment /Withdrawal[41]	Follow Up (Day 30, 60, 90)[42]
	≤28 days prior to First Dose	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 15	Day 1		
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Blood for Utomilumab PK[27]		X	X	X				X		X		X (C8 and C12 only)		
Blood for PF-04518600 PK[28]		X	X	X		X			X			X (C6 and C10 only)		
Blood for Avelumab PK[29]		X	X	X		X			X			X (C6 and C10 only)		
Archival FFPE Tumor Tissue Block[30]	X													
De Novo Tumor Biopsy [31]	X					X		X As clinically indicated for newly appearing lesions, unless clinically contraindicated.					X	
Banked Biospecimens[32]		X												
Immune Cell Phenotyping [33]	X	X	X	X	X	X	X		X					
TCR Analysis [34]	X	X		X		X			X				X	
Plasma for pharmacogenomic/ proteomic/metabolomic analysis[35]	X					X							X	
RNA Profiling[36]	X	X	X	X		X	X		X				X	
Cytokines/Chemokines/Soluble Receptors[37]	X	X	X	X	X	X	X		X				X	
Blood for Utomilumab Immunogenicity (ADA) testing[38]		X						X		X		X (C8 and C12 only)		
Blood for PF-04518600 Immunogenicity (ADA) testing[39]		X				X			X			X (C6 and C10 only)		
Blood for Avelumab Immunogenicity (ADA) testing[40]		X				X			X			X (C6 and C10 only)		

Footnotes for Schedule of Activities (Combination D)

1. **Screening:** To be obtained within 28 days prior to study entry (first dose).
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day screening period.
3. **Tumor History:** To be collected within 28 days prior to start of treatment. Includes oncology history, information on prior regimens (including dosing and duration of administration, best response observed, and recurrence date), surgery, and radiation therapy.
4. **Medical History:** To be collected within 28 days prior to study entry. Includes history of other diseases (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only. Starting on C24D1, on-treatment physical examination to be performed only when clinically indicated.
6. **Baseline Signs/Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry and record on the Medical History case report form (CRF) page. During treatment any new or worsening conditions since baseline should be reported on the Adverse Event (AE) CRF.
7. **ECOG PS:** ECOG performance scale is available as Appendix 2.
8. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
9. **Contraceptive Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner (See Section 4.3.
10. **Hematology:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. If, during the first 2 cycles of treatment, a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as dose-limiting toxicity (DLT). See Protocol Section 7.1.4 for the list of the required Laboratory Tests.
11. **Blood Chemistry:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. Results should be available for review prior to infusion of investigational products. See Section 7.1.4 for the list of the required Laboratory Tests.
12. **Coagulation:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, starting on C3D1, coagulation test to be performed when clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
13. **Urinalysis:** During the treatment period to be performed when clinically indicated. If protein ≥2+ by semi-quantitative method (eg, urine dipstick), protein will be quantified by 24-hour urine collection. Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
14. **Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and assayed in a certified laboratory on two occasions prior to starting study treatments, once at the start of screening and once at the baseline visit immediately before investigational products administration. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of study therapy, during follow-up (up to 90 days after last study treatment), 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 (See Section 7.1.1).
15. **12-Lead ECG**: All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2, before utomilumab infusion and at the end of avelumab infusion. At each time point, three (3) consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When the ECG measurements coincide with blood sample draws for PK, the PK sample should be taken as close as possible to the end of infusion time for the investigational product, with an allowance of ±10 minutes. The ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
16. **Hepatitis B and C Virus Tests:** Conduct tests for hepatitis B surface antigen, and anti-hepatitis C. Other tests may be conducted per standard practice to confirm an active hepatitis infection.
17. **ACTH and Thyroid Function Tests:** Thyroid function tests (ACTH, FT4, TSH) will be performed at Screening, Cycle 3 Day 1 and every 12 weeks thereafter, EOT visit, and 30 days after last investigational product administration, and if clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.

18. **Enrollment:** Patient number and allocation to treatment groups will be done via interactive response technology (IRT) operated by Pfizer Inc. Investigational product administration should begin within 7 days after enrollment.
19. **Avelumab Administration:** Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. Avelumab infusion will be administered at least 30 minutes (+20 minute time window, if needed) after the PF-04518600 infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Protocol Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
20. **Utomilumab Administration:** Treatment will be administered in a 4-week cycle (ie, 28-day cycle). Utomilumab will be administered as a 1-hour intravenous infusion on Day 1 of each cycle. When all 3 IPs are administered, utomilumab will be administered first, followed by the PF-04581600 infusion (second), followed by the avelumab infusion (third) at least 30 minutes (+20 minute window, if needed) after the end of the PF-04518600 infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
21. **PF-04518600 Administration:** PF-04518600 will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. When all 3 IPs are administered, utomilumab will be administered first, followed by the PF-04581600 infusion (second), followed by the avelumab infusion (third) at least 30 minutes (+20 minute window, if needed) after the end of the PF-04518600 infusion. On days when avelumab and PF-04518600 are administered, PF-04518600 will be administered first, followed by the avelumab infusion at least 30 minutes after the end of the PF-04518600 infusion. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
22. **Tumor Assessments:** The decision for body areas to be scanned will depend on the disease under study and extent of disease. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (or CT/^{18}F-FDG-PET /MRI for bone imaging). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The minimum recommended body areas to be scanned depending on malignancy are detailed in the Imaging Manual. Baseline tumor assessment must be performed within 28 days prior to enrollment. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is ±7 days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). In case partial response (PR), complete response (CR), or Progressive Disease (PD) is observed according to RECIST v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. Tumor assessments should be repeated at End of Treatment/Withdrawal if not done in the previous 4 weeks and prior response is other than confirmed PD. Timing should follow calendar days and should not be adjusted for delays in cycle starts. After 1 year from first dose, tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. Bone scans (or CT/^{18}F-FDG-PET/MRI) are required at baseline only if bone metastases are known or suspected outside the body areas scanned, then every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1 (See Section 7.6, Appendix 1).
23. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF. 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 study treatment, irrespective of any intervening treatment (see Section 8.2).
24. **Concomitant Treatments:** Concomitant treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.

25. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up.
26. **Survival:** Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after enrollment of the last patient unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anti-cancer treatment.
27. **Blood for Utomilumab Pharmacokinetics:** Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-start of infusion (ie, at the end of infusion) on Day 1 of Cycles 1, 3, 5, 8, and Cycle 12. A sample will also be collected on Days 8 and 15 of Cycle 1 (non-dosing visit).
28. **Blood for PF-04518600 Pharmacokinetics:** Blood samples (5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-start of infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
29. **Blood for Avelumab Pharmacokinetics**: Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and 1 hour post-start of infusion (ie, at the end of infusion) on Days 1 and 15 of Cycle 1, and then pre-dose and end of infusion on Day 1 of Cycles 2, 4, 6, and Cycle 10. A sample will also be collected on Day 8 of Cycle 1 (non-dosing visit).
30. **Archival FFPE Tumor Tissue Block:** Patients in Phase 1b should provide archival formalin-fixed paraffin-embedded (FFPE) tumor tissue if available. Patients in Phase 2 and additional patients enrolled during expansion of dose levels(s) determined to be safe during Phase 1b must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within one year of start of study treatment, with no intervening systemic anti-cancer therapy; if such tissue is not available then a de novo biopsy prior to study entry is required. The requirement for archival tissue may be waived if a de novo biopsy will be collected. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples.
31. **De Novo Tumor Biopsy:** A mandatory baseline de novo tumor biopsy from a locally recurrent or metastatic tumor site must be obtained for all patients except for the first 3 patients (including replacements) enrolled in each dose level in Phase 1b, if archival tissue meeting the specifications in footnote 28 and Section 6.1.1 is not available. On-treatment biopsies are required except in instances where the procedure poses unacceptable risks per investigator documentation. At end of treatment, if a patient discontinues due to disease progression, a de novo tumor sample is required except in instances where the procedure poses unacceptable risks per investigator documentation. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue. The Cycle 2 Day 1 de novo biopsy should be performed at any time between 21 days after first dose of study drug(s) ± 4 days BEFORE dosing on Cycle 2 Day 1.
32. **Banked Biospecimens:** A 4-mL blood sample will be collected on Day 1 of Cycle 1 prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the institutional review board or ethics committee (see also Section 7.5 of the protocol).
33. **Immune Cell Phenotyping:** A 6 mL whole blood sample will be collected at screening, Day 1 (pre-dose), Day 8, Day 15, and Day 22 of Cycle 1, Day 1 and Day 15 of Cycle 2 and Day 1 of Cycle 4. Immune cell phenotypes associated with anti-tumor immunity and immune regulation will be measured by flow cytometry.
34. **TCR Analysis from Peripheral Blood:** A 6 mL whole blood sample will be collected into a tube optimized for DNA preservation at screening, Day 1 pre-dose and Day 15 of Cycle 1, Day 1 of Cycles 2 and 4 and at End of Treatment/Withdrawal. DNA will be submitted to TCR sequencing analysis.
35. **Plasma for pharmacogenomic/proteomic/metabolomic analysis:** A 20 mL blood biospecimen will be collected at screening, Cycle 2 Day 1, and at End of Treatment/Withdrawal. See Section 7.4 for details.
36. **RNA Profiling of Peripheral Blood:** Two 2.5 mL whole blood samples will be collected into PAXgene (RNA) tubes at screening, Day 1 (pre-dose) and end of infusion (EOI) and Day 8, and 15 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4, and at End of Treatment/Withdrawal. RNA will be analyzed for expression profile of immune- and tumor-related transcripts.
37. **Cytokine, Chemokine and Soluble Receptor:** A 4 mL blood sample will be collected into plasma collection tubes on Screening, Day 1 (pre-dose) and end of infusion (EOI), Day 8, 15 and 22 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 4 and the End of Treatment/Withdrawal. Samples be will be analyzed for soluble factors associated with immune activation, regulation and potential pharmacodynamics activity of avelumab.
38. **Blood for Utomilumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected on Cycles 1, 3, 5,8, and 12 on Day 1 at pre-dose.
39. **Blood for PF-04518600 Immunogenicity (ADA) Testing:** Blood samples (5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.

40. **Blood for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
41. **End of Treatment:** Obtain these assessments if not completed during the previous week on study, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
42. **Follow-Up:** Patients should be evaluated for safety up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational products. See Section 6.3. Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the time of study treatment discontinuation will enter into disease follow-up. (For tumor assessment). Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADA = anti-drug antibodies; AE = adverse event; C=Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; TCR = T-cell receptor.

Table 11. Schedule of Activities: Combination F (F1: Avelumab plus CMP-001, F2: Avelumab plus CMP-001 and Utomilumab, F3: Avelumab plus CMP-001 and PF-04518600) – Safety and Efficacy Assessments (Phase 1b and Phase 2)

Protocol Activities	Screening[1]	Treatment												Post Treatment		
		CYCLE 1				CYCLE 2				CYCLES 3-23		CYCLES ≥24		End of Treatment/ Withdrawal[43]	Follow-Up (Day 30, Day 60, Day 90)[44]	Survival Follow Up
	≤28 Days prior to Randomization	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15			
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3	
Informed Consent[2]	X															
Tumor History[3], Medical History[4], Baseline Signs & Symptoms[6]	X															
Randomization[18]		X														
Adverse Events[24] Concomitant Treatments[25]	Monitored and recorded continually															
Physical Examination[5],	X	X	X	X	X	X	X	X	X	X	X	As clinically indicated		X	X (Day 30)	
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (Day 30)	
ECOG PS[7]	X	X				X				X				X	X (Day 30)	
Contraceptive Check[9]	X	X				X				X		X		X	X (Day 90)	

Protocol Activities	Screening[1]	Treatment												Post Treatment		
		CYCLE 1				CYCLE 2				CYCLES 3-23		CYCLES ≥24		End of Treatment/ Withdrawal[43]	Follow-Up (Day 30, Day 60, Day 90)[44]	Survival Follow Up
	≤28 Days prior to Randomization	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15			
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3	
Safety Labs/Measurements																
Hematology[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (Day 30)	
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (Day 30)	
Coagulation[12]	X	As clinically indicated														
Serum/Urine Pregnancy Test[13]	X	X		X		X		X		X	X	X	X		X (Day 30)	
12-Lead ECG [14]	X	X				X								X		
HBV, HCV tests[15]	X															
ACTH and cortisol and Thyroid Function Tests[16]	X	Starting C3D1 every 12 weeks												X	X (Day 30)	
Corticotropin Stimulation Test[17]	X	As clinically indicated														
Avelumab Administration[19]		X		X		X		X		X	X	X	X			

Protocol Activities	Screening[1]	Treatment												Post Treatment		
		CYCLE 1				CYCLE 2				CYCLES 3-23		CYCLES ≥24		End of Treatment/ Withdrawal[43]	Follow-Up (Day 30, Day 60, Day 90)[44]	Survival Follow Up
	≤28 Days prior to Randomization	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15			
Visit Time Window (days)			(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 7	(±) 7	(+) 7	(±) 3	
CMP- 001[20]		X	X	X	X	X	X	X		X	X	X	X			
Utomilumab[21] (Combination F2)		X				X				X		X				
PF-04518600[22] (Combination F3)		X		X		X		X		X	X	X	X			
CT or MRI Scan[23]	X	Every 8 weeks from randomization (±7 days) After 1 year from randomization, every 12 weeks (±7 days) After 2 years from randomization, every 16 weeks (±7 days)														
Subsequent Anti-Cancer Treatment[26]		NA													X	X
Survival[27]		NA														X

Table 12. Schedule of Activities: Combination F (F1: Avelumab + CMP-001, F2: Avelumab + CMP-001 + Utomilumab, F3: Avelumab + CMP-001 + PF-04518600) - Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments (Phase 1b and Phase 2)

Protocol Activities	Screening[1] ≤28 days prior to Randomization	On Treatment (1 Cycle=28 days)										Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		
Visit Window (days)			(±) 2	(±) 2	(±) 2	(±) 2		(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Blood for Avelumab PK[28]		X		X		X			X		X (C6 and C10 only)		
Blood for utomilumab PK[29] (Combination F2)		X				X			X		X (C6 and C10 only)		
Blood for PF-04518600 PK[30] (Combination F3)		X				X			X		X (C6 and C10 only)		
Archival FFPE Tumor Tissue Block[31]	X												
De Novo Tumor Biopsy [32]	X	As clinically indicated											

Protocol Activities	Screening[1] ≤28 days prior to Randomization	On Treatment (1 Cycle=28 days)										Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		
TCR Analysis[33]	X	X		X		X	X	X				X	
Whole Blood for DNA Analysis[34]		X		X		X	X	X				X	
Serum for pharmacogenomic/ proteomic/metabolomic analysis[35]		X		X									
Plasma for pharmacogenomic/ proteomic/metabolomic analysis[36]	X	X										X	
PAXGene whole blood collection optimized for RNA analysis[37]	X	X		X		X	X	X				X	
Banked biospecimens[38]		X											
Blood for Anti-Qb antibodies[39]		X		X		X			X		X (C8 only)		
Blood for Avelumab immunogenicity (ADA) testing[40]		X				X			X		X (C6 and C10 only)		

Protocol Activities	Screening[1] ≤28 days prior to Randomization	On Treatment (1 Cycle=28 days)										Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		
Blood for utomilumab immunogenicity (ADA) testing[41] (Combination F2)		X				X			X		X (C6 and C10 only)		
Blood for PF-04518600 immunogenicity (ADA) testing[42] (Combination F3)		X				X			X		X (C6 and C10 only)		

Footnotes for Schedule of Activities (Combination F)

1. **Screening:** To be obtained within 28 days prior to randomization.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.
3. **Tumor History:** To be collected within 28 days prior to randomization. Includes disease characteristics, information on prior regimens (including dosing and duration of administration, best response observed, and recurrence date), surgery, and radiation therapy.
4. **Medical History:** To be collected during the screening period. Includes history of diseases other than the primary tumor under consideration (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only. During treatment starting C24 D1 physical examination to be performed only when clinically indicated.
6. **Baseline Signs/Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry (Study entry is defined as randomization date) and recorded on the Medical History case report form (CRF) page. During treatment any new or worsening conditions since baseline should be reported on the Adverse Event (AE) CRF.
7. **ECOG PS:** ECOG performance scale is available as Appendix 2.
8. **Vital Signs:** Blood pressure (BP), pulse rate to be recorded in supine or sitting position.
9. **Contraceptive Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner (See Section 4.3).

Protocol Activities	Screening[1] ≤28 days prior to Randomization	On Treatment (1 Cycle=28 days)										Post Treatment	
		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		

10. **Hematology:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. If, during the first cycle of treatment, a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as dose-limiting toxicity (DLT). See Section 7.1.4 for the list of the required Laboratory Tests.
11. **Blood Chemistry:** It is not necessary to repeat on C1D1 if performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study treatments unless otherwise indicated. Results should be available for review prior to administration of investigational products. See Section 7.1.4 for the list of the required Laboratory Tests.
12. **Coagulation:** On treatment, to be performed when clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
13. **Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and assayed in a certified laboratory on two occasions prior to starting study treatments, once at the start of screening and once at the baseline visit immediately before investigational products administration. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of study therapy, during follow-up (up to 90 days after last study treatment), 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 (see Section 7.1.1).
14. **12-Lead ECG**: All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed before first investigational product administration and at the end of last product administration, on Day 1 of Cycle 1 and 2. At each time point, three (3) consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood sample draws for PK, the ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
15. **Hepatitis B and C Virus Tests:** Conduct tests for hepatitis B surface antigen, and anti-hepatitis C. Reflexive testing and other supporting tests may be conducted per standard practice to confirm an active hepatitis infection.
16. **ACTH, cortisol and Thyroid Function Tests:** Basal morning (fasting) Adrenocorticotropic hormone (ACTH) and cortisol and Thyroid function tests (free T4 [FT4], thyroid stimulating hormone [TSH]) will be performed at Screening, Cycle 3 Day 1 and every 12 weeks thereafter, End of Treatment (EOT) visit, and 30 days after last investigational product administration, and if clinically indicated. See Section 7.1.4 for the list of the required Laboratory Tests.
17. Serum cortisol response to acute ACTH stimulation with a 250-µg dose should be performed to establish the diagnosis of adrenal insufficiency if basal morning ACTH and cortisol results are suggestive of adrenal insufficiency (eg, cortisol level is low) at screening and when clinically indicated during treatment. The institutional standards should be followed. Patients with a history of adrenal insufficiency will require additional premedication before CMP-001 administration. See Section 5.3.5.2
18. **Randomization/Enrollment:** Patient number and dose level allocation via interactive response technology (IRT) operated by Pfizer Inc. Investigational product administration should begin within 7 days after randomization.

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)										Post Treatment	
	≤28 days prior to Randomization	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		

19. **Avelumab Administration:** Treatment will be administered every 2 weeks in 4-week cycles (ie, 28-day cycles). Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks (eg, Days 1 and 15 of each cycle). Avelumab infusion will be administered before the CMP-001 injection. See Section 5.3.5.2 for details of timing of investigational product administration. On days when PK samples are taken, avelumab infusion will start after the pre-avelumab pharmacokinetic blood samples are drawn. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.
20. **CMP-001 Administration:** Two weekly SC doses followed by 5 weekly intratumoral doses followed by biweekly intratumoral doses until progression or other discontinuation criteria are met (see Section 5.3.5).

21. **Utomilumab Administration:** For cohort F2, treatment will be administered in a 4-week cycle (ie, 28-day cycle). Utomilumab will be administered as a 1-hour intravenous infusion on Day 1 of a cycle. When all 3 drugs are administered, utomilumab will be administered first, followed by avelumab, followed by CMP-001 injection. A 30 to 50 minute window is recommended between the individual drug administration to conduct end of infusion/injection procedures (eg, sample collection) and accommodate any logistical arrangements. See Section 5.3.5.2 for details of timing of investigational product administration. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.

22. **PF-04518600 Administration:** For cohort F3 PF-04518600 will be administered as a 1-hour intravenous infusion every 2 weeks on Day 1 and Day 15 of each cycle. When all 3 drugs are administered, PF-04518600 will be administered first, followed by avelumab, followed by CMP-001 injection. A 30 to 50-minute window is recommended between the individual drug administrations to conduct the end of infusion/injection procedures (eg, sample collection) and accommodate any logistical arrangements. See Section 5.3.5.2 for details of timing of investigational product administration. Treatment will continue until disease progression is confirmed by the investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)										Post Treatment	
	≤28 days prior to Randomization	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		

23. **Tumor Assessments:** The decision for body areas to be scanned will depend on the disease under study and extent of disease. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (or CT/^{18}F-FDG-PET/MRI for bone imaging). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The minimum recommended body areas to be scanned depending on malignancy are detailed in the Imaging Manual. Baseline tumor assessment must be performed within 28 days prior to randomization. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anticancer therapy. The allowable time window for disease assessments is ±7 days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). In case partial response (PR), complete response (CR), or Progressive Disease (PD) is observed according to RECIST v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. Tumor assessments should be repeated at End of Treatment/Withdrawal if not done in the previous 4 weeks and prior response is other than confirmed PD. Timing should follow calendar days and should not be adjusted for delays in cycle starts. After 1 year from randomization, tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. Bone scans (or CT/^{18}F-FDG-PET/MRI) are required at baseline only if bone metastases are known or suspected outside the body areas scanned (CT/MRI), then every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1 (see Section 7.6, Appendix 1).
24. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative 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 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor. AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF. 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 study treatment, irrespective of any intervening treatment (see Section 8.2).
25. **Concomitant Treatments:** Concomitant treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.
26. **Subsequent Anti-Cancer Treatment:** Subsequent anticancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up.
27. **Survival:** Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after randomization of the last patient in the randomized cohorts and for at least 2 years after first dose of the last patient for the non-randomized cohorts unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anticancer treatment.

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)										Post Treatment	
	≤28 days prior to Randomization	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		

28. **Blood for Avelumab Pharmacokinetics**: Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and post-infusion (ie, ±10 min of infusion completion) on Days 1 and 15 of Cycle 1, and then on Day 1 of Cycles 2, 4, 6, and Cycle 10
29. **Blood for Utomilumab Pharmacokinetics:** Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and post-infusion (ie, ±10 min of infusion completion) on Day 1 of Cycles 1, 2, 4, 6, and Cycle 10.
30. **Blood for PF-04518600 Pharmacokinetics:** Blood samples (3.5 mL whole blood at each time point) will be collected from all patients in the study at pre dose and post-infusion (ie, ±10 min of infusion completion) on Day 1 of Cycles 1, 2, 4, 6, and Cycle 10.
31. **Archival FFPE Tumor Tissue Block:** All patients must provide archival biopsy when available. See Section 6.1.1 and Laboratory Manual for additional details on the selection of lesions and preparation of tissue samples.
32. **De Novo Tumor Biopsy:** A mandatory baseline de novo tumor biopsy from a locally recurrent or metastatic tumor site must be obtained for all patients, if archival tissue meeting the specifications in Section 6.1.1 is not available. Tissue from biopsies collected during the study period as part of the standard of care should be provided to the central lab. Refer to Section 6.1.1 and the Laboratory Manual for requirements.
33. **TCR Analysis from Peripheral Blood:** A 6 mL sample of whole blood will be collected at screening, Days 1 and Day 15 of Cycle 1 and 2; Day 1 of Cycle 3; and at End of Treatment/Withdrawal. On days when study compounds are administered, all specimens must be collected before administration of study compounds. See Section 7.4 for details.
34. **Whole Blood for DNA Analysis:** A 4 mL blood biospecimen will be collected at Days 1 and Day 15 of Cycle 1 and 2; Day 1 of Cycle 3; and at End of Treatment/Withdrawal. On days when study compounds are administered, all specimens must be collected before administration of study compounds. See Section 7.4 for details.
35. **Serum for** pharmacogenomic/**proteomic/metabolomic analysis:** A 10 mL blood biospecimen will be collected on Day 1 and Day 15 of Cycle 1. On the specified days specimens will be collected prior to any study therapy and also at 2 hours (±30 minutes) and 4 hours (±30 minutes) after start of administration of CMP-001. When the Cycle 1 Day 1 and/or Cycle 1 Day 15 study drug administration visit is spread over two days, the pre-dose sample will be collected prior to any study therapy and the post-dose sample will be collected at 2 hours (±30 minutes) and 4 hours (±30 minutes) after start of administration of CMP-001.
36. **Plasma for** pharmacogenomic/**proteomic/metabolomic analysis:** A 20 mL blood biospecimen will be collected at screening, Day 1 of Cycle 1; and at End of Treatment/Withdrawal. On days when study compounds are administered, all specimens must be collected before administration of study compounds. See Section 7.4 for details.
37. **PAXGene whole blood collection optimized for RNA analysis:** A 2.5 mL blood biospecimen will be collected at screening, Day 1 and Day 15 of Cycle 1 and 2; Day 1 of Cycle 3; and at End of Treatment/Withdrawal. On days when study compounds are administered, all specimens must be collected before administration of study compounds. See Section 7.4 for details.
38. **Banked Biospecimens:** A 4 mL blood biospecimen Prep D1 (K_2 ethylenediaminetetraacetic acid [EDTA] whole blood collection optimized for DNA analysis) will be collected at Cycle 1 Day 1 prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the IRB or EC (see also Section 7.5 of the protocol).
39. **Blood for Anti-Qb antibodies:** Blood samples (5 mL whole blood at each time point) for Anti-Qb antibodies testing will be collected pre-dose on Days 1 and 15 of Cycle 1 and Day 1 of Cycles 2, 4, and 8.

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)										Post Treatment	
	≤28 days prior to Randomization	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycles 6, 8, 10	End of Treatment /Withdrawal [43]	Follow Up (Day 30, 60, 90) [44]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		

40. **Blood for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
41. **Blood for Utomilumab Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
42. **Blood for PF-04518600 Immunogenicity (ADA) Testing:** Blood samples (3.5 mL whole blood at each time point) for PF-04518600 immunogenicity testing will be collected on Cycles 1, 2, 4, 6, and 10 on Day 1 at pre-dose.
43. **End of Treatment:** Obtain these assessments if not completed during the previous week on study, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
44. **Follow-Up:** Patients should be evaluated for safety up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational products. See Section 6.3. Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the time of study treatment discontinuation will enter into disease follow-up. (For tumor assessment). Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADA = anti-drug antibodies; AE = adverse event; C=Cycle; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; TCR = T cell receptor.

1. INTRODUCTION

This is a Phase 1b/2 dose-finding study to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of avelumab (MSB0010718C), a programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb) in combination with other cancer immunotherapies in patients with locally advanced or metastatic solid tumors (eg, non-small cell lung cancer [NSCLC], melanoma, squamous cell carcinoma of the head and neck [SCCHN]), and triple-negative breast cancer [TNBC]). Avelumab reversal of T cell inhibition via PD-L1 is only one potential mechanism which can augment anti-tumor immunity and it appears that in many patients simply blocking this resistance pathway is insufficient to trigger a robust anti-tumor response. As detailed in this protocol, mouse tumor modeling suggests that combining avelumab with 4-1BB or OX40 agonist mAbs as doublets leads to increased anti-tumor activity compared with mice treated with any of the single agents. In addition, macrophage-colony stimulating factor (M-CSF) blocking antibodies when combined with 4-1BB agonist mAbs and avelumab as a triplet in models where myeloid suppressive cells may be important exhibits greater anti-tumor tumor activity than the respective doublets. Furthermore, triplet combinations of 4-1BB and OX40 agonist mAbs showed a marked increase in anti-tumor activity in these models compared with the respective doublets. It is thought that triplets may be more effective compared with doublets as it is likely that doublet therapies, while potentially effective, do not address mechanisms of immune homeostasis as well as select triplets. Therefore, after the evaluation of respective doublets in this study for safety and preliminary clinical activity, triplet combinations may be explored in specific clinical settings where these combinations might be more effective.

While the above combinations address mechanisms thought to be active in tumors harboring a pre-existing immune response, they do not address the growing unmet medical need of patients who progress on PD-1/PD-L1 therapy due to absent or inactive immune responses. Preclinical studies detailed in this protocol suggest a Toll-like Receptor 9 (TLR9) receptor agonist may initiate immune responses that could be further enhanced by a PD-L1 pathway inhibitor in settings where single agent inhibition of the PD-L1 pathway is less effective. These preclinical studies also support the hypothesis that 4-1BB and OX40 agonist mAbs may further activate T cell responses activated by the TLR9/PD-L1 combination.

The primary purpose of this study is to assess the safety and early signs of efficacy of the above mentioned avelumab doublet combinations followed by the evaluation of a triplet combination of these agents based on the safety of the respective doublets. The proposed combinations are as follows:

- Combination A: avelumab plus utomilumab, a fully human immunoglobulin (Ig) G2 isotype mAb agonist of 4-1BB (CD137, TNFRSF9) that promotes survival and function of T cells, especially CD8+ T cells.

- Combination B: avelumab plus PF-04518600, a fully human IgG2 mAb agonist of OX40 (CD134) that promotes survival and function of T cells, especially CD4+ T cells.

- Combination C: avelumab plus PD 0360324, a fully human IgG2 mAb directed against M-CSF that may inhibit tumor infiltration by immunosuppressive macrophages. (Sites in the United Kingdom [UK] will not participate in this combination).

- Combination D: avelumab plus utomilumab and PF-04518600 that is expected to provide complementary support for CD8+ and CD4+ T cells.

- Combination F: avelumab plus CMP-001, an encapsulated TLR9 agonist that is expected to activate tumor-infiltrating plasmacytoid dendritic cells (pDCs) leading to activation and recruitment of anti-tumor T-cells to the tumor microenvironment. CMP-001 is expected to elicit T cell priming and infiltration into the tumor microenvironment, whereas avelumab is expected to block T cell inhibition by PD-L1 that is induced by CMP-001. Utomilumab or PF-04518600 will be evaluated in combination with avelumab and CMP-001 for the promotion of survival and function of T-cells activated by the combination. (Only sites in the United States [US] will participate in this combination).

Additional combinations of avelumab with other immune modulators may be incorporated into this protocol, based on emerging preclinical and clinical data.

1.1. Indication

Avelumab is a fully human anti-PD-L1 mAb of the Ig G1 isotype that is currently being investigated in combination with other cancer immunotherapies to enhance anti-tumor activity over that expected by avelumab alone in patients with locally advanced or metastatic solid tumors. Avelumab is expected to increase the effectiveness of anti-tumor T cells by preventing inhibition of T cell activation. This effect is expected to be enhanced by agents that promote anti-tumor immunity by complementary mechanisms such as promotion of T cell survival or removal of inhibitory myeloid cells.

1.2. Background and Rationale

1.2.1. Avelumab

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death protein-1 (PD-1). Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells and therefore expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death-ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[1] For complete details of the in vitro and nonclinical studies, refer to avelumab Investigator's Brochure (IB).[2]

1.2.1.1. Avelumab Clinical Experience

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in Phase 1, 2, and 3 clinical protocols in a wide variety of cancers, including non-small cell lung cancer, gastric cancer, Merkel cell carcinoma (MCC), renal cell

carcinoma (RCC), ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors (TKIs), or other immune-modulating agents.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI


CCI
CCI
CCI
CCI
CCI


CCI
CCI
CCI
CCI
CCI
CCI

CCI [redacted]

1.2.2. Utomilumab (4-1BB Agonist)

4-1BB (CD137, TNFRSF9), first identified as an inducible costimulatory receptor expressed on activated T-cells, is a membrane spanning glycoprotein of the Tumor Necrosis Factor receptor (TNFR) superfamily (TNFRSF). Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated natural killer (NK) and natural killer T (NKT) cells; regulatory T-cells; dendritic cells (DC) including follicular DC; stimulated mast T-cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils and activated B cells.[4,5] 4-1BB expression has also been demonstrated on tumor vasculature and atherosclerotic endothelium.[6,7,8] The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells.

4-1BB is undetectable on the surface of T-cells but expression increases upon activation. Based on homology to other members of the TNFRSF, ligand binding is expected to induce receptor trimerization resulting in activation.[9] Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble 4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers.[10,11,12]

Upon 4-1BB activation, TRAF 1 and TRAF 2, pro-survival members of the TNFR-associated factor (TRAF) family are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of NFkB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to up regulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner.[13]

Numerous studies of murine and human T-cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production.[14] Reports have shown that 4-1BB agonist mAbs increase costimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T-cell memory responses.[15] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models.[16] This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance.

Interaction of 4-1BB on activated normal human B cells with its ligand at the time of B cell receptor engagement stimulates proliferation and enhances survival.[5] The potential impact of 4-1BB engagement in B cell lymphoma has been investigated in two published studies. Evaluation of several types of human primary non-Hodgkin's lymphoma (NHL) samples indicated that 4-1BB was expressed predominantly on infiltrating T-cells rather than the

lymphoma cells.[17] The addition of 4-1BB agonists to *in vitro* cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing.[18]

Utomilumab is a novel fully human IgG2 mAb agonist of 4-1BB (CD137, TNFRSF9). In addition to the studies described above to characterize 4-1BB, B cell immunophenotyping was performed in two experiments using utomilumab in cynomolgus monkeys with doses from 0.001-100 mg/kg; in these experiments peripheral blood B cell numbers were either unchanged or decreased.

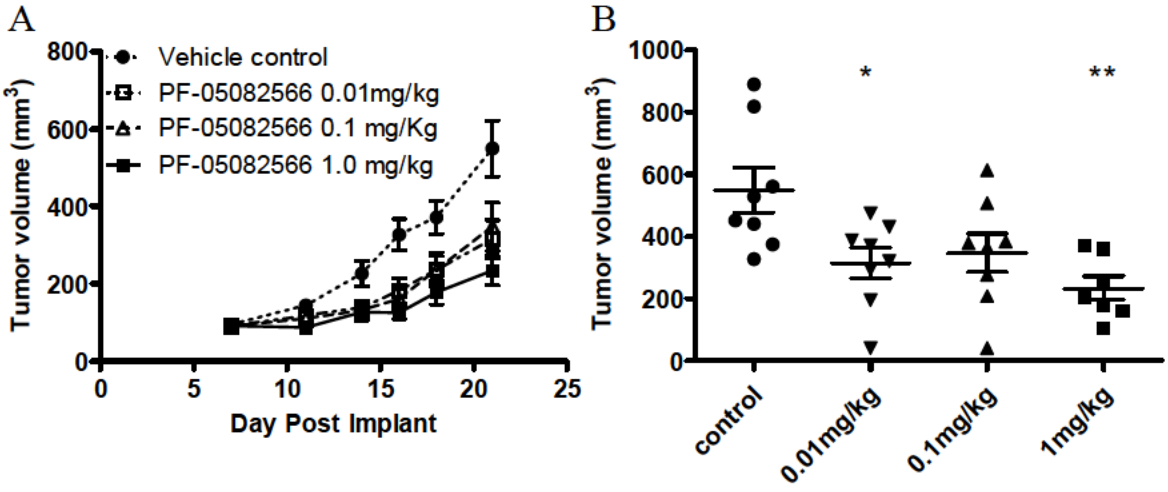
1.2.2.1. *In Vivo* Data: Functional Activity of Utomilumab

In pre-clinical studies, utomilumab has exhibited the ability to increase lymphocyte proliferation. In small animal models developed to test the *in vivo* function of utomilumab, utomilumab was able to enhance expansion of human leukocytes in a dose dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted mice. Similarly, a dose dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, utomilumab treatment of cynomolgus monkeys in single or multiple dose studies increased proliferation among cytotoxic central memory T-cells (CD8 T_{CM}) in peripheral blood mononuclear cell (PBMC) samples. Taken together, these data demonstrate evidence of utomilumab's ability to enhance lymphocyte response *in vivo*.

1.2.2.2. *In Vivo* Data: Anti-Tumor Activity of Utomilumab

Single-agent utomilumab has demonstrated the ability to promote anti-tumor immune activity in pre-clinical studies. Human tumor cell lines representing melanoma, colon, and prostate tumor types were tested in a xenogenic transplant model. Utomilumab does not bind to murine 4-1BB; therefore, primary human PBMC from a healthy volunteer donor were mixed with tumor cells to set up the animal model. Once tumors were established, animals were treated with utomilumab. Utomilumab was found to be efficacious against all 3 tumor types. An example growth curve demonstrating the response to a prostate carcinoma is shown in Figure 8.

Figure 8. Effect of Utomilumab on the Growth of PC3 Prostate Carcinoma in a huPBL SCID Model

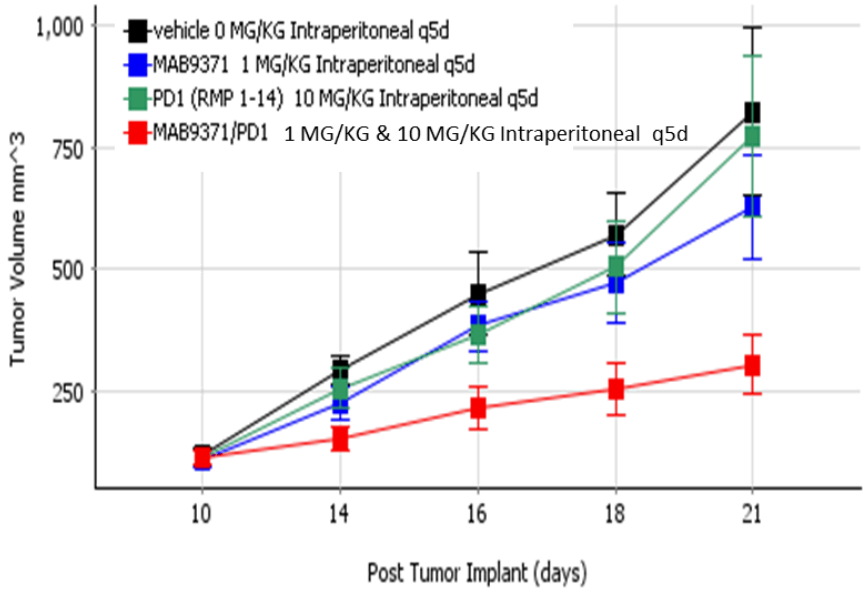


Utomilumab inhibits the growth of the PC3 prostate carcinoma *in vivo* Panel A: mean tumor volume at each time point measured. Panel B: volume of each tumor on the final study day (Day 21). The mean and standard error of the mean (SEM) are indicated by bars. *p<0.05, ** p<0.005.

1.2.2.3. Pre-Clinical Combination Studies

PD-L1 has been observed to limit tumor cell recognition by cytotoxic T-cells.[19] 4-1BB agonists have been found to support T-cell activity in the presence of target tumor cells. These observations suggest that blocking PD-1/PD-L1 interactions would increase the frequency of effective tumor cell recognition by T-cells, whereas 4-1BB agonists would promote more robust T-cell responses following tumor recognition, overall resulting in more effective tumor growth inhibition. The PD-1/PD-L1 hypothesis was tested using mouse tumor models. Figure 9 shows the results of a representative experiment, in which statistically significant anti-tumor activity versus the vehicle control is observed in the cohort of mice that received a combination of a PD-1 antagonist antibody with a 4-1BB agonist antibody but not with either antibody administered as a single agent. Consistent with the proposed mechanism for the combination, significant increases in CD8+ effector memory cells and tumor responsive interferon gamma (IFN-γ) producing cells were found in the spleens of mice treated with the combination (data not shown). In addition, preliminary toxicology data in mice suggest that the toxicity of an anti-4-1BB agonist is not increased by addition of an anti-PD-1 antagonist (data not shown).

Figure 9. Combinatorial Efficacy of Surrogate Anti-4-1BB Combined with Surrogate Anti-PD-1 in a Colorectal Carcinoma Model



Combination of a 4-1BB agonist antibody with a PD-1 antagonist antibody shows significant inhibition tumor growth in a colon carcinoma model. C57BL6 mice were subcutaneously (SC) implanted with $1x10^6$ MC38 murine colon carcinoma cells. Tumor growth was monitored and animals randomized to four groups of 8 each when the tumors reached an average size of 150 mm^3 and intraperitoneal (IP) dosed with vehicle (phosphate-buffered saline; PBS), 1 mg/kg anti-mouse 4-1BB agonist (MAB9371), 10 mg/kg anti-mouse PD-1 antagonist (RMP1-14), or the simultaneous combination of the two once every 5 days for a total of two doses. The study was terminated when tumor sizes of the controls reached 1000 mm^3. Combination treatment of animals with 4-1BB agonist plus PD-1 antagonist resulted in 63.2% reduction in tumor growth when compared to vehicle controls (unpaired t test *p = 0.0125). Significant tumor growth inhibition by either agent dosed individually was not observed.

1.2.2.4. Utomilumab Clinical Experience

The anti-tumor activity of single-agent utomilumab in patients with advanced malignancies, including MCC, melanoma, and NSCLC, and utomilumab in combination with rituximab in patients with B-cell NHL is being assessed in ongoing Study B1641001. In addition, Study B1641003, a Phase 1b study of utomilumab in combination with pembrolizumab and Study B1641004, a Phase 1b study of utomilumab in combination with mogamulizumab (an anti-CCR4 mAb), are ongoing in patients with advanced solid tumors.

1.2.2.4.1. Safety and Efficacy

Study B1641001

As of 06 June 2016, a total of 133 patients have been treated in Study B1641001: 86 patients in Portion A have received utomilumab in dose levels between 0.006 and 10 mg/kg and 47 patients in Portion B have received with utomilumab in dose levels between 0.03 and 10 mg/kg in combination with rituximab 375 mg/m^2.

Among patients treated in Portion A, the most frequently reported TEAEs (≥10% of patients, all grades) regardless of causality were fatigue (24.4%), nausea (18.6%), decreased appetite (16.3%), vomiting (16.3%) abdominal pain (15.1%), diarrhea (11.6%), dizziness (11.6%), constipation (10.5%), and pyrexia (10.5%). There were 2 Grade 5 AEs reported (malignant neoplasm progression and death), which were considered not related to the study drug. Treatment-related TEAEs were mostly Grade 1 or Grade 2 with only three Grade 3 AEs reported (fatigue, ALT elevation, and hyponatremia). *Note: After the data cut-off date causality of the Grade 3 ALT elevation was re-assessed as not related to utomilumab by the Investigator.* The reported Grade 3 fatigue was of limited duration approximately 20 days and seen at the highest dose tested of 10 mg/kg of utomilumab. No Grade 4 treatment-related AEs were observed. Only 1 patient permanently discontinued treatment with PF-05082566 for a Grade 2 treatment-related AE of enterocolitis. Only 3 treatment-related serious AEs (SAEs) were reported in 2 patients: enterocolitis, decreased appetite and pneumonitis.

Among patients treated in Portion B, the most frequently reported TEAEs (≥10% of patients; all grades) regardless of causality were fatigue (31.9%), infusion-related reaction (21.3%), upper respiratory tract infection (14.9%), diarrhea (12.8%), pyrexia (12.8%), chills (10.6%), cough (10.6%), and headache (10.6%). There was one Grade 5 AE (death) reported (due to disease progression), which was considered not related to the study drug. The most commonly reported treatment-related TEAEs (≥10% of patients; all grades) that were considered treatment-related were fatigue (23.4%) and infusion-related reaction (21.3%). Treatment-related TEAEs were mostly Grade 1 or Grade 2. Grade 3 AEs were reported in 4 patients: infusion-related reaction (2 patients), lymphocyte count decreased and neutropenia (1 patient each). All Grade 3 AEs were related to rituximab treatment only, per Investigator assessment. None of the Grade 3 AEs were related to utomilumab. No Grade 4 treatment-related AEs were observed.

Overall, the safety profile of utomilumab, based on a data cutoff date of 06 June 2016, supports its use as both a single agent and in combination with rituximab. Treatment-related AEs were generally mild or moderate with only two Grade 3 AEs (hyponatremia and fatigue) reported as related to utomilumab in Portion A.

Study B1641003

As of 06 June 2016, a total of 23 solid tumor patients have been treated with the combination of utomilumab and pembrolizumab at the fixed dose of 2 mg/kg. Utomilumab doses administered include 0.45 mg/kg (n=5); and 0.9 mg/kg, 1.8 mg/kg, and 3.6 mg/kg (n=3 patients each); and 5 mg/kg (n=9).

The most frequently reported TEAEs (≥10% of patients; all grades) regardless of causality, were fatigue (43.5%), cough (34.8%), decreased appetite (30.4%), nausea (30.4%), constipation, pruritus, rash maculo-papular (26.1% each), pyrexia and vomiting (21.7% each), anemia, dyspepsia, rash, and upper respiratory tract infection (17.4%, each), arthralgia, asthenia, back pain, dry mouth, dry skin, dyspnea, fall, haemoptysis, hypokalaemia, hyponatraemia, muscle spasms, oedema peripheral, pleural effusion, pneumonia, sinusitis,

and stomatitis (13.0% each). There was one Grade 5 AE (death) reported (due to disease progression) which was considered not related to the study drug.

The most frequently observed treatment-related TEAEs (≥10% of patients; all grades) were fatigue (34.8%), rash maculo-papular (26.1%), pruritus (21.7%), pyrexia (17.4%), nausea, decreased appetite, dry skin, dry mouth (13.0% each) and are shown in Table 6.2-14. Treatment-related TEAEs were mostly Grade 1 or Grade 2. There were only 2 treatment-related (utomilumab and pembrolizumab) Grade 3 AEs reported in 2 patients: adrenal insufficiency (no evidence of associated hypophysitis reported) and hypokalaemia (1 patient each). No Grade 4 or 5 treatment-related AEs were observed.

In summary, the observed safety profile, based on a data cut-off date of 06 June 2016 for B1641003, supports utomilumab use in combination with pembrolizumab. Treatment-related AEs were generally mild or moderate with only two Grade 3 AEs reported as treatment-related to both utomilumab and pembrolizumab.

Study B9991004

In the B9991004 study, the DLT observation period in Phase 1b portion of Combination A is complete. All 3 dose levels utomilumab at 500 mg (Cohort A1), 100 mg (Cohort A2), or 20 mg (Cohort A3) in combination with 10 mg/kg have been well tolerated and no DLT has been observed in 18 enrolled patients. Including Phase 2, 273 patients with NSCLC, SCCHN, melanoma, TNBC, and SCLC received utomilumab at dose levels of 20 mg, 100 mg, and 500 mg in combination with avelumab 10 mg/kg Q2W. The combination is well tolerated. The AE profile of the combination therapy is consistent with either of the single agent therapies in terms of incidence and severity of the adverse events (unpublished data).

Efficacy

Study B1641001

As of the data cut-off date 06 June 2016, in Portion A, 1 confirmed CR and 1 confirmed PR in MCC were reported in patients who were treated at 0.24 mg/kg and 0.6 mg/kg respectively. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a PR that was not yet confirmed at the time of data cut-off date; however, this response was confirmed at a subsequent assessment. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a greater than 30% reduction in the diameters of multiple target tumors but was considered to have stable disease (irSD) per Immune-related Response Criteria derived from Response Evaluation Criteria for Solid Tumors (RECIST) version (v) 1.1. After the IB cutoff date, one out of 5 NSCLC patients treated with single agent utomilumab at 0.24 mg/kg experienced partial response (pending confirmation).

In Portion B, 8 patients with follicular lymphoma (7 patients were refractory to prior rituximab-containing regimen) achieved an objective response: 4 patients achieved a CR (2 treated at 1.2 mg/kg, 1 at 0.12 mg/kg, and 1 at 0.03 mg/kg) and 4 patients achieved a PR (2 treated at treated at 0.18 mg/kg, 1 treated at 1.2 mg/kg, and 1 treated at 5.0 mg/kg). One

(1) patient with CD20 + Hodgkin's lymphoma treated at 1.2 mg/kg achieved a PR and 1 patient with Mantle Cell Lymphoma (MCL) treated at 2.4 mg/kg achieved a PR.

Study B1641003

As of 06 June 2016, among the 23 patients treated in Study B1641003, 6 had confirmed objective response providing an ORR of 26.0%. Two (2) patients had a confirmed CR (1 patient with RCC treated at 1.8 mg/kg and 1 patient with SCLC treated at 5.0 mg/kg). Four (4) patients achieved a PR: 1 patient with RCC and 1 patient with NSCLC treated at 0.45 mg/kg; 1 patient with anaplastic thyroid disease treated at 3.6 mg/kg, and 1 patient with SCCHN treated at 5 mg/kg.

1.2.2.5. Pharmacokinetics of Utomilumab in Humans

Study B1641001

Preliminary PK data following single-dose treatments are available for 81 patients (46 in Portion A and 35 in Portion B) in Study B1641001. Following the attainment of C_{max}, utomilumab serum concentrations showed a bi-exponential decline, with a mean terminal elimination half-life ($t_{1/2}$) of 208-349 hrs, a low systemic clearance (CL = 0.265 to 0.389 mL/hr/kg) and a small volume of distribution (V_{ss} = 83.3-231 mL/kg) in Cycle 1 of Portion A. In Portion B, utomilumab also showed a bi-exponential decline with a mean terminal elimination half-life of 274-550 hrs, a low systemic clearance (CL = 0.175 to 0.335 mL/hr/kg) and a small volume of distribution (Vss = 88.4-164 mL/kg). A dose proportional increase in utomilumab exposure was observed.

Study B1641003

Blood samples were collected for characterizing the PK and ADA of both utomilumab and pembrolizumab. The utomilumab exposure appeared to increase with increasing doses. The utomilumab $t_{1/2}$ ranged from 136 to 179 hours.

1.2.2.6. Immunogenicity of Utomilumab in Humans

Study B1641001

Based on preliminary data from Study B1641001, 9 of 61 (14.8%) patients in Portion A exhibited positive ADAs prior to treatment with utomilumab. Thirty-five out of 61 patients (57.4%) were positive for ADA for at least one time point regardless of baseline ADA status. Among 35 ADA-positive patients, 7 (20%) exhibited positive neutralizing antibody (Nab) against PF- 05082566 In Portion B, 2 out of 41 (4.9%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus rituximab. Three of 41 patients (7.3%) were positive for ADA for at least one time point regardless of baseline ADA status when administered in combination with rituximab. Among 3 ADA-positive patients, 1 (33.3%) exhibited positive Nab against utomilumab.

The impact of ADA on PK of utomilumab was also characterized. The utomilumab CL was similar in ADA negative and ADA positive patients suggesting that ADA status has minimal impact on the PK of utomilumab.

Study B1641003

Preliminary ADA data show 2 of 23 (8.7%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus pembrolizumab. Seventeen of 23 patients (73.9%) were positive for ADA for at least one time point regardless of baseline ADA status when administered in combination with pembrolizumab. Among 14 ADA positive patients who were tested for Nab analysis, 5 (35.7%) patients had a positive Nab against utomilumab. Complete pre-clinical and clinical information for utomilumab, including PK data in patients, may be found in the SRSD, which for this study is the utomilumab IB.[20]

1.2.3. PF-04518600 (OX40 Agonist)

OX40 (CD134) is a co stimulatory receptor that acts on antigen stimulated T-cells but not native T-cells.[36,37] OX40 expression is transient, and peaks 48 to 72 hours following T-cell receptor (TCR) stimulation. High numbers of OX40 positive infiltrating T-cells have been found within tumor biopsies, and lymph nodes of primary melanoma, breast, colon and head and neck cancer patients.[38-41] OX40 plays a key role in T-cell survival, proliferation, and activation. Following binding to OX40 ligand (also known as OX40L, CD252 or TNFSF4), OX40 signaling activates both the canonical and noncanonical NF-κB (nuclear factor kappa light chain enhancer of activated B cells) survival pathways, leading to an upregulation of anti-apoptotic molecules including Bcl-2, Bcl-xL, and surviving.[42] Furthermore, OX40 engagement may enhance IL-2, IL-4, IL-5, IFNγ cytokine secretion by activated CD4 T-cells. It is interesting to note that OX40 activation has been shown to not require co-stimulation from other co-stimulatory receptors.[43] OX40L is usually expressed on activated B cells and dendritic cells, but due to the immunosuppressive environment within a tumor, OX40L was not detected in the tumor mass of several syngeneic mouse models.[52] Mechanistically, it is therefore possible that an agonistic mAb to OX40 may reverse T-cell's anergic state, and enhance tumor immunity. Indeed, eradication of tumor growth has been observed by using agonistic OX40 mAbs and OX40 agonists in preclinical models of melanoma, sarcoma, and glioma, and colon, breast, prostate, and renal cancers.[37,39,44,45] Given the potential for OX40 agonistic mAbs to enhance anti-tumor T-cell responses, and induce tumor regression, a Phase 1 clinical trial with a murine anti OX40 antibody has been completed.[46] In this study, tumor regression was observed in 12 of 30 advanced cancer patients, as well as an acceptable toxicity profile. Pfizer has generated a fully human IgG2 monoclonal antibody specific for the human OX40 (PF-04518600).

PF-04518600 has been demonstrated to be an agonistic antibody against OX40. Furthermore, PF-04518600 can selectively and reversibly bind to human OX40 with a high affinity, and in conjunction with TCR signals, is able to functionally co stimulate T-cells as measured by IL-2, IL-6, tumor necrosis factor (TNF) and IFNγ release in vitro. In a syngeneic mouse model, a murine surrogate anti OX40 agonistic antibody (OX86) demonstrated growth inhibition of colon tumors (see Section 1.2.3.1).

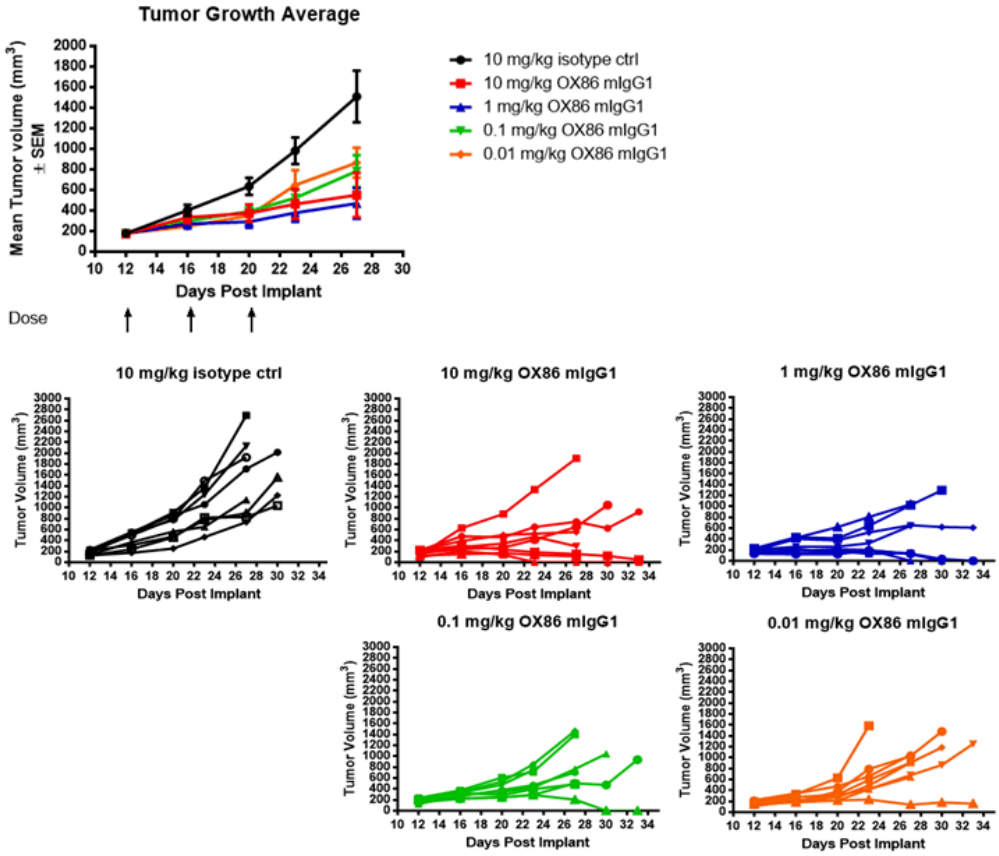
1.2.3.1. PF-04518600 Nonclinical Efficacy

PF-04518600 is a fully human IgG2 mAb that is highly selective for human OX40 (CD134). PF-04518600's agonistic potential was demonstrated in a luciferase reporter assay, and selectivity studies using a Biacore assay also showed PF-04518600 to be highly selective for OX40, with no cross activity with other members of the TNFR super family, including CD40 receptor, 4 1BB receptor (CD137), and glucocorticoid-induced TNFR family-related gene (GITR).[51]

1.2.3.1.1. Single-Agent Studies

To determine in vivo efficacy, a murine surrogate agonist antibody against OX40, OX86, was utilized in murine tumor models. In a syngeneic tumor model, OX86 inhibited the growth of CT26 colon tumor cells (Figure 10).[51] Dosing of 10, 1, 0.1, or 0.01 mg/kg OX86 mIgG1 every 4 days for 3 doses starting 12 days after the implantation of 0.2 million CT26 cells led to a 63.5%, 68.9%, 48.0%, and 42.6% decrease in tumor volume respectively.

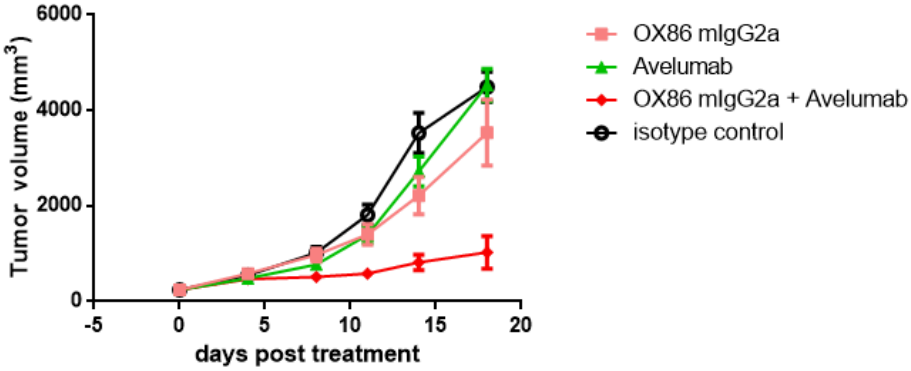
Figure 10. Mouse Surrogate Antibody OX86 mIgG1 Prevented Growth of CT26 Colon Carcinoma



1.2.3.1.2. Combination Studies

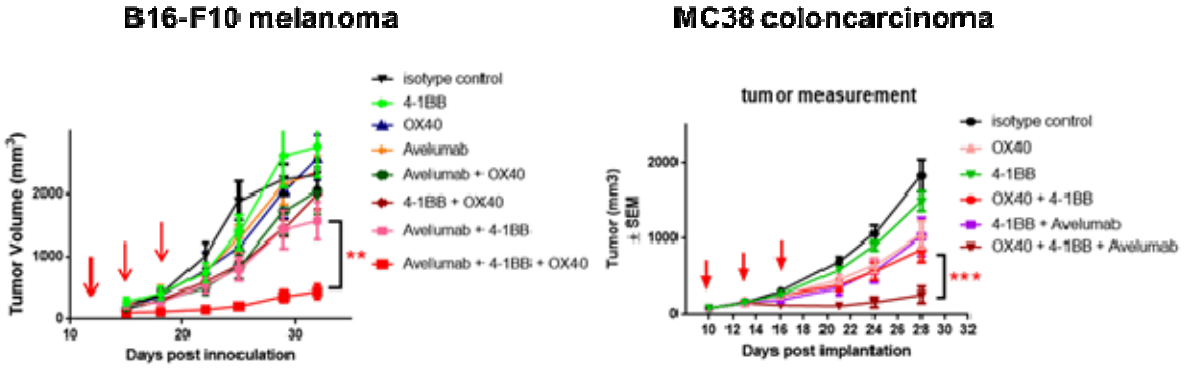
In a syngeneic tumor model, the murine surrogate anti OX40 agonistic antibody OX86 combined with avelumab inhibited the growth of CT26 colon tumor cells (Figure 11). Doses of 0.3 mg/kg OX86 mIgG2a in combination with 10 mg/kg avelumab were used. Treatment was started when the tumors reached an average of 230-252 mm^3 in size. Animals were dosed twice per week for 3 doses. The combination of avelumab and anti-OX40 led to a decrease in tumor volume of 67.9% 11 days post-treatment ($p<0.05$), 76.8% 14 days post-treatment ($p<0.0001$), and 77.2% 18 days post-treatment ($p<0.0001$).

Figure 11. Mouse Surrogate Antibody OX86 mIgG2a plus Avelumab Prevented Growth of CT26 Colon Carcinoma



The triple combination of the surrogate mouse OX40 mAb and surrogate 4-1BB mAb with avelumab led to significant tumor growth inhibition in the established colon carcinoma MC38 model and the less immunogenic melanoma model B16-F10 (Figure 12), in comparison with the single-agent and double combination treatments. Animals were dosed twice per week for 3 doses.

Figure 12. Inhibition of Tumor Growth by the Triplet Combination of Avelumab/Utomilumab/PF-04518600 in Melanoma and Colorectal Carcinoma Models



4-1-BB: 1 mg/kg; avelumab: 20 mg/kg (B16-F10 melanoma model), 10 mg/kg (MC38 colon carcinoma model); 4-1BB: 1 mg/kg. **p=0.002; ***p=0.0006.

1.2.3.2. PF-04518600 Nonclinical Toxicology

The nonclinical safety profile of PF-04518600 has been well characterized in nonclinical toxicology studies that are described in the PF-04518600 IB.[51] Repeated administration of PF-04518600 was well tolerated in male and female cynomolgus monkeys when administered intravenously once weekly for 1 month (5 times in total) at dosages up to 100 mg/kg. Toxicology results revealed that systemic exposure to PF-04518600 increased with increasing doses, and there were no apparent gender-related differences in exposure.

The potential for PF-04518600 to stimulate cytokine release was tested at concentrations ranging from 1-100 μg/mL in human whole blood from healthy volunteers. In addition, plate bound PF-04518600 was tested at concentrations ranging from 1-100 μg/mL for stimulation of pro inflammatory cytokine release from human PBMCs from healthy volunteers. PF-04518600 did not induce significant release of TNFα, IL-6 or IFNγ in the human whole blood or PBMCs.[51]

1.2.3.3. *In Vitro* Cytokine Release Assays (Avelumab plus Utomilumab plus PF-04518600)

The potential for PF-04518600 and avelumab together with utomilumab to stimulate cytokine release was tested at concentrations ranging from 1-100 μg/mL in human whole blood from 8 healthy volunteers. In addition, plate bound PF-04518600, avelumab, and utomilumab were tested at concentrations ranging from 1-100 μg/mL for stimulation of pro inflammatory cytokine release from human peripheral blood mononuclear cells (PBMCs) from 8 healthy volunteers. The combination of PF-04518600, avelumab, and utomilumab did not induce significant release of TNFα, IL-6 or IFNγ in the human whole blood or PBMCs.

1.2.3.4. PF-04518600 Clinical Experience

PF-04518600 is currently being evaluated in an ongoing, Phase 1, open-label, 2-part dose escalation and expansion study in patients with select advanced solid tumors (Study B0601002). As of 31 August 2018, a total of 163 patients have received PF-04518600 as either single agent at doses between 0.01 and 10 mg/kg (Part A; n=81) or as the combination of PF-0418600 (0.1 or 3 mg/kg) plus utomilumab (Part B; n=82).

1.2.3.4.1. Safety and Efficacy

Safety

Study B0601002 (Part A: PF-04518600 Single Agent, Part B: PF-04518600 Plus Utomilumab)

Part A: As of the data cut-off date of 31 August 2018, 81 patients were treated with PF-04518600 across 6 dose levels (0.01, 0.1, 0.3, 1.5, 3 and 10 mg/kg) in Part A of Study B0601002.

The most frequent AEs that occurred in ≥10% of patients are: fatigue (33.3%), nausea (22.2%), decreased appetite (23.5%), pruritus (19.8%), aspartate aminotransferase increased (21.0%), anemia (17.3%), abdominal pain (18.5%), constipation (14.8%), dyspnea (18.5%), headache (11.1%), chills (11.1%), pyrexia (17.3%), diarrhea (13.6%), vomiting (14.8%), alanine aminotransferase increased (11.1%), cough (13.6%), rash (13.6%), back pain (12.3%), hypertension (11.1%), and blood bilirubin increased (11.1%).

The most frequent treatment related AE experienced by ≥10% of patients in Part A was fatigue (18.5%). The majority of treatment-related AEs reported were Grade 3 or below except for two Grade 4 AEs (preferred term [PT]: lipase increased). Two (2) patients discontinued treatment with PF-04518600 for treatment-related AEs: one patient for congestive cardiac failure and one patient for aspartate aminotransferase increased.

Part B: As of the data cut-off date of 31 August 2018, 82 patients were treated with PF-04518600 across 4 dose levels of PF-04518600 (0.1,0.3, 1 and 3 mg/kg) in combination with 20 mg or 100 mg utomilumab or 30 mg PF-04518600 in combination with 20 mg utomilumab. The most frequently reported AEs that occurred in ≥10% of patients included: decreased appetite (26.8%), fatigue (26.8%), anaemia (26.8%), nausea (19.5%), pyrexia (15.9%), abdominal pain (12.2%), constipation (18.3%), diarrhea (14.6%), cough (12.2%), dyspnea (13.4%), and aspartate aminotransferase increased (11.0%).

The most frequent treatment-related AE experienced by 2 or more patients include fatigue (12.2%), anaemia (8.5%), nausea, pruritus, and decreased appetite (6.1% each), alanine aminotransferase increased, rash, and vomiting (4.9% each). The majority of treatment-related AEs reported were Grade 3 or below except for a single Grade 4 AE (PT: lipase increased). One (1) patient discontinued due to treatment-related infusion related reaction (patient treated at 1 mg/kg PF-04518600 plus 100 mg utomilumab).

In summary, the safety profile of PF-04518600, based on a data cut-off date of 31 August 2018 for Study B0601002, shows a manageable safety profile as single agent and in combination with utomilumab. Grade 1/2 fatigue represents the most common (33.3%) AE related to PF-04518600 monotherapy, and the most common (26.8%) AE related to PF-04518600 plus utomilumab. The majority of treatment-related AEs were Grade 3 or below except two cases of Grade 3 lipase increased (PF-04518600 monotherapy) and one case of Grade 4 lipase increase (PF-04518600 plus utomilumab).

Study B9991004

In study B9991004, the Phase 1b part of Combination B is completed. All three dose levels of PF-04518600 at 0.3 mg/kg (Cohort B12), 1.0 mg/kg (Cohort B13) and 3.0 mg/kg (Cohort B14) in combination with avelumab 10 mg/kg have been well tolerated and no DLT has been observed. The PF-04518600 0.3 mg/kg IV Q2W dose in combination with avelumab 10 mg/kg has been selected for Phase 2. A total of 71 patients have been treated with 0.3 mg, 1 mg, or 3 mg/kg PF-04518600 Q2W combined with 10 mg/kg avelumab. The combination is well tolerated. The AE profile of the combination therapy is consistent with the either of the single agent therapies in terms of incidence and severity of the AEs (unpublished data).

Efficacy

Study B0601002

Part A1 (PF-04518600 monotherapy)

As of the data cutoff date of 19 August 2018 (Part A1 efficacy only), 3 partial responses (PRs) were reported in Study B0601002 Part A1 confirmed by RECIST; 1 PR was reported in a cutaneous melanoma patient treated at the 0.1 mg/kg dose level who had a duration of response of 10.3 weeks, an additional PR was reported in a hepatocellular carcinoma (HCC) patient treated at the 0.3 mg/kg dose level who had a duration of response of 93.1 weeks, and the other PR was in a cutaneous melanoma patient treated at the 10 mg/kg dose level who has a duration of response of 35.9 weeks. A total of 26/52 (50%) patients treated in Part A1, experienced a best overall response of stable disease (SD).

Part B1 (PF-04518600 plus Utomilumab)

As of the data cutoff date of 19 August 2018 (Part B1 efficacy only), 2 PRs reported during Part B1 were confirmed by RECIST; 1 PR was reported in a malignant melanoma patient treated at 0.3 mg/kg PF-04518600 + 20 mg utomilumab who had a duration of response of at least 56.1 weeks, and a second PR was reported in an ocular melanoma patient treated at 0.3 mg/kg PF-04518600 + 100 mg utomilumab who had a duration of response of 12.1 weeks. A third patient with cutaneous melanoma treated at 0.3 mg/kg PF-04518600 + 100 mg utomilumab dose level developed an unconfirmed PR after initial progression. A total of 18/57 (31.6%) patients treated in Part B1, experienced a best overall response of SD.

1.2.3.5. Pharmacokinetics of PF-04518600

As of 27 October 2017, preliminary PK data were available for 52 patients at the 0.01, 0.1, 0.3, 1.5, 3, and 10 mg/kg dose levels from the monotherapy dose escalation phase (Part A1) of the B0601002 study.

Following single IV infusion of PF-04518600, PF-04518600 peak concentrations were observed at the end of infusion or at 3 hours after the end of infusion, followed by a decline in PF-04518600 concentrations exhibiting multiphasic disposition characteristics. At the 0.1 mg/kg dose, PF-04518600 PK profiles exhibited a pattern consistent with target mediated drug disposition compared with higher doses. The exposure (AUCτ) during the first cycle following PF-04518600 administration increased with increasing dose levels in an approximately dose-proportional manner between the doses of 0.3 and 10 mg/kg. The mean t½ values ranged from 4 to 10.1 days at the dose range of 0.1 to 10 mg/kg.

Following multiple IV infusions of PF-04518600 once every 14 days, the mean (± standard deviation) accumulation ratios (calculated as AUCτ, Cycle 3/AUCτ, Cycle 1) were 1.4 ± 0.5, 1.7 ± 0.4, 1.8 ± 0.2, 2.0 ± 0.2, and 2.0 ± 0.3 at the dose levels of 0.1, 0.3, 1.5, 3, and 10 mg/kg, respectively, based on a total of 28 patients with full PK profiles from both Cycle 1 and Cycle 3.

1.2.3.6. Immunogenicity of PF-04518600

As of 30 October 2017, preliminary data were available for 49 patients who had the baseline and at least one post-dose ADA sample analyzed from the monotherapy dose escalation phase (Part A1) of the B0601002 study. A total of 4 patients (8.2%) tested positive for ADA at baseline. A total of 16 patients (33%) were ADA positive at a minimum of one post-dose time point. The majority of ADA titers were low with no noticeable effect on the PK of PF-04518600, except for 2 patients at the 0.1 mg/kg dose level; these 2 patients had the highest titers in that group and the C_{trough} of PF-04518600 appeared to be lower compared to the expected profiles at later cycles.

Complete pre-clinical and clinical information for PF-04518600 may be found in the SRSD, which for this study is the PF-04518600 IB.[51]

1.2.4. PD 0360324 (Anti-M-CSF)

M-CSF, also known as colony-stimulating factor -1 (CSF-1), is a pleiotropic cytokine that is produced by a wide range of cells, including several tumor types. It is the primary regulator of the survival, proliferation, and differentiation of mononuclear phagocytes such as monocytes and tumor/tissue macrophages.[53] M-CSF delivers a signal through the M-CSF receptor (also referred to as M-CSFR, CSF 1R, or CD115), a type III receptor tyrosine kinase that is mainly restricted to cells of the mononuclear phagocyte lineage.[54] Blockade of M-CSF/M-CSFR signaling pathway by mAbs to the ligand M-CSF or the receptor M CSFR, and small molecule antagonists to the M-CSFR tyrosine kinase inhibitor (TKI), has been the subject of extensive preclinical investigations.[53,55] Tumor-associated macrophage (TAM) reduction or re-programming and the resulting delayed tumor growth have been shown in many murine tumor models.[53,55,56] Clinically, administration of a monoclonal antibody (RG7155) that inhibits CSF-1 receptor (CSF-1R) activation to patients led to striking reductions of tumor macrophages and objective responses in patients with diffuse-type giant cell tumors.[57]

PD 0360324 is a fully human IgG2 mAb that binds M-CSF with high affinity (dissociation constant [KD] = 281 pM) and selectivity, and prevents the binding of M-CSF to its receptor (>100-fold potency for M-CSF over c-fms).

1.2.4.1. Preclinical Studies

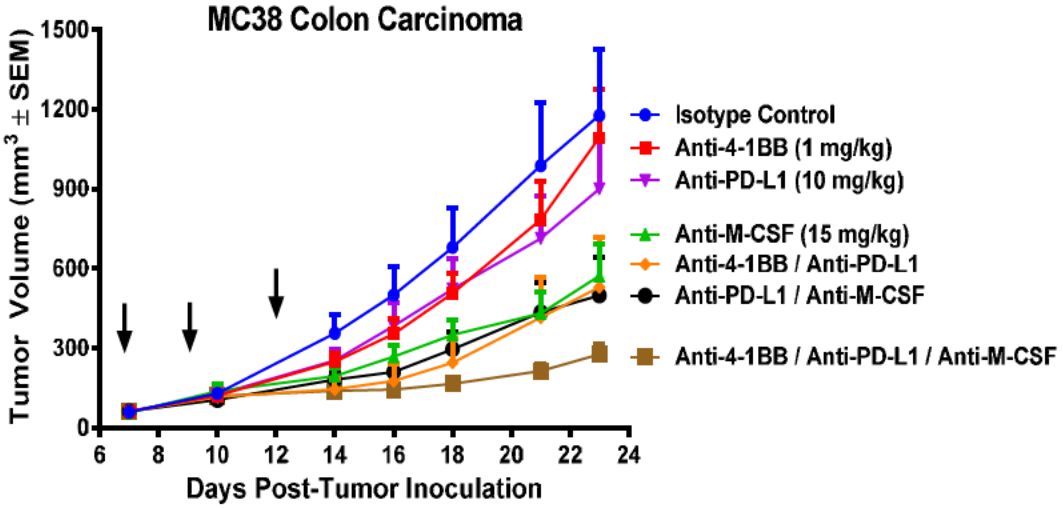
PD 0360324 does not cross-react with murine M-CSF, therefore, a surrogate antibody was used in murine models of arthritis and lupus. In these studies, the surrogate antibody was efficacious in reducing paw swelling and reducing proteinuria and macrophage infiltration, respectively. In addition, a rat anti-mouse M-CSF surrogate (Clone 5A1) was utilized in a mouse MC-38 tumor model. Antibody treatment led to a reduction of tumor-associated macrophages, resulting in delayed tumor growth.

1.2.4.2. Preclinical Combination Studies

In a syngeneic tumor model, the anti-M-CSF antibody combined with avelumab inhibited the growth of MC38 colon carcinoma cells, although not significantly more than anti-M-CSF by itself (Figure 13). A dose of 15 mg/kg anti-M-CSF antibody in combination with 10 mg/kg

avelumab was used. Animals were dosed Day 7, Day 9, and Day 12 post-tumor inoculation. While in this model anti-M-CSF appeared to be as active as avelumab plus anti-M-CSF, enhanced anti-tumor activity was observed in the triple combination of anti-4-1BB/ anti-M-CSF/avelumab.

Figure 13. Inhibition of Tumor Growth by the Combination of Avelumab and anti-M-CSF in a Colorectal Carcinoma Model



1.2.4.3. Clinical Safety and Efficacy

As of June 2015, PD 0360324 has been studied in humans at single doses ranging from 3 mg to 300 mg (A6261001), multiple doses up to 100 mg every 4 weeks (Q4W) in patients with rheumatoid arthritis (RA; A6261002), multiple doses with 100 and 150 mg Q2W in patients with cutaneous lupus erythematosus (CLE; A6261008), and multiple doses escalating from 100 to 150 mg in patients with sarcoidosis (A6261009). In these studies, 104 healthy subjects or patients received one or more doses of PD 0360324 and 51 healthy subjects or patients have received placebo.

TEAE occurring in ≥5 of the 104 subjects/patients (approximately 5%) who have received PD 0360324 include blood creatinine phosphokinase increased (n=17, 16.3%); headache (n=11, 10.5%), fatigue (n=9, 8.7%); oropharyngeal pain (n=8, 7.7%); cutaneous lupus erythematosus, diarrhea, eye swelling, upper respiratory tract infection (n=6 each, 5.8%); and dizziness, nasal congestion, nausea, periorbital oedema, pruritus, and pyrexia (n=5 each, 4.8%). Blood creatine phosphokinase increased, headache, eye swelling, fatigue, periorbital oedema, cutaneous lupus erythematosus, nausea, pain, or pruritus were considered treatment-related in over half of patients experiencing these events. Of note, 2 patients treated in these studies also experienced eyelid edema, for which both events were considered treatment-related.

There have been no serious infections, SAEs, or discontinuations related to infections reported to date. There were no infusion reactions to suggest hypersensitivity or cytokine release in response to the drug product. Tests for the production of anti- PD 0360324

antibodies, performed when PD 0360324 levels reached the lower limit of quantitation, were negative.

Periorbital soft tissue swelling related events have been observed in a total of 13 patients who received M-CSF at doses ranging from 50 mg to 300 mg IV. It included periorbital edema and eyelid swelling, which appears to be a class effect of M-CSF/CSF-1 inhibitors. The observed time of onset of the soft tissue swelling has ranged from shortly after dosing (Day 2) in one subject to several weeks or more for most subjects. All of these swelling events resolved spontaneously with approximate durations ranging from 1 day to 157 days. The intensity of the periorbital soft tissue swelling was mild to moderate in all cases except for one subject with a severe event. The severity decreased to moderate within 3 days and subsequently resolved within 32 days. All the events resolved subsequently, 6 of the 13 events required discontinuation of therapy. Most of the events were observed at dose of 100 mg and above. The significance of these soft tissue swelling findings are not clear, but may be related to deposition of hyaluronic acid (HA) in the connective tissue spaces, including around extra ocular tissue. It is known that macrophages have a significant role in the turnover of HA, and increased HA in interstitial matrix would be consistent with decreased tissue macrophage presence due to M-CSF inhibition.

In the clinical studies, transient, dose- and treatment-related elevations in AST, ALT, and CK have been observed and were generally mild. Transient changes in creatine kinase – muscle and brain subunits (CK-MB) have been associated with mild to moderate CK elevations. No associated cardiac troponin 1 changes or electrocardiogram (ECG) abnormalities have been observed. Mild increases in AST and CK from baseline are expected in subjects receiving PD 0360324 as a decrease in tissue macrophages may lead to decreased clearance of these enzymes.

The 300 mg dose of PD 0360324 in Protocol A6261001 was determined to have exceeded the limits of acceptable safety and tolerability due to severe periorbital edema, CK elevation, and myoglobinemia in healthy adults. This dose will not be used in the B9991004 study. Doses as high as 150 mg were tolerated in patients with lupus erythematosis in Study A6261008.

The clinical efficacy of PD 0360324 in cancer patients is being studied for the first time in this study. However, M-CSF/CSF-1R inhibition was reported to have significant clinical activity in patients with tenosynovial giant tumor.[64] This is a tumor that is driven in most cases by a gene translocation that results in most tumor cells expressing M-CSF.

1.2.4.4. Pharmacokinetics of PD 0360324

The PK of PD 0360324 has been evaluated in healthy subjects following a single IV dose at 3 mg to 300 mg, in patients with rheumatoid arthritis following multiple IV doses from 20 mg to 100 mg Q4W, and in patients with cutaneous lupus erythematosus following multiple IV doses at 100 mg and 150 mg Q2W.

After a single IV dose over the range of 3 mg to 300 mg, the concentration-time profiles of PD 0360324 indicated concentration-dependent (saturable) elimination, possibly due to

target-mediated disposition. The increase in PD 0360324 dose from 3 mg to 300 mg led to a more than dose proportional increase in systemic exposure. There was minimal accumulation in exposure after multiple dosing Q4W. The peak (C_{max}) and trough (C_{trough}) concentrations after multiple dosing increased in a greater than dose proportional manner as doses increased from 100 mg to 150 mg Q2W.

1.2.4.5. Immunogenicity of PD 0360324

In healthy subjects (Study A6261001), ADA against PD 0360324 was not detected following a single IV dose over the range of 3 mg to 300 mg. In patients with rheumatoid arthritis (Study A6261002), no ADA was detected after multiple IV dosing from 20 mg to 100 mg. In patients with cutaneous lupus erythematosus (Study A6261008), 2 (1 patient from each of the 100-mg and 150-mg dose groups) out of 22 patients tested positive for ADA. In both patients, ADA appeared to be transient. There was no obvious effect of positive ADA on PK levels, safety or efficacy. The positive ADA samples tested negative for neutralizing activity.

1.2.5. CMP-001 (QbG10)

The active drug substance of CMP-001 is designated QbG10, a virus-like particle (VLP) composed of a Toll-Like Receptor 9 (TLR9) agonist (G10, an oligodeoxynucleotide [ODN]) containing a cytosine linked to a guanine by a phosphate bond (CpG) encapsulated in bacteriophage Qbeta capsid proteins. Qbeta serves as a biological carrier for G10 and protects the TLR9 agonist from immediate degradation by nucleases in vivo.

CMP-001 is designed to activate pDCs via TLR9. The TLR9-dependent activation of pDCs causes secretion of very large quantities of type I interferons, increased expression of costimulatory molecules, and recruitment and activation of other dendritic cell (DC) subsets to enhance tumor antigen presentation to T cells, culminating in the generation of effective anti-tumor T cell responses.

Subcutaneous administration of CMP-001 leads to formation of anti-Qbeta antibodies that enable fragment crystallizable gamma receptor (FcγR)-mediated CMP-001 delivery to tumor-resident pDC after subsequent IT injections. As the TLR9 receptors are intracellular, uptake of the TLR9 agonist leads to tumor-associated pDC activation and release of interferon alpha (IFNα), with the induction of T-helper cell type 1 (Th1)-biased innate and adaptive antitumor immune responses.

CMP-001 is currently under development by Checkmate Pharmaceuticals (Checkmate) for the treatment of multiple tumor types in combination with checkpoint inhibitors (eg, pembrolizumab) and/or other anticancer agents and cancer treatment modalities.

QbG10 has been previously studied in nonclinical and clinical trials under the name CYT003.

1.2.5.1. Preclinical Studies

The ability of QbG10 to affect TLR9 dependent activation of DCs has been investigated in several in vitro pharmacodynamic studies using mouse, rat, and human cells. QbG10

efficiently induced secretion of interleukin 12 (IL-12) in mouse bone marrow-derived dendritic cells (BMDCs) in vitro. No such effect was observed when BMDCs were treated with QbpGlu component (Qb reassembled in the presence of polyglutamic acid thus devoid of nucleic acids) demonstrating that G10 nucleotide is critical for TLR9-dependent activation of DCs.

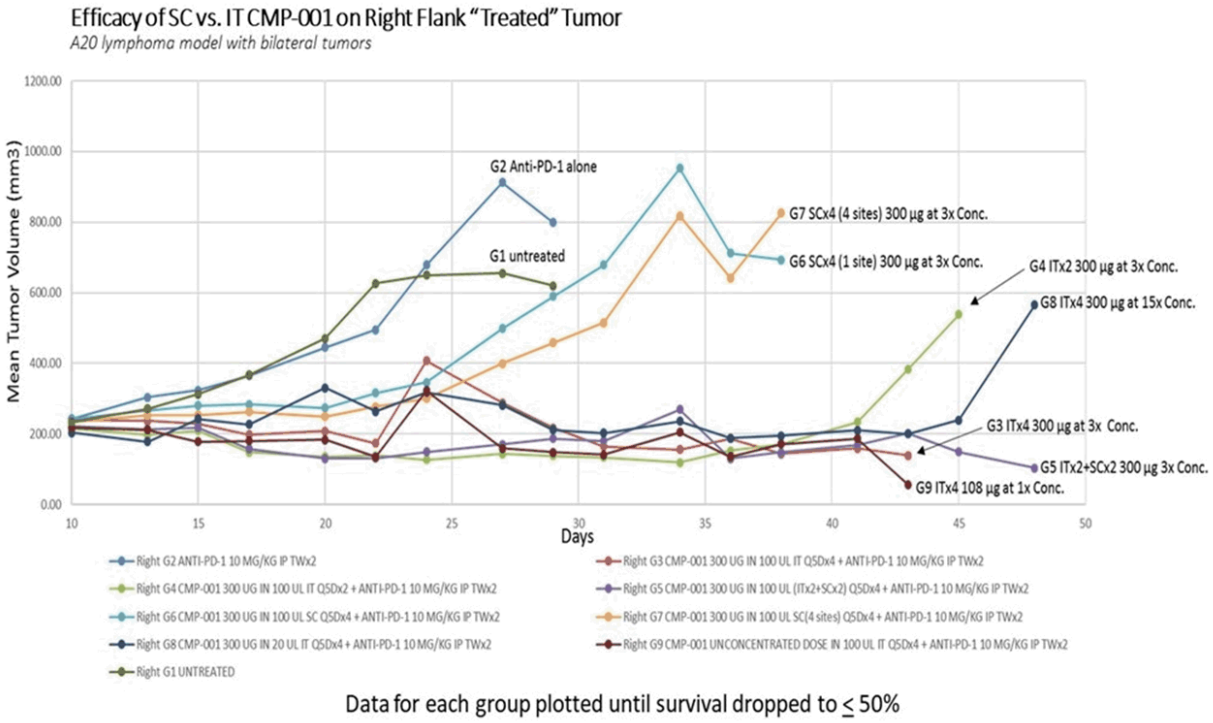
The in vitro studies also confirmed the crucial role of anti-Qb antibodies that are induced during treatment in the QbG10 uptake by pDCs. Upon treatment of PBMCs with QbG10, high levels of IFNα were only detected in the samples incubated with QbG10 in the presence of immune serum or a monoclonal Qb-specific antibody (Qb5IgG1) while incubation of PBMCs with QbG10 in the presence of naïve serum did not induce IFNα. Blood DC antigen-4 (BDCA-4) positive CD11c-negative pDCs appeared to be the main source of IFNα expression in human PBMCs treated with QbG10 in the presence of immune serum.

In vivo pharmacodynamic studies evaluated the efficacy of QbG10 in a mouse allergy and asthma model and in rats to characterize the dominant antibody response.

1.2.5.2. Preclinical Combination Studies

The preclinical anti-tumor efficacy of CMP-001 when combined with anti-PD-1 was tested in vivo in BALB/cAnN mice bearing syngeneic A20 lyphoma tumor (Checkmate CMP Study No. 160263). The 300 µg CMP-001 dose with two different dosing regimens (a total of 2 or 4 doses given every 5 days) and routes of administration (SC and IT) when combined with anti-PD-1 (intraperitoneal twice a week for 2 weeks at 10 mg/kg) was evaluated in 9 treatment groups (including untreated control and anti-PD-1 alone) of 12 female mice each (n=108). At Day -14 a SC priming dose of CMP-001 was given to all mice to initiate an anti-Qb immune response. A20 tumors were implanted in the right flanks of the mice at Day 0 and in the left flanks at Day 3. Treatments began on Day 5. IT administration was into right flank tumors and SC dosing was either in the nape of the neck or the base of each limb. The delayed implantation of left flank tumor was to increase the window of time for evaluation of abscopal effects from IT injections. Systemic antitumor immunity was observed with all IT administration groups, regardless of CMP-001 concentration or number of administrations. SC administration also demonstrated significant systemic anti- tumor efficacy (Figure 14).[65]

Figure 14. Anti-tumor Efficacy of CMP-001 Regimen and Route of Administration in A20 Syngeneic Mouse Lymphoma Model - Study 160263: Injected Tumor - Right Flank



Abbreviations: D = day; IT = intratumoral; PD-1 = programmed cell death protein; Q = every; SC = subcutaneous; TW = twice weekly.

In a separate study using a syngeneic CT-26 colon tumor model, IT administered CMP-001 in combination with an intraperitoneally administered PD-1 antagonist and an OX40 agonist resulted in cures of both treated and untreated CT-26 tumors in 40% of the mice demonstrating direct and abscopal/systemic anti-tumor activity of the triplet. The median survival time was increased for animals treated with the triplet compared to those treated with only vehicle or one or two immune modulators (50 days versus 18 days versus 21 or 23-28 days, respectively). Similar results were observed in the syngeneic MBT-2 bladder tumor model (and to a lesser extent in renal cancer RenCa model) though no complete responses were recorded. These data support the clinical investigation of these combinations in cancer patients.[66]

1.2.5.3. Clinical Safety and Efficacy

CMP-001 in combination with a PD-L1 agonist or as monotherapy is currently being evaluated in three Checkmate Pharmaceuticals Inc. phase 1b studies: CMP-001-001(NCT02680184), CMP-001-002 (NCT03084640) and CMP-001-003 (NCT03438318).[67]

As of 31 October 2018, a total of 159 patients have received at least one IT or SC dose of CMP-001.

Safety

Study CMP-001-001

Study CMP-001-001 is evaluating CMP-001 alone or in combination with pembrolizumab in patients with advanced melanoma resistant/refractory to checkpoint inhibitors.

As of 31 October 2018, 128 patients have received at least one CMP-001 by IT administration including, 113 patients who have received CMP-001 in combination with pembrolizumab 200 mg Q3W and 15 patients who have received CMP-001 alone.

In the Part 1 Dose Escalation and Part 1 Dose Expansion phases, patients have received CMP-001 at doses of 1 mg (n=3), 3 mg (n=16), 5 mg (n=70), 7.5 mg (n=6) and 10 mg (n=18) in combination with pembrolizumab (2 mg/kg Q3W) at 2 different dosing schedules (Schedule A: CMP-001 administered IT once a week for 7 weeks [Prime Phase] followed by Q3W administration [Boost Phase] and Schedule B: CMP-001 administered IT once a week for 2 weeks, then 5 times Q3W [Prime Phase] followed by Q3W [Boost Phase]). Fifteen (15) patients who have received CMP-001 in the Part 2 Monotherapy Arm have received CMP-001 at 5 mg (n=14) and 10 mg (n=1) doses.

As of 31 October 2018, 112 of the 113 (99.1%) patients enrolled in the Part 1 Dose Escalation and Part 1 Dose Expansion Phases of the CMP-001-001 study have experienced at least 1 TEAE, and 56 (49.6%) patients have experienced Grade 3 or higher TEAEs. The most commonly occurring TEAEs for all grades include chills (80 patients; 70.8%), fever (pyrexia) (67 patients; 59.3%), nausea (61 patients; 54.0%), fatigue (56 patients; 49.6%), vomiting (45 patients; 39.8%), headache (37 patients; 32.7%), hypotension, diarrhea, and decreased appetite (30 patients, 26.5%, each event), constipation (28 patients; 24.8%), injection site pain (24 patients; 21.2%), and cough and back pain (23 patients; 20.4%, each event). The only Grade 3 or higher TEAE occurring in 5% or more of patients is hypotension (10 patients; 8.8%).

Treatment-related TEAEs have been reported in 109 (96.5%) patients. The most commonly occurring treatment-related TEAEs for all grades include chills (79 patients; 69.9%); fever (pyrexia) (66 patients; 58.4%), nausea (53 patients; 46.9%), fatigue (50 patients; 44.2%), vomiting (34 patients; 30.1%), headache (32 patients; 28.3%), decreased appetite and injection site pain (24 patients; 21.2%, each event), and diarrhea (23 patients; 20.4%). The only Grade 3 or higher treatment-related TEAE occurring in 5% or more of patients is hypotension (9 patients; 8.0%).

Thirty-seven (32.7%) patients have experienced at least 1 SAE. Serious AEs reported in more than 1 patient include hypotension (7 patients; 6.2%), sepsis (3 patients; 2.7%), and fever (pyrexia), cytokine release syndrome, encephalopathy, hypoxia, and respiratory failure (2 patients; 1.8%, each event). Most SAEs are not considered related to study treatment, however, SAEs that are considered related to combination study treatment reported in more

than 1 patient include hypotension (6 patients; 5.3%) and cytokine release syndrome (2 patients; 1.8%).

Study CMP-001-002

Study CMP-001-002, is evaluating CMP-001 administered as a SC injection in Part 1 and as a SC and IT injection in Part 2 in combination with pembrolizumab in patients with advanced melanoma.

As of 31 October 2018, 18 patients have received at least 1 dose of CMP-001 by SC or IT injection in the Part 1 Dose Escalation Phase of the CMP-001-002 study. Patients received CMP-001 at starting doses of 5 mg (n=10) or 10 mg (n=8; note: 2 of these 8 patients enrolled in the 10 mg dosing cohort were initially dosed with 5 mg) in combination with pembrolizumab 200 mg Q3W. No patients have been enrolled in the Part 1 Dose Expansion Phase or Part 2.

In the Part 1 Dose Escalation Phase, all 18 (100%) patients have experienced at least 1 TEAE and 11 (61.1%) patients have experienced Grade 3 or higher TEAEs. The most commonly occurring TEAEs for all grades include fatigue (11 patients; 61.1%), nausea (8 patients; 44.4%), chills (6 patients; 33.3%), fever (pyrexia) (5 patients; 27.8%), and diarrhea, headache, and rash (4 patients; 22.2%, each event). Grade 3 or higher TEAEs of anemia and tumor pain have been reported in 2 (11.1%) patients each.

Treatment-related TEAEs have been reported in 16 (88.9%) patients. The most commonly occurring treatment-related TEAEs for all grades include fatigue (11 patients; 61.1%), chills (6 patients; 33.3%), nausea and fever (pyrexia) (5 patients; 27.8%, each event), and headache and rash (4 patients, 22.2%, each event). No Grade 3 or higher treatment-related TEAEs have been reported in 2 or more patients.

Nine (50.0%) patients have experienced at least 1 SAE. Serious AEs reported in more than 1 patient include tumor pain (2 patients; 11.1%). Only 1 of the SAEs of tumor pain (5.6%) is considered treatment-related and resulted in treatment delay.

Study CMP-001-003

Study CMP-001-003 is evaluating CMP-001 administered SC and IT in combination with atezolizumab with and without radiation therapy in patients with advanced NSCLC.

In Part A Stage 1 of the Study, 13 patients have received at least 1 dose of CMP-001 by SC injection at a dose of 5 mg in combination with atezolizumab 1200 mg Q3W.

As of 31 October 2018, 12 (92.3%) of 13 patient have experienced at least 1 TEAE, and 8 (61.5%) patients have experienced Grade 3 or higher TEAEs. The most commonly occurring TEAEs for all grades include fatigue (6 patients; 46.2%), fever (pyrexia) (5 patients; 38.5%), hypotension (5 patients; 38.5%), chills, decreased appetite, headache, and hyponatremia (4 patients; 30.8%, each event), and anemia, nausea, blood creatinine increased, platelet count decreased, back pain, and rash (3 patients, 23.1%, each event).

Grade 3 or higher TEAEs reported in 2 or more patients include pneumonia, decreased appetite, and hypotension (2 patients; 15.4%, each event).

Treatment-related TEAEs have been reported in 12 (92.3%) patients. The most commonly occurring treatment-related TEAEs for all grades include fever (pyrexia) (5 patients; 38.5%) and fatigue, headache, and hypotension (4 patients; 30.8%, each event). Grade 3 or higher treatment-related TEAEs have been reported in 4 (30.8%) patients.

Nine (69.2%) patients have experienced at least 1 SAE. Serious AEs reported in more than 1 patient include fever (pyrexia), pneumonia, and dyspnea (2 patients; 15.4%, each event). Most SAEs are considered not related to study treatment, but both SAEs of fever (pyrexia) (15.4%) are considered related to study treatment.

Safety Summary

Preliminary analysis of safety data appears to demonstrate an acute toxicity profile for all 3 studies that consists predominately of Grade 1 to Grade 2 AEs including fever (pyrexia), chills, nausea, vomiting, diarrhea, headache, rash, and hypotension resembling interferon-related toxicities as well as symptoms associated with cytokine release. The most common Grade 3 or higher TEAE is hypotension. These AEs typically present within 1 to 4 hours after the third CMP-001 dose and generally resolve within a few hours with standard supportive care and/or stress dose steroids.

Mild to moderate injection site reactions following IT injections, such as pain, itching, erythema, swelling, and induration have been reported. These injection site reactions were mostly grade 1 or 2 events.

Efficacy

Study CMP-001-001

Preliminary efficacy data across the Part 1 Dose Escalation and Part 1 Dose Expansion Phases show an objective response rate (ORR) in 18 of 113 melanoma patients of 15.9% and is comprised of 2 CRs and 16 PRs. The 95% CI is 9.7% to 24.0%. The ORR using the combination of RECIST/immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) is 19.5% (22 of 113 patients; 95% CI = 12.6% to 28.0%). An additional 4 patients are included as responders based on the irRECIST assessment due to achieving a PR after initial progression. There are 30 (26.3%) patients with a RECIST best response of SD, 50 (44.2%) patients with a RECIST best response of PD, and 11 (9.7%) patients who discontinued prior to having a follow-up scan.

Of the 18 patients with RECIST responses, 8 patients have responses of at least 48 weeks in duration, with 1 of these patients having an ongoing response at Week 108 and another patient with an ongoing response at Week 84. Three patients have a response duration of 24 weeks, 2 patients have a response duration of 12 weeks, and 1 elderly patient discontinued treatment after the Week 12 tumor assessment scan. As of the data cutoff date, 8 of the 18 patients with RECIST responses remain on treatment and 10 patients are off treatment.

Study CMP-001-002

Preliminary efficacy data across the Part 1 Dose Escalation Phase in the CMP-001-002 study show an ORR of 11.8% in 2 of 17 melanoma patients with a 95% CI of 1.5% to 36.5%. Overall, there are 5 (29.4%) patients with a RECIST best response of SD, 7 (41.2%) patients with a RECIST best response of PD, and 3 (17.6%) patients who discontinued prior to having a follow-up tumor assessment (1 patient discontinued due to an AE of tumor pain, 1 patient discontinued to enter hospice, and 1 patient discontinued because of Investigator decision).

Both patients with a RECIST best response of PR continue to have a response at the time of the data cutoff, with their latest tumor assessments confirming response performed at Week 24 for 1 patient and Week 36 for the other patient. As of the database cut-off, 1 patient is still pending their first follow-up tumor assessment.

Study CMP-001-003

There are no patients with a response across the preliminary efficacy data in Part A Stage 1. To date, 3 (23.1%) NSCLC patients have a RECIST best response of SD, 8 (61.5%) patients have a RECIST best response of PD, and 2 (15.4%) patients discontinued from the study before having a follow-up tumor assessment (1 patient died and 1 patient discontinued due to an unrelated SAE of pneumonitis.

Additional information for this compound may be found in the SRSD, which for this study is the IB.

1.2.5.4. Pharmacokinetics of CMP-001

The PK studies performed in mice and rats demonstrate that QbG10 blood concentrations peaked between 6 and 24 hours after SC dosing; declined in a monoexponential manner; and have a $t_{1/2}$ of 7 to 10 hours. Following SC injection, the QbG10 VLPs nanoparticles (30 nm in size) circulate rapidly through the lymphatic vessels into the draining lymph nodes, and subsequently into the systemic circulation.[68] Intratumoral injection of QbG10 is expected to behave with similar PK to the SC route because, although tumors generally have poorly developed lymphatic vessels, they also have compensating elevated oncotic pressures that lead to nanoparticle circulation into the draining lymph nodes.[69]

Based on PK results in the rat model, concentrations of CMP-001 are expected to be low and below the lower limit of quantification (LLOQ), therefore, conventional PK parameters of CMP-001 cannot be determined in humans.

To date, CMP-001 has not been studied in formal clinical drug-drug interaction studies. Pharmacokinetic interactions between CMP-001 and checkpoint inhibitors are not expected and have not been observed to date.

1.2.5.5. Immunogenicity of CMP-001

Anti-Qb antibodies reach levels above 100 µg/mL by the third CMP-001 dose. Based on evaluation of IgG levels from 24 patients in the Checkmate Dose Escalation Phase of

CMP-001-001 study who received IT CMP-001 doses of 1, 3, 5, 7.5 or 10 mg, there is no demonstrable relationship between CMP-001 dose and the level of anti-Qb antibodies. The mean level of IgG across tested patients at timepoints beyond 3 weeks of treatment was 575 μg/mL, and the median level was 442 μg/mL. The IgG antibody levels were significantly higher than the IgM. There has been no association observed between levels of anti-Qb antibody and either CMP-001 treatment efficacy or toxicity.

1.2.6. Study Rationale

1.2.6.1. Rationale for the Individual Combinations Under Evaluation

Immunomodulators are proposed for combination with avelumab based on clinical safety and anti-tumor activity for the individual agents and at least one the following considerations: (a) pre-clinical data suggesting increased efficacy of the combination without noticeable toxicity, (b) gene expression profiling data from human tumors suggesting coexpression of the respective target with PD-L1 and genes associated with effective immune responses to tumors, (c) proposed complementary mechanisms of action that might lead to increased anti-tumor activity.

1.2.6.1.1. Combination A (Avelumab plus Utomilumab)

As noted in Section 1.2.2.2 and Section 1.2.2.3, murine tumor experiments demonstrated significant immune-modulatory activity and anti-tumor activity of utomilumab and surrogate anti-mouse 4-1BB mAbs when dosed as a single agent in some tumor models. Combinations of agonist anti 4-1BB antibodies with antagonists of PD-1/PD-L1 have shown significantly improved anti-tumor activity compared with either single agent. These data are consistent with the hypothesis that addition of 4-1BB agonism to PD-L1 blockade results in a more robust anti-tumor immune response following PD-L1 blockade. The implication is that combining an agonist mAb (utomilumab) with an anti-PD-L1 mAb (avelumab) will increase the proportion of objective responses and increase the clinical benefit. Available non-clinical safety data indicates that the addition of an anti PD-1 antibody did not add to the toxicity of an anti-4-1BB agonist antibody.

1.2.6.1.2. Combination B (Avelumab plus PF-04518600)

Ribonucleic acid (RNA)-seq data generated by the cancer genome atlas (TCGA) research network (http://cancergenome.nih.gov/) across multiple tumor types was used to assess potential utility of the combination of avelumab and PF-04518600. Given that the RNA-seq data is generated from bulk tumors, spearman correlations of mRNA expression of target of interest (avelumab or OX40) to mRNA expression of markers of specific immune cell subsets was completed. This correlation was used as a guide for the determination of OX40 or PD1-IFNγ inflammatory immune gene signature expression levels within different immune cells.[48] For PD-1/PD-L1 mAbs such as avelumab, response to PD-1 blockade with pembrolizumab is associated with an interferon inflammatory immune gene signature, correlation of PD-1 expression to the expression of the IFN inflammatory immune gene signature (predictive of response and including the following 10 genes: HLA-DRA, CXCL9, GZMA, PRF1, CCR5, IFNγ, CXCL10, IDO1, STAT1, CXCL11) was completed. For OX40, since anti-OX40 agonists are expected to stimulate CD4 cells, correlation of

OX40 expression to CD4 expression was completed. Scatter plot of OX40-CD4 correlations and PD-1-IFNγ signature correlations across all the TCGA tumor types were computed. The correlation between PD-L1, OX40, and the IFN inflammatory immune gene signature suggests that OX40 agonism may be effective in the majority of patients with targetable PD-L1.

1.2.6.1.3. Combination C (Avelumab plus PD 0360324)

In multiple mouse tumor models, the combination of a blocking CSF-1R/M-CSFR antibody with an anti-PD-1 antibody significantly enhanced anti-tumor activity.[59] In a preclinical model of colon carcinoma, anti-M-CSF in combination with avelumab inhibited tumor growth and appeared to be most potent when combined with a 4-1BB agonist antibody (Figure 13). Myeloid cell reduction represents an active area of clinical investigation for the treatment of solid tumors, with multiple clinical studies under way with other agents that either block M-CSF or the M-CSFR.

1.2.6.1.4. Combination D (Avelumab plus Utomilumab plus PF-04518600)

In mouse tumor modeling experiments, addition of both surrogate 4-1BB and OX40 agonists to avelumab led to greater tumor inhibition than was achievable by the component doublet combinations (Figure 12). Importantly, the addition of a triplet combination of avelumab/utomilumab/PF-04518600 to vitro cytokine release assays with normal human blood cells indicated that the concentrations of cytokines (TNF-α, IL-6, IFN-γ) induced by the combination of all 3 antibodies were similar to or lower than avelumab alone in assays using whole blood or PBMCs (see Section 1.2.3.3). This assay is used to assess the potential for cytokine release syndrome and the results indicate that the potential for this type of AE is low.

Clinical safety and PK data from Combination A (utomilumab plus avelumab) and Combination B (avelumab plus PF-04518600) will be evaluated on an ongoing basis to confirm safety of each of the doublets. At least 6 patients will be evaluated for DLTs in Combination B at the 1 mg/kg PF-04518600 dose level before the first dose level for Combination D (D11), 0.1 mg/kg PF-04518600 plus 20 mg utomilumab plus 10 mg/kg avelumab) can be initiated.

In this study, as of 30 September 2016, the utomilumab plus avelumab doublet (Combination A) was found to be well tolerated at all utomilumab dose levels evaluated in Phase 1b with no DLTs and the PF-04518600 and avelumab doublet (Combination B) has also been well tolerated at the first dose level, B12 (0.3 mg/kg PF-04518600), with no DLTs. Based on monotherapy data, this is considered to be within a pharmacologically-active dose range. The initiation of the utomilumab plus PF-04518600 plus avelumab triplet (Combination D) is dependent upon an adequate safety profile at the next dose level (ie, no more than 1 DLT) of Combination B, B13 (1 mg/kg PF-04518600), in 6 patients (see Sections 1.2.2.4.1 and 1.2.3.4.1 for updated safety information for Combination A and Combination B, respectively).

1.2.6.1.5. Combination F (Avelumab plus CMP-001)

Intratumoral injection of TLR9 agonists have elicited strong cytotoxic T cell (CTL) responses in human clinical trials in patients with melanoma, but the CTL responses are transient and objective tumor responses are rare. T cells, induced following TLR9 agonist therapy in humans, express high levels of PD-1[70, 71, 72] suggesting that PD-1 may inhibit CTL activity mobilized by TLR9. Adding anti-PD-1 to TLR9 treatment increased tumor growth inhibition and survival in mouse tumor models, including bladder[73] and ovarian cancer models.[74] Combination of TLR9 agonist and anti-PD1 was associated with increased tumor-specific CD8+ T cells, activated CD4 T cells, and decreased regulatory T cells in the tumor area. As noted in Section 1.2.5.2, combination benefit was observed following co-administration of CMP-001 and anti-PD1 to mice bearing A20 lymphoma tumors. In vitro culture with anti-PD-1 antibodies significantly increased cytokine production by CD8+ T cells from melanoma patients treated with a TLR9 agonist, suggesting that potentially a similar additive benefit might be seen in humans.[70] As discussed in Section 1.2.5.3, this has been clinically validated based on preliminary efficacy data obtained in patients with PD-1 refractory melanoma treated with pembrolizumab (anti-PD-1) and CMP-001.

A different investigational synthetic TLR9 agonist, SD-101, has been investigated in SCCHN patients. SD-101 stimulates human pDCs to release IFNα and mature into efficient antigen-presenting cells, enhancing both innate and adaptive immune responses. The combination of IT SD-101 and pembrolizumab (anti-PD-1) was tested in an ongoing Phase 1b/2, study (NCT02521870, SYNERGY-001 DV3-MEL-01/Keynote-184) in 33 advanced/metastatic SCCHN patients. The treatment was well tolerated with no evidence of an increased incidence or severity of AEs over pembrolizumab monotherapy. No increase in immune-related AEs over pembrolizumab monotherapy was observed. Adverse events associated with SD-101 were transient, mainly mild to moderate injection-site reactions and flu-like symptoms that were manageable with over-the-counter medications. The combination therapy demonstrated promising efficacy in patients with SCCHN (Prior anti-PD-1/PD-L1 naïve), with an ORR of 27%. Responses were observed in both SD-101 injected and non-injected lesions and in both PD-L1 negative and positive tumors. The study provides preliminary evidence of safety and therapeutic activity of intratumoral TLR agonist and check point inhibitor combination in SCCHN treatment.[75]

Combination of avelumab plus CMP-001 and utomilumab or PF-04518600

T cell activation by antigen-presenting cells, anticipated to occur in tumor-draining lymph nodes, results in upregulation of 4-1BB[76] and OX40.[77] It is thought that in most cancer patients, 4-1BB and OX40 are not significantly induced in the absence of activation of these antigen presenting cells. Therefore, it is reasonable to predict that TLR9-activated pDCs will induce 4-1BB and/or OX40 in patients and thus increase expression of targets for utomilumab and PF-04518600, respectively. As noted in Section 1.2.5.2, this prediction is supported by tumor growth control and increased survival following combination of CMP-001, OX40 agonist, and PD-1 antagonist in the CT26 colon tumor model.[66] In this study, combining 4-1BB and OX40 agonists with PD-1 blockade and IT treatment with TLR9 agonists led to at least additive tumor growth inhibition in a mouse melanoma model, supporting the clinical evaluation of the hypothesis.[78] Whether 4-1BB and/or OX40 is

induced on T cells may depend on the specific tumor antigens presented to T cells by the pDCs. At this time, the specific tumor antigens recognized by T cells from patients with SCCHN are unknown, justifying separate study arms to evaluate these agonist mAbs in combination with CMP-001 and avelumab.

1.2.7. Rationale for the Tumor Types to be Evaluated

The tumor types were selected based one or more of the following in settings of unmet medical need: (a) an agent of the same class has shown clinical activity in the tumor type of interest, (b) clinical response to the study compounds, either as single agents or in combination with compounds having related mechanisms of action, (c) expression of the target(s) in the tumor by immunohistochemistry and/or gene expression profiling (eg, TCGA analysis), (d) correlation of target expression with expression of genes related to anti-tumor immunity, such as IFN-γ. For all tumor types, settings were chosen where the study treatments would not unreasonably delay any available survival-benefiting therapy. Other tumor types may be added based on emerging data.

1.2.7.1. Combination A (Avelumab plus Utomilumab)

The tumor types selected for this combination (NSCLC, melanoma, SCCHN, TNBC) have shown clinical response to single-agent avelumab and expression of the 4-1BB target in the tumor. Based on clinical data showing a CR in SCLC with the combination of utomilumab and pembrolizumab,[58] and the observation that a subset of these tumors may be immuno-responsive,[61,62] the combination of avelumab plus utomilumab may also be evaluated in patients with SCLC.

1.2.7.1.1. Rationale for Inclusion of First-Line Patients with Advanced Non-Small Cell Lung Cancer in Combination A

PD-1/PD-L1 blockade was first shown to result in an improved response rate, as well as longer survival in patients with advanced NSCLC in a second-line setting compared with docetaxel, which led the regulatory approval of two PD-1 blocking mAbs in this setting.[65,80,81]

More recently, interim results of a Phase 1b study of avelumab as a first-line treatment for patients with advanced NSCLC were presented (Study EMR 100070-0001).[83] In accord with the enrollment criteria for Combination A in the current B9991004 Javelin Medley study, patients with metastatic or recurrent NSCLC negative for epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocations who had not received prior treatment for metastatic or recurrent disease were eligible for treatment. Patients were required to have tumor material available for biopsy but were not pre-selected based on tumor PD-L1 expression, and received continued treatment with 10 mg/kg avelumab Q2W as a single agent until confirmed disease progression, unacceptable toxicity, or other withdrawal criteria were met. The primary objective was safety and tolerability of avelumab and secondary objectives included best overall response, progression-free survival (PFS), and overall survival (OS), as well as an evaluation of the association between PD-L1 expression in the tumor microenvironment and clinical activity.

As of 23 October 2015, among 75 of 145 (51.7%) patients who were treated with avelumab as a first-line therapy for advanced NSCLC who had at least a 13-week follow–up period for responses by RECIST, the objective response rate (ORR) was 18.7% (14/75), with 1 CR and 13 PRs, and the disease control rate (DCR) was 64% based on 14 responses and 34 patients with stable disease. Patients with PD-L1 expression in tumor cells with a threshold of ≥1% had an ORR of 20.0% (7/35) and patients with PD-L1 negative tumors did not respond (0/10). Median duration of response had not been reached at the time of the data analysis and 85.7% of responses (12/14), including 1 CR, were ongoing. The PFS rate at 6 months in all patients was 35.6% and the median PFS was 11.6 weeks. OS data were not yet mature. Safety-related data on all 145 patients with advanced NSCLC treated in this setting indicated that avelumab was well tolerated as a single agent, with 2.8% (4/145) of patients experiencing treatment associated immune-related AEs of Grades 1 or 2 at maximum intensity.

As stated in Section 1.2.2.3, animal modeling suggests that there will be a synergy in anti-tumor activity in combining avelumab (PD-L1 inhibition) with utomilumab (4-1BB agonism). Importantly, this increased activity was not associated with increased toxicity and is supported by preliminary data from Combination A Phase 1b of this study. As of 30 September 2016, no DLTs have been reported at any of the doses of utomilumab (20 mg, 100 mg, or 500 mg) every 4 weeks (Q4W) combined with avelumab 10 mg/kg Q2W in patients with advanced NSCLC who had received at least one prior therapy. As the study has continued to expand the number of advanced NSCLC patients treated in Phase 2 with this combination, the combination continues to be well tolerated, with a low frequency of Grade 3 events and no apparent increase in treatment-associated immune-related AEs CCI and no study drug-related deaths. In addition, preliminary data from the Combination A Phase 2 cohort have emerged which suggests that advanced NSCLC patients who were either previously untreated or had not received prior chemotherapy had rapid tumor responses (noted by the first on-treatment assessment), including in one case, a CR on brain lesions. These data are preliminary and patients remain under treatment, along with a continued assessment for tumor responses. In the context of these data, the potential risk/benefit supports the continued exploration of the combination of utomilumab with avelumab in previously untreated patients with advanced NSCLC (see Enrollment Criteria in Section 4.1) to obtain additional safety and clinical activity information.

1.2.7.1.2. Rationale for Evaluation of Sequenced Administration of Avelumab and Utomilumab (Cohorts A9 and A10)

Emerging preclinical evidence indicates that the order in which immune cells are exposed to activating stimuli can influence the potency of the immune response. For instance, exposure of dendritic cells to tumor antigen plus interleukin-2 (IL-2) followed by IFN-α elicits more effective anti-tumor immunity than simultaneous exposure to all three components.[90] Removal of tumor-infiltrating lymphocytes (TIL) from the tumor microenvironment and re-exposure to cognate antigen in vitro leads to upregulation of 4-1BB,[91] suggesting that release of TIL from microenvironmental inhibition can prepare them for activation by 4-1BB agonists such as utomilumab. On the other hand, 4-1BB signaling can protect chimeric

antigen receptor (CAR)-T cells from exhaustion induced by tonic receptor signaling,[92] which suggests that utomilumab may be best administered prior to re-initiation of TCR signaling by avelumab.

Limited early data from Cohorts A1, A2, and A3 of this study suggest that patients with previously untreated advanced NSCLC may benefit from the concurrent administration of utomilumab and avelumab. To potentially optimize the clinical benefit of this combination in this clinical setting, Cohorts A9 and A10 introduce the sequenced administration of avelumab and utomilumab into this study (see Combination A Schedule of Activities).

1.2.7.2. Combination B (Avelumab plus PF-04518600)

Tumor types selected for this combination may include advanced NSCLC, melanoma, and SCCHN, which have shown clinical response to single-agent avelumab and expression of the OX40 target in the tumor. One melanoma patient achieved a PR on PF-04518600 monotherapy treatment after anti-PD-1 and anti-CTLA-4 therapy had failed.[82] In Protocol Amendment 6, advanced/metastatic CRC has been removed as a tumor type for this combination for strategic reasons after critical review of emerging biomarker data from both internal and published reports, which suggest that OX40 agonists might not be effective as doublets with PD-1/PD-L1 pathway inhibitors for the treatment of patients with CRC.

1.2.7.3. Combination C (Avelumab plus PD 0360324)

Tumor types selected for this combination may include advanced ovarian cancer, SCCHN, and NSCLC, which have shown clinical response to single-agent avelumab as well as M-CSF and PD-1-IFNγ signature correlations and/or association of higher TAM density with negative prognosis. Gastric cancer may be added to the expansion phase if activity is observed during the dose escalation phase. Patients with Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS) are allowed during Phase 1b. These tumors often express CSF-1 and shown to be responsive to inhibition of signaling between CSF-1 and CSF-1R.[96,97]

1.2.7.4. Combination D (Avelumab plus Utomilumab plus PF-04518600)

Tumor types selected for this combination may include advanced NSCLC, melanoma, SCCHN, bladder cancer, which have shown response to single-agent avelumab and expression of the 4-1BB and OX40 targets in the tumor. Tumor types will be further prioritized based on the clinical activity observed for the respective doublets evaluated in this study in Combinations A and B. Other tumor types may be considered based on emerging data from the study across all combinations, as applicable.

1.2.7.5. Combination F1 (Avelumab plus CMP-001); F2 (Avelumab plus CMP-001 and utomilumab); F3 (Avelumab plus CMP-001 and PF-04518600)

SCCHN has been selected for these combinations for the following reasons. Firstly, as noted in previous sections, SCCHN is expected to respond to avelumab. Secondly, TLR9-responsive pDCs have been observed in SCCHN[98] and a combination of TLR9 agonist and checkpoint inhibitor has demonstrated safety and preliminary signs of clinical activity in

SCCHN patients.[75] The anatomic location upon local recurrence as well as sites of metastases are frequently feasible for intratumoral injections. In addition, patients with SCCHN tumors that progress on or after PD1/PD-L1 therapy represent a high unmet medical need population, with very limited treatment options and otherwise poor outcomes.

1.2.8. Rationale for Investigational Product Doses

1.2.8.1. Avelumab

In this clinical trial, the avelumab dose will be 10 mg/kg administered as 1-hour IV infusions Q2W. CCI

1.2.8.2. Utomilumab

Clinically active single-agent utomilumab doses ranged from 0.24 mg/kg to 0.6 mg/kg administered every 4 weeks (Q4W) in patients with MCC and melanoma. The clinical activity of higher doses is being studied in patients with melanoma. Responses were also observed with the combination of utomilumab and rituximab (R) in R-refractory NHL as low as 0.03 mg/kg with highest active dose of 5.0 mg/kg. These data suggest that the active dose range of utomilumab is quite broad, spanning an approximate 100-fold dose range. Therefore, in Combination A of this clinical trial, 3 utomilumab doses will be evaluated: 20 mg (approximately 0.2 mg/kg), 100 mg (approximately 1.2 mg/kg), and 500 mg (approximately 6 mg/kg), in combination with avelumab. In Combination D of this study, in which utomilumab plus PF-04518600 will be evaluated in combination with avelumab, 2 lower doses of utomilumab (20 mg and 50 mg) will be tested.

Preliminary population PK analysis showed that body weight accounts for only a small percentage (~7%) of the variability in drug exposure. Simulations indicated that utomilumab exposure profiles are similar in both body weight and fixed utomilumab dosing regimens. Therefore, it is suggested a fixed dosing regimen be utilized for ease of use and to minimize potential medication errors.

1.2.8.2.1. Utomilumab Dose for Combination F

Utomilumab as single agent has been well tolerated up to a dose of 10 mg/kg (the highest planned dose level), and no DLTs were observed in Study B1641001. Previous data suggest that the active dose range of utomilumab is quite broad, spanning an approximate 100-fold dose range. In the current study, utomilumab doses of 20 mg (approximately 0.2 mg/kg), 100 mg (approximately 1.2 mg/kg), and 500 mg (approximately 6 mg/kg) Q4W were tested in combination with 10 mg/kg Q2W of avelumab. No differential effects were observed between doses, as dose-response relationship was not observed for safety or efficacy endpoints. Based on this information, the middle tested dose level (100 mg Q4W) was chosen for further evaluation.

1.2.8.3. PF-04518600

Doses of PF-04518600 proposed for the Phase 1b dose escalation cohorts include 0.3, 1.0, and 3.0 mg/kg Q2W, with 0.1 mg/kg as the starting dose for Combination D. This lower dose is two dose levels below the Combination B dose level of 1.0 mg/kg that will be evaluated for DLTs before initiating Combination D. Safety information observed for PF-04518600 monotherapy includes completed safety evaluation of 5 dose levels (0.01, 0.1, 0.3, 1.5, and 3.0 mg/kg, see Section 1.2.3.4). To date, all treatment-related AEs have been mild or moderate (Grade 1 and 2) in severity. One treatment-related SAE, Grade 2 congestive heart failure occurring in a patient with pre-existing risk factors to atherosclerosis and cardiac disease and prior cardiotoxic cytotoxic therapy (doxorubicine) 55 days following first PF-04518600 treatment, has been reported. In addition, peripheral blood receptor occupancy has indicated full receptor occupancy in peripheral blood at the 0.3 mg/kg dose. For Combination B, the starting dose is 0.3 mg/kg PF-04518600 with the option to de-escalate to a dose of 0.1 mg/kg in the event of unacceptable toxicity at the 0.3 mg/kg dose.

1.2.8.3.1. PF-04518600 Dose for Combination F

In a monotherapy setting, the activity of PF-04518600 was observed at the 0.3 mg/kg dose level and full receptor occupancy was achieved for all patients at doses ≥0.3 mg/kg. In the current study, PF-04518600 at 0.3 mg/kg, 1 mg/kg, and 3 mg/kg given Q2W was tested in combination with 10 mg/kg Q2W avelumab. No DLTs were observed and no dose-response relationship was observed for safety or efficacy endpoints. Based on the collective monotherapy and combination data, the lowest dose level (0.3 mg/kg Q2W) was chosen for further evaluation.

1.2.8.4. PD 0360324

Doses of PD 0360324 to be used for the Phase 1b dose escalation part of Combination C of this study are 50 mg, 100 mg, and 150 mg Q2W. Although clinical efficacy has not been demonstrated, PD 0360324 appears to be well tolerated. Across the 4 clinical studies of PD 0360324 in autoimmune indications (Section 1.2.4.3), no DLTs were observed for patients treated up to 150 mg Q2W. PD 0360324 appeared to maximally inhibit circulating CD14+ CD16+ monocytes at doses ≥30 mg, and dose/exposure-dependent periorbital edema was observed in previous clinical studies with Q2W dosing up to 150 mg. Therefore, based on a wide safety margin of 2 dose levels and the anticipated pharmacodynamic activity range, a 50 mg dose administered Q2W has been selected as the starting dose of PD 0360324 in combination with avelumab.

1.2.8.5. CMP-001

1.2.8.5.1. Rationale for CMP-001 Dose Selected

The 1, 3, 5, 7.5 and 10 mg CMP-001 IT doses at two different concentrations (1 mg/mL and 6 mg/mL) in combination with the standard dose of IV pembrolizumab have been evaluated in the Dose Escalation Phase of the Checkmate CMP-001-001 study. Durable responses have been seen at the 3 mg, 5 mg, 7.5 mg, and 10 mg dose levels. Analysis of pharmacodynamic, toxicity and clinical response does not indicate a dose-response

relationship. Therefore, the highest dose tested of 10 mg has been chosen for further evaluation for Combination F.

1.2.8.5.2. Rationale for CMP-001 Route of Administration

Tumors recruit immature, inactivated pDC. The highest concentrations of pDC are believed to reside within tumors. Therefore, the administration of one or more doses of CMP-001 directly into the tumor, is believed to deliver a local concentration of drug that is effective in activating the highest numbers of tumor-antigen-bearing pDC. The rationale, for using a hybrid route of administration that begins with SC dosing and switching to IT dosing, is to provide a dosing regimen whereby the initial SC doses of CMP-001 induce the production of anti-Qb antibodies (the Qb component of the VLP capsid protein), and upon IT dosing, the induced anti-Qb antibodies will opsonize the VLP and direct its uptake into the pDC endosomal compartment through a specific FcγR, FcγRII. In the absence of the anti-Qb antibodies, the VLP is not efficiently taken up by the pDC, nor does it effectively activate the pDC. Following endosomal uptake, the G10 (the CpG component of CMP-001) activates TLR9, stimulating the pDC to switch from the immature state to a mature, fully activated state. Activated pDC then traffic to tumor-draining lymph nodes where presentation of tumor antigens to T cells occurs, thus inducing the anti-tumor T cell response. The hybrid route of administration that begins with SC dosing followed by IT dosing is currently the recommended dosing regimen for CMP-001 and PDx combination studies. The SC dosing, if administered peritumorally, may also induce pDC activation, although this is expected to be less efficient compared with IT administration and limited data are available to support this route of administration.

Both the SC and IT routes of administration (ROA) have been evaluated in ongoing studies with CMP-001. Both ROAs have demonstrated an acceptable safety profile and durable clinical responses. This protocol allows the investigator to switch to a SC route after initial IT injections. It is acknowledged that this may create a degree of dosing variability. However, continued IT injections may not be feasible for patients that either have limited accessible tumors, or who are not tolerating the IT injections. The recommended schedule and ROA of IT and SC route for CMP-001 ensures that the sufficient level of TLR9 activation will occur in these patients enabling the chance for clinical activity.

1.3. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

The benefit-risk relationship has been carefully considered in the planning of the trial. Avelumab demonstrated clinical activity in patients with advanced solid tumors in an expansion cohort of an ongoing Phase 1 study. The clinical safety data available to date, with single-agent avelumab in patients with advanced solid tumors, suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and immune-related adverse events (irAEs)/autoimmune disorders have been identified as

important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a H1 blocker and acetaminophen.

The 4-1BB mAb, utomilumab, has also demonstrated clinical activity as monotherapy in patients with advanced solid tumors and in combination with rituximab in patients with NHL in an ongoing Phase 1 study. The clinical safety profile of utomilumab supports its use as both a single agent and in combination with rituximab. Treatment-related AEs were generally mild or moderate with only two Grade 3 AEs (hyponatremia and fatigue) related to utolimumab monotherapy. No AEs Grade ≥3 AEs related to utolimumab have been reported among patients receiving utomilumab in combination with rituximab.

The OX40 mAb, PF-04518600, is being evaluated as a single agent or in combination with utolimumab in an ongoing Phase 1 dose escalation study in patients with advanced or metastatic cancer (Study B0601002).[60] As of 27 October 2016, DLTs were not observed in patients treated up to 3.0 mg/kg. The safety profile of PF-04518600 supports its use as a single agent, and a dose escalation approach is being taken in this study in combination with avelumab. Combination B and Combination D will start with 0.3 mg/kg and 0.1 mg/kg PF-04518600, 2 and 3 dose levels below the highest safe single agent dose level tested thus far, respectively, in the ongoing Study B0601002. In order to mitigate safety risks with the triplet Combination D, at least 6 patients will be evaluated for DLTs in Combination B at the 1 mg/kg PF-04518600 and 10 mg/kg avelumab dose level before Combination D Cohort D11 (0.1 mg/kg PF-04518600 plus 20 mg utomilumab plus 10 mg/kg avelumab) can be initiated.

As of June 2017, multiple doses of single-agent PD 0360324 have been administered to a total of 68 patients with autoimmune diseases at doses ranging from 20 to 150 mg. The observed safety events in these studies appear to be acceptable in developing PD 0360324 for an oncology indication. There have been no deaths or SAEs with PD 0360324. For Combination C, the starting dose of PD 0360324 is 50 mg (2 dose levels under the MTD of 150 mg), with possible escalation to 100 and 150 mg.

CMP-001 administered IT to patients with melanoma, either as a single agent or in combination with pembrolizumab (anti-PD-1), has shown a clinically manageable safety profile in a study of escalating CMP-001 IT doses up to 10 mg (see Section 1.2.5.3). According to the information in the CMP-001 IB, AEs typically present on or after the third CMP-001 dose and generally resolve within a few hours with standard supportive care. Clinical activity was observed for the combination of CMP-001 and pembrolizumab in patients with melanoma in Study CMP-001-001. In addition, a combination of another IT administered TLR9 agonist, SD-101, and another PD-L1/PD-1 checkpoint inhibitor, pembrolizumab, showed a favorable safety and clinical activity profile in SCCHN patients.[75]

As detailed in Sections 1.2.2.4 and 1.2.3.4, the doublets of avelumab plus utomilumab and avelumab plus PF-04518600, have shown a favorable safety profile, clinical activity, and signs of pharmacodynamic activity.

Combination F will test combinations of avelumab plus CMP-001, avelumab plus CMP-001 and utomilumab, and avelumab plus CMP-001 and PF-04518600, with concurrent enrollment using 1:1:1 randomization. In these combinations, CMP-001 will first be administered SC in two weekly doses, followed by IT administration of CMP-001. The decision of concurrent enrollment is based in part on the data generated in this study for the doublets of avelumab plus utomilumab and avelumab plus PF-04518600, which did not show evidence of any additional safety risk as compared to single agent use of these study drugs. In addition, concurrent enrollment can also be justified by the previous finding in the clinic that AEs associated with CMP-001 were clinically manageable and were not likely to be associated with the first dose. Therefore, the above triplet combinations are not expected to confer significant additional toxicity as compared to avelumab as single agent or avelumab in combination with CMP-001. The proposed 4-week DLT observation period is based on the observed acute safety profile of CMP-001, when administered intratumorally, and the observation in this study that DLTs were not observed for the avelumab plus utomilumab and avelumab plus PF-04518600 doublets.

Based on the nonclinical and Phase 1 data available to date for avelumab, utomilumab, PF-04518600, PD 0360324, and CMP-001, the conduct of the trial is considered justifiable using the dose and frequency of administration of avelumab and the dose, frequency and mode of administration of these other immune modulators as specified in this clinical trial protocol. As the clinical safety profiles for PF-04518600, and PD 0360324 are less well understood compared with utomilumab and CMP-001, a dose-escalation approach has been planned during Phase 1b evaluation for Combinations B, C, and D.

Combination D will be initiated only after the respective doublets in Combinations A and B are observed to provide a safety margin of at least 2 dose levels (no more than 1 DLT out of 6 patients at the respective 500 mg utomilumab [A1] or 1 mg/kg PF-04518600 [B13] Phase 1b dose levels) above the starting doses in Combination D. Of note, no DLTs have been observed in the Phase 1b cohorts for Combination A, meeting the criterion for that combination, and no DLTs have been observed at the 0.3 mg/kg (B12) and 1 mg/kg (B13) PF-04518600 dose levels of Combination B. Six (6) patients will be enrolled at 1 mg/kg PF-04518600 during Phase 1b of Combination B and evaluated for safety prior to initiating Combination D.

Any combination in this study shall be discontinued in the event of any new findings that indicate a significant deterioration of the risk-benefit relationship that would render continuation of the combination unjustifiable.

While clinically significant irAEs have not been observed with utomilumab, PF-04518600, or PD 0360324, risk mitigation measures have been implemented in ongoing clinical studies for each of these investigational products, which are also included in this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of treatment-related irAEs. Avelumab has been approved in the US for the treatment of metastatic Merkel cell carcinoma. In addition, avelumab has demonstrated anti-tumor activity in various tumor types (eg, NSCLC, urothelial cancers, mesothelioma, ovarian cancer, and gastric cancer). It is expected that various

mechanistically complementary immunotherapy combination partners will enhance the efficacy of avelumab.

Thus, the projected benefit/risk of avelumab given in combination with utomilumab (Combination A), PF-04518600 (Combination B), PD 0360324 (Combination C), utomilumab plus PF-04518600 (Combination D), and CMP-001 (Combination F) is anticipated to be favorable for investigation in this population of patients with advanced solid tumors.

1.4. Biomarker Rationale

This study intends to characterize the ability of various immunomodulators to increase the clinical benefit seen with single-agent avelumab. As the immunomodulators may vary with respect to targets engaged, target modulation needed for optimal activity, potential for the combination of avelumab and a given immunomodulator to generate unexpected pharmacological outcomes, and amount of prior clinical experience with each immunomodulator, some customization of the biomarker strategy will be needed for each combination tested. The following represents an overview of the planned strategy, followed by comments specific to each combination.

The success of the combinations will be contingent on selection of active doses for each agent, and these doses may be different in the setting of the combination relative to each single agent. For this reason, a given combination may incorporate measurements of target engagement on immune cells in peripheral blood, levels of circulating soluble target, and other biomarkers in blood and tumor. Such assessments may be discontinued if the sponsor considers sufficient data has been obtained to recommend a given dose for further development.

The success of the combinations will also be contingent on identifying the specific tumor types most likely to respond to the combination, which in turn will be shaped at the start of therapy by the number, type, and activation state of the tumor infiltrating lymphocytes, the level of target expression by the appropriate cell types, and the presence of immune inhibitory mechanisms that are may continue to suppress the effect of the combination. The collection of pre-treatment biopsies, archival and/or *de novo*, is mandatory in order to enable such assessments. These parameters will be assessed by multiple methods that may include but not be limited to assessment of target expression by tumor and/or immune cell types in the tumor using immunohistochemistry, relative expression of genes representative of immune activation versus suppression by gene expression profiling, and the number and diversity of TCR sequences by DNA sequencing.

Evaluation of target modulation in the tumor may be needed to confirm synergistic PD effects of the combinations tested. In the event that clinical benefit is not observed or is transient, assessment of reasons for lack of benefit may help guide patient selection for future development of the combinations. For these reasons, biopsies on treatment and at end of treatment in the event of discontinuation due to disease progression are requested from patients with specified tumor types unless clinically contraindicated. Collection of these

biopsies may be discontinued if the sponsor considers sufficient data has been obtained to confirm the PD behavior of the combination or possible causes for lack of clinical benefit.

1.4.1. Specific Features of Combination A: Avelumab plus Utomilumab

As summarized in Section 1.2.2.4, prior clinical experience with utomilumab has indicated that clinical activity may be observed across a broad dose range without notable safety or tolerability concerns at any dose level. The biomarker strategy for this combination is therefore to confirm PD activity at 3 doses of PF-050592566 considered active based on this experience, and test hypotheses regarding which patients are most likely to benefit.

1.4.2. Specific Features of Combination B: Avelumab plus PF-04518600

The aim of biomarker collections and analyses for Combination B is to provide evidence of differentiated, PD and immune-modulatory activity for the combination of avelumab and PF-04518600. In the peripheral blood, PD measures that will be used to test for enhancement of PD activites observed in single agent studies include the expression of proliferation and activation markers (Ki67 and HLA-DR/CD38, respectively) on T cell subsets in peripheral blood and the quantity and phenotype of TIL infiltration by immunohistochemistry (IHC). These and other biomarker assessments will contribute to the broad objectives of characterizing the degree and nature of enhanced PD activity, its relationship to tumor responses to better understand the most relevant mechanisms and the identification of patient immunophenotypes more likely to benefit from this combination therapy.

1.4.3. Specific Features of Combination C: Avelumab plus PD 0340324

An objective of the biomarker plan unique to Combination C is the measurement of PD effects on the numbers and distribution of tumor associated macrophages in tumor tissue. Targets selected for analysis by flow cytometry, immunoassay, and IHC may include those associated with both T cells and mononocytes/macrophages. Examples of these may include, but not be limited to, soluble M-CSF by immunoassay and CD68+ macrophages by IHC. Furthermore, the effect of PD 0340324 on the macrophage content of tumor-associated ascites fluid will be measured in tumor types such as ovarian cancer, when samples are available.

1.4.4. Specific Features of Combination D: Avelumab plus Utomilumab plus PF-04518600

The biomarker collections in Combination D will be used to characterize combinatorial agonistic activity of utomilumab and PF-04518600 in the presence of checkpoint blockade mediated by avelumab. To this end, assessment of T cell proliferation markers such as Ki-67 and T cell activation such as HLA-DR may be assessed via peripheral blood flow cytometry. Other biomarkers of particular importance will be the quantity and phenotype of tumor-infiltrating lymphocyte (TIL) infiltration by IHC and potential effects on T cell diversity by TCR sequencing. Plasma samples will be collected and may be used to confirm or further characterize clinical events of interest, such as cytokine release syndrome (CRS).

1.4.5. Specific Features of Combination F: Avelumab plus CMP-001 and Utomilumab or PF-04518600)

Intratumoral injection of CMP-001 coupled with avelumab is expected to increase (a) the expression of genes and proteins supportive of adaptive immunity in the tumor, and (b) tumor neoantigen presentation to and activation of T cells. Monitoring changes in gene expression profile in tumor and clonal expansion of circulating TCRs will be of particular importance for this combination.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

- Phase 1b lead-in: To assess safety and tolerability of a single dose level of avelumab in combination with increasing dose levels of other immune modulators in patients with locally advanced or metastatic solid tumors in order to select the RP2D(s)/schedule for the combination.

- Phase 2: To assess objective response (OR) of avelumab in combination with other immune modulators in patients with locally advanced or metastatic solid tumors.

Secondary Objectives

- To assess the overall safety and tolerability of avelumab and other immune modulators when given in combination;

- To characterize the PK of avelumab and other immune modulators when given in combination;

- To evaluate the immunogenicity of avelumab and other immune modulators when given in combination;

- To assess the antitumor activity of avelumab and other immune modulators when given in combination in patients with locally advanced or metastatic solid tumors;

- To assess the correlation of antitumor activity of avelumab and other immune modulators with immune biomarkers in baseline tumor tissue.

Exploratory Objectives

- CCI [redacted]

- CCI [redacted]

2.2. Endpoints

Primary Endpoints

- Phase 1b lead-in:
  - First 2 Cycles DLT(s) for Combination A, B, C and D;
  - First Cycle DLT(s) for Combination F only.
- Phase 2: Confirmed OR, as assessed by the Investigator using RECIST v1.1.

Secondary Endpoints

- AEs as characterized by type, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03), timing, seriousness, and relationship to study treatments;
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;
- PK parameters (C_{max} and C_{trough});
- ADA levels;
- Time-to-event endpoints including Time to Tumor Response (TTR), duration of response (DR), progression-free survival (PFS) as assessed by the investigator using RECIST v1.1, and overall survival (OS);
- Confirmed OR during Phase 1b, as assessed by the investigator using RECIST v1.1;
- Biomarkers such as PD-L1 expression and tumor infiltrating CD8+ lymphocytes in baseline tumor tissue.

Exploratory Endpoints

- CCI [redacted]
- CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b/2, open-label, multi-center, multiple-dose, safety, clinical activity, PK, and PD study of avelumab in combination with other immune modulators in adult patients with locally advanced or metastatic solid tumors (eg, NSCLC, melanoma, SCCHN, TNBC, gastric cancer, ovarian cancer, bladder cancer, or SCLC). In Phase 1b and Phase 2, enrollment criteria vary by tumor type and are described in detail in Section 4.1. Incorporation of the other immune modulators into this study is based on preclinical and clinical data supportive of single-agent tolerability and potential clinical benefit, as well as non-clinical data suggesting safety, tolerability, and clinical benefit of agent(s) in combination with avelumab. Combinations of avelumab plus other immune modulator(s) to be evaluated are as follows:

- Combination A: Avelumab plus utomilumab (4-1BB agonist mAb);
- Combination B: Avelumab plus PF-04518600 (OX40 agonist mAb);
- Combination C: Avelumab plus PD 0360324 (M-CSF mAb);
- Combination D: Avelumab plus utomilumab plus PF-04518600.
- Combination F: avelumab plus CMP-001 (TLR9 agonist) and utomilumab or PF-04518600:
    - Cohort F1: avelumab plus CMP-001;
    - Cohort F2: avelumab plus CMP-001 and utomilumab;
    - Cohort F3: avelumab plus CMP-001 and PF-04518600.

For Phase 1b dose escalation and Phase 2 expansion cohorts, patients may be enrolled into different combinations in parallel. In non-randomized cohorts, slot assignments will be managed by the study team and sites will be notified in advance of cohort initiations. Patients are not allowed to crossover between the different combinations evaluated in this study.

Each combination will be studied individually in 2 study parts: 1) a Phase 1b lead-in part to evaluate safety, and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and RP2D (if applicable), of the combination, and 2) a Phase 2 part to evaluate efficacy and further evaluate safety of the selected dose from the Phase 1b portion in prespecified patient populations. Enrollment of patients in different combinations may be staged in order of combination alphabetical order and by tumor type. Therefore, for Phase 1b dose escalation cohorts and Phase 2 expansion cohorts, staging of patient recruitment will be communicated to clinical sites in advance of the opening of new cohorts. Study design details for each combination are provided Section 3.2.

Additional combinations of avelumab with other immune modulators may be added to this protocol based on emerging preclinical and clinical data.

For all combinations, treatment with investigational products will continue until disease progression is confirmed by the Investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. See Section 5.3.5.3 for details of treatment after initial determination of radiological disease progression.

Patients who stop avelumab or the other immune modulator(s) may continue on treatment with the investigational product(s) that is/are not considered to be responsible for any severe AE in consultation with the Sponsor's Medical Monitor.

It is recommended that patients who have experienced a confirmed complete response (CR) should continue to be treated with investigational products at the discretion of the Investigator after discussion with the Sponsor.

Patients who stop treatment and experience radiologic disease progression shortly thereafter will be eligible for re-treatment with either avelumab and/or the other immune modulator(s) at the discretion of the Investigator and after discussion with the Sponsor.

3.1.1. Tumor Assessments

Anti-tumor activity will be assessed by radiological tumor assessments at 8-week intervals, using RECIST version 1.1. In case partial response (PR), CR, or PD is observed according to RECIST v.1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. After 1 year from randomization in the study (randomized cohorts) or the first dose (non-randomized cohorts), tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the End of Treatment/Withdrawal (if not done in the previous 4 weeks and prior response is other than confirmed PD). Details of the treatment after initial evidence of radiological disease progression are provided in Section 5.3.5.3.

Further specific guidance on tumor imaging is provided in Section 7.6.

3.1.2. Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as reported in the Schedule of Activities and described in Section 7.1.

The results of safety assessments on dosing days that potentially require dose modifications must be reviewed prior to dosing as specified in Section 7.1.4.

3.1.3. Pharmacokinetic/Immunogenicity Assessments

PK/immunogenicity blood sampling will be collected as described in the Schedule of Activities for each combination and described in Section 7.2.

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

3.1.4. Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and other immune modulator(s). In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the combination of avelumab plus other immune modulator(s), as well as potential mechanisms of resistance. Biomarkers that correlate with pharmacodynamics effects may be considered when prioritizing dose levels for further exploration. Biomarker assessments are described in Section 7.4.

3.1.5. Modified Toxicity Probability Interval Dose Escalation Design (Combinations B, C, and D)

In Phase 1b for Combinations B, C, and D, the escalation/de-escalation rules for the immune modulator(s) tested in combination with avelumab will follow the modified toxicity probability interval (mTPI) method (overview provided here and described in greater detail in (Section 9.2.2). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level (DL) to determine whether future cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. The detailed dose finding rules based on the mTPI are illustrated in Table 13.

Table 13. Detailed Dose Escalation/De Escalation Scheme

Number of dose limiting toxicities (DLTs)	Number of patients treated at current dose									
	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	E	E	E	E	E
2	D	D	S	S	S	S	S	S	S	S
3	DU	DU	DU	D	S	S	S	S	S	S
4		DU	DU	DU	DU	DU	D	S	S	S
5			DU	DU	DU	DU	DU	DU	D	S
6				DU	DU	DU	DU	DU	DU	DU
7					DU	DU	DU	DU	DU	DU
8						DU	DU	DU	DU	DU
9							DU	DU	DU	DU
10								DU	DU	DU
11									DU	DU
12										DU

E = Escalate to the next higher dose

S = Stay at the current dose.

D = De-escalate to the next lower dose level.

U = The current dose is unacceptably toxic.

Targeted DLT rate at MTD =25%.

As an example, if the total number of patients treated at DL0 is 3, then the following dosing rules are to be applied:

- 0 DLT → escalate to DL1;
- 1 DLT → remain at the same DL (DL0);
- 2 DLTs → de-escalate to DL-1 and allow for possible re-escalation back to DL0;
- 3 DLTs → de-escalate to DL-1 as DL0 is intolerable.

Rules for dose finding using the mTPI method include the following:

- The target enrollment cohort size is 3-6 patients.
- The next cohort will be enrolled, if necessary, when at least 3 patients evaluable for DLT at the current dose cohort have been evaluated (each patient completes the initial 2 cycles [ie, the 8-week DLT observation period] or experiences a DLT, whichever comes first). The next cohort will receive the DL as assigned by mTPI approach even if a dose modification is required at the current dose level.

- If a patient does not receive the protocol-specified administrations of avelumab and the other immune modulator(s) (at least 75% of planned doses) within the DLT observation period (2 cycles = 8 weeks) for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.

Phase 2 can be initiated if not more than 3 in 10 (Combination C) or 12 (Combinations B, and D) DLT-evaluable patients have experienced a DLT at the recommended Phase 2 dose level (see Section 9.2.2).

For Combinations B, C, and D once the MTD or MAD is identified in Phase 1b, Phase 2 will begin with enrollment into tumor type specific cohorts.

3.2. Study Designs for Each Combination

For the purpose of this study, a cycle is defined as the time from the Day 1 dose to the next Day 1 dose of avelumab. The planned treatment cycle duration is 4 weeks (28 days).

Each combination will be administered in cycles according to avelumab dosing. The DLT observation period for evaluation of each dose level during Phase 1b (Combination A, B, C, and D) is the first 2 cycles (8 weeks) of treatment. The DLT observation period during Phase 1b of Combination F is the first treatment cycle (4 weeks).

3.2.1. Combination A (Avelumab plus Utomilumab)

Combination A includes a Phase 1b lead-in part and a Phase 2 part. During Phase 1b, up to 18 NSCLC patients will be randomized 1:1:1 to 1 of 3 cohorts (6 patients each) to receive utomilumab at 500 mg (Cohort A1), 100 mg (Cohort A2), or 20 mg (Cohort A3) administered intravenously (IV) every 4 weeks (Q4W) in combination with 10 mg/kg of avelumab administered IV every 2 weeks (Q2W) for 2 cycles (ie, 8 weeks). If a DLT is observed in at least 2 of 6 DLT-evaluable patients treated within a cohort, further evaluation of the cohort will be stopped (DLT definitions are provided in Section 3.3). Patients treated in Phase 1b who are not considered DLT evaluable (as defined in Section 9.1) will be replaced for the assessment of the DLT rate in the cohort to which they were randomized. The study treatments to be evaluated in patients with NSCLC during Phase 1b are presented in Table 14.

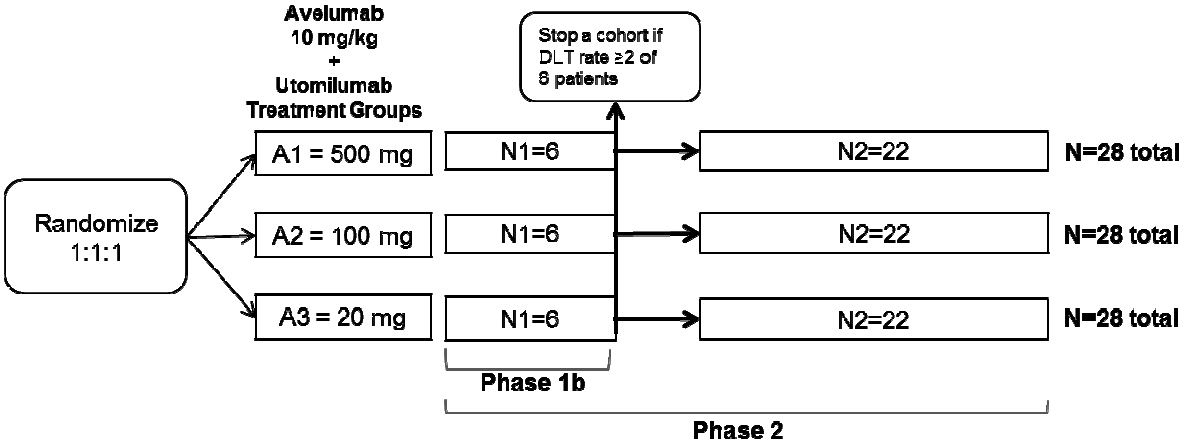
Table 14. Combination A (Avelumab Plus Utomilumab) Phase 1b Study Treatments – NSCLC Only

Treatment Group[a]	Utomilumab Dose	Avelumab Dose
A1	500 mg IV Q4W	10 mg/kg IV Q2W
A2	100 mg IV Q4W	10 mg/kg IV Q2W
A3	20 mg IV Q4W	10 mg/kg IV Q2W

a. Parallel evaluation of utomilumab treatment groups in combination with avelumab.

For each PF-05082566 dose level that is tolerated (ie, not meeting the DLT criteria) in the Phase 1b lead-in, the corresponding dose level cohort(s) will continue enrollment for Phase 2 with up to 22 additional patients each. Therefore, all 3 cohorts could potentially enroll additional patients.

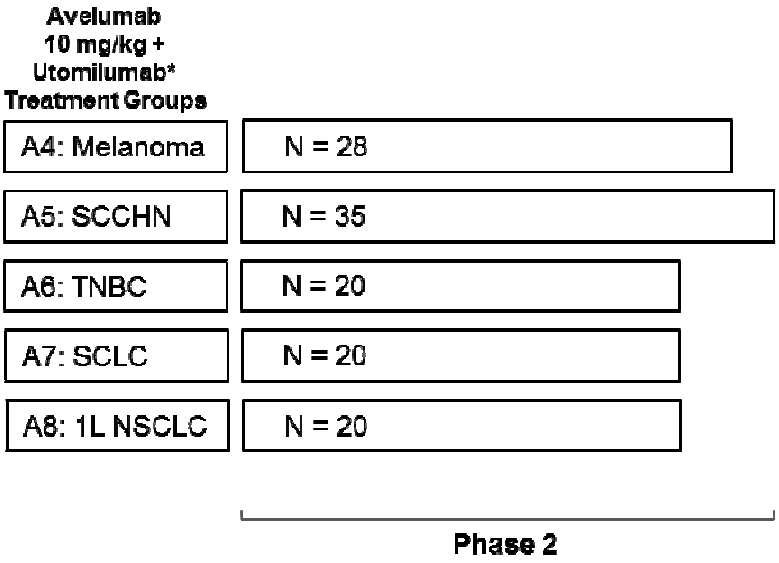
Figure 15. Combination A Phase 1b and Phase 2 Study Design Schema - NSCLC Only (Cohorts A1, A2, A3)



In addition to potential expansion of enrollment of patients with NSCLC to Cohorts A1, A2, or A3, Phase 2 will also enroll patients with melanoma (Cohort A4; N=28), SCCHN (Cohort A5; N=35), TNBC (Cohort A6; N=20), SCLC (Cohort A7; N=20), and first-line advanced NSCLC (Cohort A8; N=20, up to 26 patients will be enrolled to achieve a minimum of 20 PD-L1-positive patients (Figure 16). Enrollment into Cohorts A7 and A8 may be staged based on activity observed during the Phase 1b portion of the combination (ie, new cohorts may be opened based on activity data emerging from the randomized dose level cohorts of Combination A).

For Cohorts A4 through A8, the projected utomilumab dose to be used in each of these cohorts is 100 mg which may be modified based upon emerging safety data for utomilumab from randomized dose cohorts of Combination A. In the event that the utomilumab dose is modified after the initiation of Cohorts A4 through A8, additional patients will be enrolled to achieve the target number of patients treated at the modified dose.

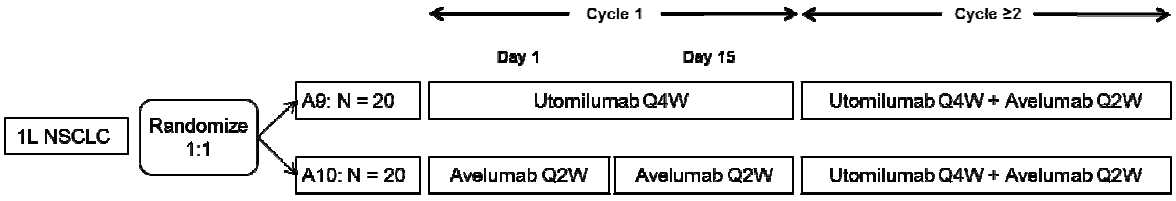
Figure 16. Combination A Phase 2 Study Design Schema - Melanoma (Cohort A4), SCCHN (Cohort A5), TNBC (Cohort A6), SCLC (Cohort A7), and First-Line NSCLC (Cohort A8)



* Utomilumab dose = 100 mg (may be modified based on emerging data)

Sequenced (single agent administration for 1 cycle followed by combination therapy) administration of single agent avelumab or utomilumab for 1 cycle followed by administration of combination (avelumab plus utomilumab) will be evaluated in 2 additional cohorts. Both cohorts will enroll 20 patients each with PD-L1 positive, 1L advanced NSCLC. Cohort A9 will evaluate utomilumab single-agent administration, one month prior to initiation of combination treatment on Cycle 2 Day 1 (28 days after start of the single-agent treatment). Cohort A10 will evaluate avelumab single-agent administration, one month prior to initiation of combination treatment on Cycle 2 Day 1 (28 days after start of the single-agent treatment). Patients will be randomized 1:1 to Cohorts A9 and A10.

Figure 17. Combination A Phase 2 Study Design Schema – Sequenced Administration in Patients with First-Line NSCLC (Cohort A9 and Cohort A10)



In Phase 2, efficacy and safety will be assessed separately for each cohort of utomilumab plus avelumab in the NSCLC Cohorts A1, A2, and A3, as well as for Cohorts A4 (melanoma), A5 (SCCHN), A6 (TNBC), A7 (SCLC), and A8-A10 (first-line NSCLC).

Additional details on the study design for Combination A are provided in Section 9.2.1 and the Statistical Analysis Plan (SAP).

Originally, approximately 253 patients with solid tumors were planned to be enrolled in Combination A across all cohorts. Enrollment of patients into Cohorts A1 to A6 and A8 were completed as planned. In Cohort A7, 10 SCLC patients were enrolled. However, the level of clinical activity observed in Cohort A7 does not support further clinical development and further enrollment in this cohort is not planned. In addition, due to recent improvements in the standard of care for 1L NSCLC patients, the level of clinical activity observed in Cohort A10 does not support further development. Given that Cohort A9 and A10 use 1:1 randomization for enrollment, further enrollment in Cohort A9 alone would not conform with the study design. Therefore, further enrollment in Cohorts A7, A9, and A10 is not planned.

3.2.2. Combination B (Avelumab plus PF-04518600)

Combination B includes a Phase 1b dose-escalation part and Phase 2 part. In the Phase 1b part for Combination B, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus PF-04518600 using the mTPI design described in Section 3.1.5. Patients will receive PF-04518600 Q2W in combination with 10 mg/kg avelumab Q2W for 2 cycles (8 weeks). The study treatments to be evaluated during Phase 1b of Combination B are presented in Table 15.

Table 15. Combination B Phase 1b Study Treatments (Avelumab plus PF-04518600)

Treatment Group[a]	PF-04518600 Dose	Avelumab Dose
B14	3 mg/ kg IV Q2W	10 mg/kg IV Q2W
B13	1 mg/kg IV Q2W	10 mg/kg IV Q2W
B12	0.3 mg/kg IV Q2W	10 mg/kg IV Q2W
B11	0.1 mg/kg IV Q2W	10 mg/kg IV Q2W

a. Sequential evaluation of PF-04518600 doses starting with B12.

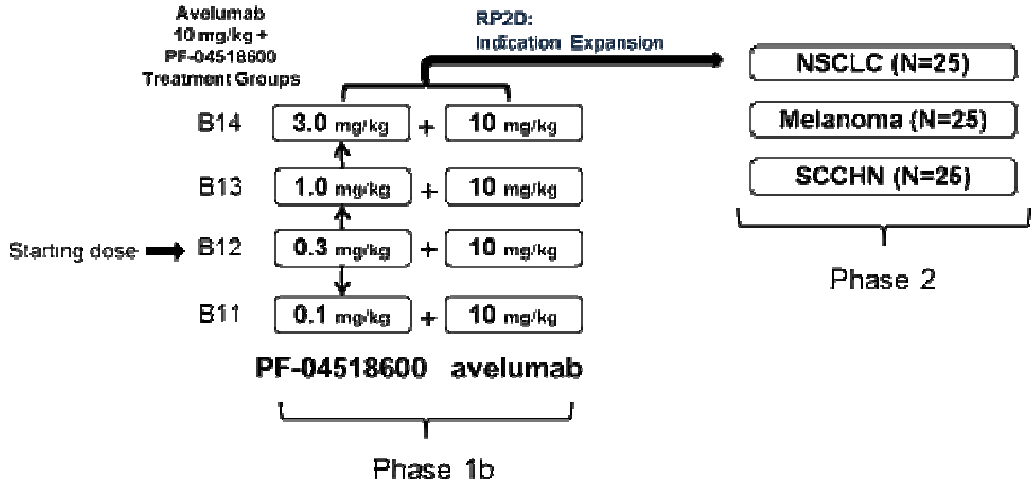
The starting dose level (B12) for Combination B is 0.3 mg/kg PF-04518600 Q2W plus 10 mg/kg avelumab Q2W. Initially 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. If recommended by the mTPI design, the dose level can be a) expanded in cohorts of up to 3 patients and then up to an additional 6 patients, b) escalated to the next dose level, or c) de-escalated to a lower dose level. A total of 12 patients will be treated at the RP2D. If at any point the mTPI requires a de-escalation, the next 3 patients will be enrolled at the lower dose level according to Section 3.1.5. Dose escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

Following the 8-week DLT observation period, if no patients experience DLTs, the next higher dose cohort may be initiated. Initially 3 patients will be assigned to a new open dose level. Up to 3 patients can be added at the same dose level if no DLTs are observed after 4 weeks of observation. After the first 3 patients enrolled in a dose escalation cohort have

completed the 8-week DLT period, additional cohorts of up to 6 patients each may be enrolled into any dose level that has been deemed safe (if recommended by the mTPI design) for a total of 12 patients to obtain additional safety and PD data. See the subsection for all combination in Inclusion Criterion 1 (Section 4.1) for biopsy requirements.

Once the Phase 1b part is completed and the MTD or MAD is determined, the Phase 2 portion of Combination B will be initiated. During Phase 2, patients with NSCLC, melanoma, or SCCHN will be enrolled into 3 separate cohorts of 25 patients each to evaluate safety and efficacy at the RP2D determined during Phase 1b for those tumor types. Each cohort will provide preliminary estimates for objective response rate (ORR) to help inform future trials. The study design for Combination B is illustrated in Figure 18.

Figure 18. Combination B Phase 1b and Phase 2 Study Design Schema



Originally, approximately 105 patients were planned to be enrolled in Combination B. Enrollment in Phase 1 was completed and enrollment in the Phase 2 SCCHN cohort was also completed. The safety profile on this combination was acceptable and there was evidence of pharmacodynamic activity. However, the observed clinical activity does not support further development. Therefore, the completion of patient enrollment into the Phase 2 NSCLC cohort and the initiation of enrollment into the Phase 2 melanoma cohort are not planned.

3.2.3. Combination C (Avelumab plus PD 0360324)

Combination C includes a Phase 1b sequential dose-escalation lead-in part and Phase 2 part. In the Phase 1b lead-in part for Combination C, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus PD 0360324 using the mTPI design described in Section 3.1.5. Patients will receive PD 0360324 Q2W in combination with 10 mg/kg avelumab Q2W for 2 cycles (8 weeks). The study treatments to be evaluated the Phase 1b portion of Combination C are presented in Table 16.

Table 16. Combination C Phase 1b Study Treatments (Avelumab Plus PD 0360324)

Treatment Group[a]	PD 0360324 Dose	Avelumab Dose
C13	150 mg IV Q2W	10 mg/kg IV Q2W
C12	100 mg IV Q2W	10 mg/kg IV Q2W
C11	50 mg IV Q2W	10 mg/kg IV Q2W

a. Sequential evaluation of PD 0360324 doses starting with C11.

If recommended by the mTPI design, a dose level may be a) expanded in cohorts of up to 3 patients and then up to an additional 4 patients, b) escalated to the next dose level, or c) de-escalated to a lower dose level.

The starting dose level (C11) of Combination C is 50 mg PD 0360324 Q2W plus 10 mg/kg avelumab Q2W. Starting with dose level C11, 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. Fresh biopsies will not be required for the first 3 patients enrolled in each dose level. If at any point the mTPI requires a de-escalation, the next 3 patients will be enrolled at the lower dose level according to Section 3.1.5. Dose escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

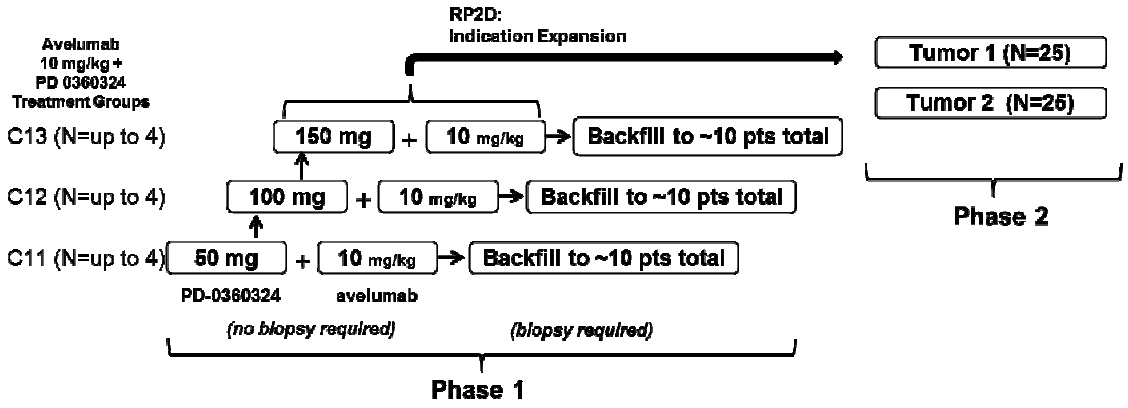
In addition, if a DLT is observed in a lower dose level previously determined to be safe per mTPI, enrollment of additional patients in the higher dose levels will be delayed until the safety of the lower dose is re-confirmed per mTPI design.

During Phase 1b, if allowed by the mTPI design, a cohort may be expanded to approximately 10 patients total to collect additional safety, clinical activity, and biomarker related data.

Once the Phase 1b is completed and the MTD or MAD is determined, the Phase 2 portion of Combination C will be initiated to evaluate safety and efficacy at the RP2D determined during Phase 1b. Up to 2 tumor types among the following will be selected for evaluation: ovarian cancer, SCCHN, NSCLC, gastric cancer.

The study design for Combination C is illustrated in Figure 19.

Figure 19. Combination C Phase 1b and Phase 2 Study Design Schema



Originally, approximately 80 patients were planned to be enrolled in Combination C. However, the level of clinical activity observed in cohorts C11, C12, and C13, did not support development beyond Phase 1b. Therefore, Phase 2 is not planned.

3.2.4. Combination D (Avelumab plus Utomilumab plus PF-04518600)

Combination D includes a Phase 1b sequential dose escalation part and a Phase 2 part. In the Phase 1b part for Combination D, patients with locally advanced or metastatic solid tumors as defined in Section 4.1 will be evaluated to identify the MTD or MAD of avelumab plus utomilumab plus PF-04518600 using the mTPI design described in Section 3.1.5. Patients will receive utomilumab plus PF-04518600 in combination with avelumab Q2W for 2 cycles (8 weeks) and will be evaluated for DLT. The study treatments to be evaluated during the Phase 1b portion of Combination D are presented in Table 17.

Table 17. Combination D (Utomilumab Plus PF-04518600 Plus Avelumab) Phase 1b Study Treatments

Treatment Group	Utomilumab Dose	PF-04518600 Dose	Avelumab Dose
D11[a]	20 mg IV Q4W	0.1 mg/kg IV Q2W	10 mg/kg IV Q2W
D21[b]	20 mg IV Q4W	0.3 mg/kg IV Q2W	10 mg/kg IV Q2W
D12[b]	50 mg IV Q4W	0.1 mg/kg IV Q2W	10 mg/kg IV Q2W
D22[c]	50 mg IV Q4W	0.3 mg/kg IV Q2W	10 mg/kg IV Q2W
D31[d]	20 mg IV Q4W	1.0 mg/kg IV Q2W	10 mg/kg IV Q2W
D32[e]	50 mg IV Q4W	1.0 mg/kg IV Q2W	10 mg/kg IV Q2W

a. Sequential evaluation of utomilumab and PF-04518600 doses starting with D11.
b. D21 and D12 to be evaluated in parallel if D11 is safe.
c. D22 to be evaluated only if D21 and D12 are safe.
d. D31 can be evaluated if D21 is safe.
e. D32 to be evaluated only if D22 and D31 are safe.

The starting dose level (D11) for Combination D is 20 mg utomilumab Q4W plus 0.1 mg/kg PF-04518600 Q2W plus 10 mg/kg avelumab Q2W. The initiation of patient recruitment at

D11 is dependent upon the observation of no more than 1 DLT out of 6 patients treated in Phase 1b Combinations A and B at 500 mg utomilumab and 1 mg/kg PF-04518600, respectively. As of 30 September 2016, this study has completed the Phase 1b part of Combination A with no DLTs observed and, for the Phase 1b part of Combination B, no DLTs have been observed at the starting dose level of 0.3 mg/kg PF-04518600 (B12) with evaluation of the 1 mg/kg PF-04158600 dose level ongoing. Since no DLTs were observed during Phase 1b of Combination A, Combination D will be initiated once the safety of the 1 mg/kg PF-04518600 dose level of Combination B is confirmed (eg, dose is acceptable per mTPI design following treatment of at least 6 patients treated at that dose or higher).

If recommended by the mTPI design, a dose level can be a) expanded in cohorts of up to 3 patients and then up to an additional 6 patients, b) escalated to the next dose level, or c) de-escalated to a lower dose level.

Starting with dose level D11, 3 patients will be enrolled, treated, and monitored during the 8-week DLT period. Fresh biopsies will not be required for the first 3 patients enrolled in each dose level. If at any point the mTPI requires de-escalation, the next 3 patients will be enrolled at the lower dose level according to Section 3.1.5. Dose escalation will be allowed as the dose level satisfies the mTPI criteria.

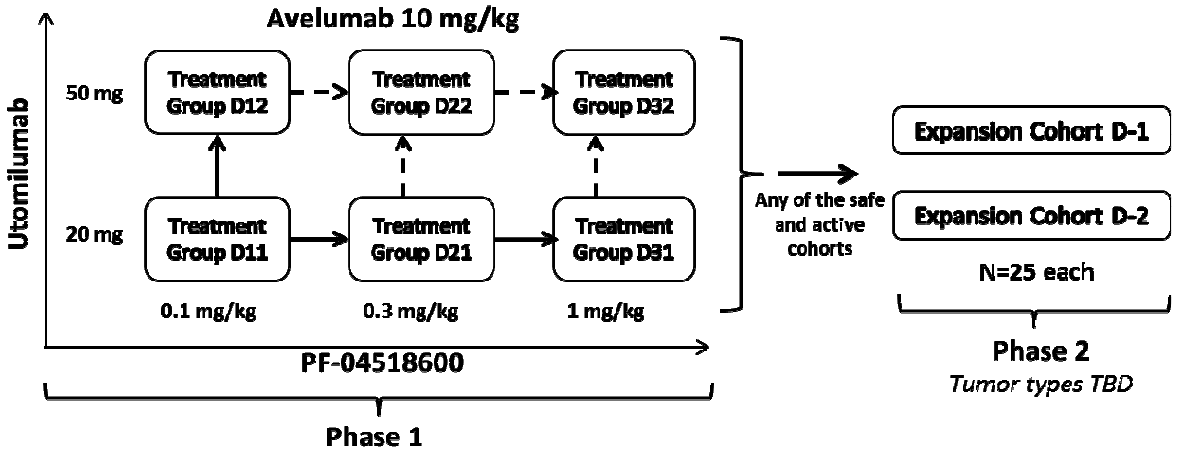
In addition, if a DLT is observed in a lower dose level previously determined to be safe per mTPI, enrollment of additional patients in the higher dose levels will be delayed until the safety of the lower dose is re-confirmed per mTPI design.

During Phase 1b, if allowed by the mTPI design, a cohort maybe expanded to approximately 12 patients total to collect additional safety, clinical activity, and biomarker related data.

Once the Phase 1b lead-in is completed and the MTD or MAD is determined, the Phase 2 portion of Combination D may be initiated to evaluate the safety and efficacy at the RP2D (one or more dose levels) determined during Phase 1b, if the safety and clinical activity are supportive of further development. Up to 2 tumor types among the following may be selected for evaluation: NSCLC, melanoma, SCCHN, or bladder cancer.

The study design for Combination D is illustrated in Figure 20.

Figure 20. Combination D Phase 1b and Phase 2 Study Design Schema*



* A solid arrow to a dose level implies that only the dose level from which the arrow is originating needs to be safe (escalate per mTPI design) for that dose level to be opened. For example, D21 can be opened if D11 is safe and D31 can be opened if D21 is safe. A dashed arrow to a dose level implies that more than 1 dose level is required to be safe (escalate per mTPI design for more than 1 dose level) for that dose level to be opened. For example, D12 and D21 both need to be safe (escalate per mTPI design for both) for D22 to be opened, and D31 and D22 both need to be safe for D32 to be opened. Cohorts D12 and D21 and Cohorts D22 and D31 may be opened and enroll patients in parallel since only either utomilumab or PF-04518600 is escalated at a time.

Originally, approximately 122 patients were planned to be enrolled in Combination D. However, the level of clinical activity observed in cohorts D11 to D32, did not support development beyond Phase 1b. Therefore, Phase 2 is not planned. Overall 71 patients were enrolled for Combination D treatment.

3.2.5. Combination F (Avelumab plus CMP-001 and Utomilumab or PF-04518600)

Combination F includes a Phase 1b safety lead-in part and a Phase 2 part. Eligible patients will have recurrent or metastatic SCCHN, will have been previously treated with an anti-PD-1 or anti-PD-L1 containing therapy, and will have experienced disease progression prior to study entry (see Inclusion Criteria in Section 4.1).

In the Phase 1b safety lead-in part, patients will initially be randomized 1:1:1 into each of Cohorts F1, F2, and F3. Six DLT evaluable patients are needed to assess safety in each cohort. Patients who are not evaluable for DLTs, might be replaced by enrolling patients without randomization.

Up to 12 patients will be randomized into each cohort in the Phase 1b safety lead-in part and evaluated for DLT during the first treatment cycle (4 weeks) as follows:

- If ≤1 of 6 patients experience DLT, the cohort will be expanded to enroll up to 14 additional patients in the Phase 2 cohort expansion;

- If 2 of 6 patients experience DLT, the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b lead-in part of the study:
  - If ≤3 of 12 patients experience DLT, the cohort will be expanded to enroll up to 8 additional patients in the Phase 2 cohort expansion;
  - If ≥4 of up to 12 patients experience DLT, enrollment in the specific cohort will be discontinued.
- If ≥3 of up to 6 patients experience DLT, enrollment in the specific cohort will be discontinued.

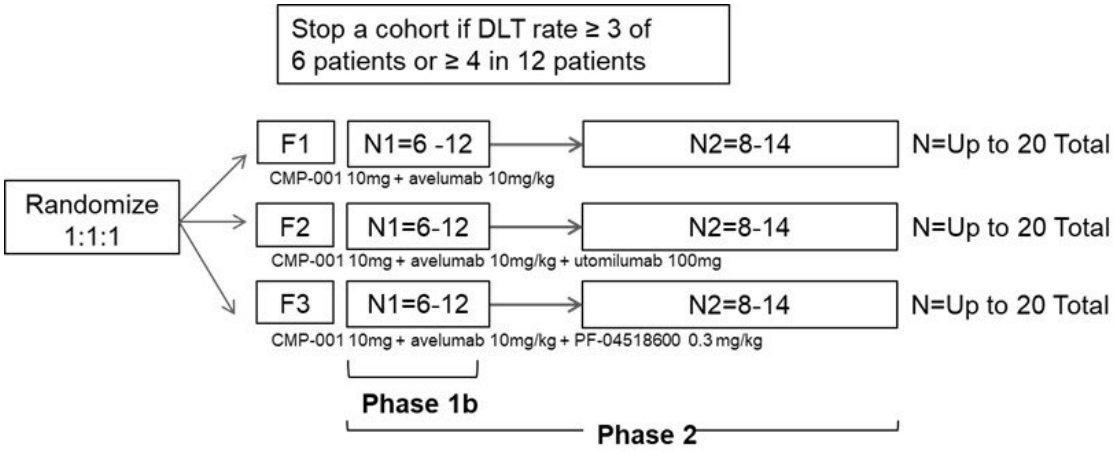
If one cohort is discontinued, patients will be randomized to the remaining cohorts in a 1:1 ratio. Therefore, the total number of possible enrolled patients per cohort may be approximately 20 patients for cohorts that do not meet the stopping criteria and the total number of patients enrolled for this combination may be approximately 60 patients.

In addition to the rules for the continuation of a cohort based on DLTs, the Sponsor will monitor DLTs across the cohorts and may elect to pause or discontinue patient enrollment at any time based on emerging safety and efficacy data from the current study or other studies with CMP-001.

The following 3 cohorts will be evaluated (see Figure 21):

- Cohort F1: avelumab plus CMP-001;
- Cohort F2: avelumab plus CMP-001 and utomilumab;
- Cohort F3: avelumab plus CMP-001 and PF-04518600.

Figure 21. Combination F Phase 1b and Phase 2 Study Design Schema



The dose levels of the study treatments to be evaluated during the Combination F are presented in Table 18.

Table 18. Combination F (Avelumab Plus CMP-001 Plus Utomilumab or PF-04518600) Study Treatments

Cohort	CMP-001 (SC and IT)[a]	Utomilumab Dose	PF-04518600 Dose (IV)	Avelumab Dose (IV)
F1	10 mg	NA	NA	10 mg/kg Q2W
F2	10 mg	100 mg Q4W	NA	10 mg/kg Q2W
F3	10 mg	NA	0.3 mg/kg Q2W	10 mg/kg Q2W

IV=intravenous; SC=subcutaneous; NA = not applicable; IT= intratumoral.
a. CMP-001 will be administered initially as 2 weekly SC doses, followed by IT dosing at weekly intervals for 5 additional doses (Q2W) (all cohorts). From C2D1, if IT administration is no longer feasible, then CMP-001 should be administered in peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh or anterior abdominal wall) administration should be implemented (see Section 5.3.5 and guidance in Appendix 4).

3.3. Dose-Limiting Toxicity Definition

Severity of AEs will be graded according to CTCAE v.4.03. For the purpose of the Phase 1b lead-in, any of the following AEs occurring during the DLT observation period (the first 2 cycles of treatment [8 weeks] for combinations A to D, and the first treatment cycle [4 weeks] for combination F) which are attributable to one or more of the investigational products in the combination will be classified as DLTs:

Hematologic:

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

Non-Hematologic (Non-Laboratory):

- Any Grade ≥3 toxicity, except for any of the following:
  - Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤1;

- Grade 3-4 nausea and vomiting controlled by optimal medical therapy within 72 hours;
- Grade 3 hypertension controlled by medical therapy;
- Grade 3 diarrhea that improves to Grade ≤2 within 72 hrs after medical management has been initiated;
- Grade 3 skin toxicity that resolves to Grade ≤1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated;
- Any Grade ≥3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis;
- Grade 3 endocrinopathies controlled with medical therapy;
- Tumors flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

- Grade 4 CRS or Grade 3 CRS lasting >24 hours despite optimal treatment.

Important for Combination F: CMP-001 activates pDCs through agonism of TLR9. Upon activation by CMP-001, pDCs will induce large amounts of IFNα and Th1-promoting cytokines. Therefore, it is expected that toxicities associated with CMP-001 dosing may resemble interferon-related toxicities and symptoms associated with cytokine release, such as fever, flu-like symptoms, tachypnea, headache, tachycardia, hypotension, rash, and hypoxia which may present hours after CMP-001 injection. Therefore, AEs such as headache, fever, flu-like symptoms and/or hypotension that are ≤ Grade 3 AND resolved to ≤ Grade 1 within 24 hours with standard supportive care will not be considered as DLTs.

- Non-hematologic Grade ≥3 laboratory abnormality if medical intervention is required to treat the patient or the abnormality leads to hospitalization.
  - Single laboratory values out of normal range that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management are not to be considered DLTs;
  - ALT or AST >3 x upper limit of normal (ULN) (if normal at baseline) or >3 x ULN and doubling the baseline (if > ULN at baseline) associated with bilirubin >2 x ULN.

Non-Adherence to Treatment Schedule:

- Delay of ≥3 weeks in receiving the next scheduled administration due to persisting treatment-related toxicities;

- Failure to receive at least 75% of the planned doses each of the investigational products during the DLT observation period due to treatment-related toxicities.

In the absence of associated clinical abnormalities, abnormal laboratory tests should be repeated to confirm relevance.

While the rules for adjudicating DLTs in the context of the dose determination phase (Phase 1b) are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between Sponsor and Investigator, based on the emerging safety profile.

3.4. Maximum Tolerated Dose Definitions

The MTD estimate is the highest dose level of an immune modulator being tested in combination with 10 mg/kg of avelumab associated with a DLT rate of <33% among the patients treated at that dose level provided that a higher dose level of the immune modulator in combination with 10 mg/kg of avelumab was tested and had an associated DLT rate ≥33%.

For Combinations B and C, there can be only 1 MTD. For Combination D, there can be 1 (eg, D32) or 2 (eg, D31 and D22) MTDs.

3.5. Maximum Administered Dose Definitions

The MAD is the highest dose of the other immune modulator administered in combination with 10 mg/kg avelumab.

3.6. Recommended Phase 2 Dose Definition

The RP2D or doses will be chosen for further clinical development based on data for the primary and secondary endpoints of this study. Given the broad active dose range for many immunotherapies, significant clinical activity, and PK/PD relationships observed at doses lower than the MTD or MAD will also be factors considered when choosing the RP2D.

4. 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 participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

Eligibility criteria specific to each unique combination of avelumab and the other immune modulator(s) are highlighted.

Study entry is defined as randomization date for randomized cohorts and first dose date for non-randomized cohorts.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histological or cytological diagnosis of advanced/metastatic solid tumor as follows

    - For all combinations:

        - Measurable disease by RECIST v1.1 with at least 1 measurable lesion that has not previously been irradiated.

        - Availability of tumor specimens: For Phase 1b: Archival formalin-fixed paraffin-embedded (FFPE) tissue is required if available for the first 3 patients enrolled in a cohort, including replacement patients. For additional patients enrolled in each Phase 1b cohort and Phase 2, FFPE tissue must be available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy, taken within 1 year prior to study entry, with no intervening systemic anti-cancer therapy. This tissue may be prepared from a de novo biopsy obtained prior to study entry. Core needle or excision biopsies are preferred.

        - The following baseline data should be available for each respective tumor type: human papilloma virus (HPV) status based on locally approved testing for patients with SCCHN, EGFR, ALK and ROS-1 status for non-squamous NSCLC and PD-L1 status based on locally approved testing for first-line NSCLC patients.

        - Unless specified, the prior therapy requirements apply to anti-cancer drug treatment in advanced stage/metastatic disease. If patient relapses within 1 year of adjuvant/neoadjuvant treatment, the respective therapy must be counted as treatment in advanced disease/metastatic setting.

    - Combination A:

        - Phase 1b: NSCLC that has progressed on standard therapy or for which no standard therapy is available.

- Phase 2:
  - Cohorts A1 – A5: NSCLC, melanoma, or SCCHN in any line of therapy;

    NSCLC patients with tumor anaplastic lymphoma kinase (ALK) translocations or epidermal growth factor receptor (EGFR) mutations must have received, or been refractory/intolerant to standard therapy.
  - Cohort A6: TNBC that has progressed after 1 line of therapy or is ineligible for/intolerant to SOC; or
  - Cohort A7: SCLC that has progressed after up to 1 line of prior therapy in advanced metastatic setting or is ineligible for/intolerant to standard of care (SOC). No prior PD-1/PD-L1 therapy allowed.
  - Cohorts A8, A9, and A10:
    - NSCLC first-line Stage IV (per 7th International Association for the Study of Lung Cancer [IASLC] classification) or recurrent NSCLC that is histologically proven and is demonstrated to express PD-L1 (Tumor Proportion Score [TPS] ≥1%) as determined by a bioanalytically validated test (eg. Dako 22C3 or Ventana SP263).

      Patients must not have received treatment for their metastatic or recurrent disease. Neither activating EGFR mutation nor ALK or ROS1 translocation/rearrangement are permitted (non-squamous cell histologies require testing if status is unknown).

      Patients could have received adjuvant chemotherapy or locoregional treatment that included chemotherapy for locally advanced disease as long as disease treatment occurred at least 6 months prior to study entry. No prior PD-1/PD-L1 therapy allowed.

- Combination B:
  - Phase 1b:
    - NSCLC, melanoma, or SCCHN that has progressed after at least 1 line of standard therapy or is ineligible for/intolerant to SOC; No prior PD-1/ PD-L1 therapy allowed.

- Phase 2:
  - NSCLC: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed. Neither activating EGFR mutation nor ALK or ROS1 translocation/rearrangement are permitted (non-squamous cell histologies require testing if status is unknown).
  - Cutaneous or mucosal metastatic melanoma: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed.
  - SCCHN: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed.

- Combination C:
  - Phase 1b:
    - NSCLC: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed. Neither activating EGFR mutation nor ALK or ROS1 translocation/rearrangement are permitted (non-squamous cell histologies require testing if status is unknown).
    - SCCHN: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed.
    - Gastric cancer that has progressed after at least 1 line or is ineligible for/intolerant to SOC and not more than 2 lines of standard therapy in advanced/metastatic disease settings or is ineligible for/intolerant to SOC. No prior PD-1/PD-L1 therapy allowed.
    - Platinum resistant ovarian cancer that has not received more than 2 lines of standard therapy in the platinum resistant setting or is ineligible for/intolerant to SOC. No prior PD-1/PD-L1 therapy allowed. Platinum resistant is defined as progression of disease within 6 months of last dose of platinum based treatment.
    - Progressing Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS) that is either inoperable or requires extensive surgery for resection, as determined by a qualified surgeon or multi-disciplinary tumor board. Prior treatment with agents targeting CSF-1 or CSF-1R is not allowed.

- Phase 2: Up to 2 of the tumor types included in Phase 1b will be selected and communicated to the sites by protocol administrative change letter.

- Combination D:
  - Phase 1b:
    - NSCLC: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed. Neither activating EGFR mutation nor ALK or ROS1 translocation/rearrangement are permitted (non-squamous cell histologies require testing if status is unknown).
    - Cutaneous or mucosal metastatic melanoma: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed.
    - SCCHN: Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed.
    - Bladder cancer (transitional cell carcinoma of the urothelium): Up to 2 lines of prior therapy in advanced/metastatic disease settings allowed. No prior PD-1/PD-L1 therapy allowed. Other urothelial transitional cell tumor types may be considered upon consultation with the Sponsor.
  - Phase 2: Up to 2 of the tumor types included in Phase 1b will be selected and communicated to the sites by protocol administrative change letter.

- Combination F:
  - Recurrent or metastatic SCCHN.
  - One to three prior lines of systemic therapy for advanced (can be locally recurrent not amenable to local treatment) or metastatic disease.
  - Patients must have received anti-PD-1/PD-L1-containing therapy (requires at least two doses of PD-1/PD-L1 agent). Disease progression no earlier than 6 weeks from the initiation of the latest anticancer therapy. Study entry requires evidence of radiographic progression.
  - Patient must be a candidate for intralesional administration with at least one tumor lesion which can be injected safely. The criteria for lesion selection are described in Appendix 4.

- Patient must not have received previous OX-40 agonists or 4-1BB agonists or IT anticancer treatment including, talimogene laherparepvec, other oncolytic virus therapies, or other TLR agonists.

2. Age ≥18 years (≥20 years where applicable according to local regulation).

3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

4. Estimated life expectancy of at least 3 months.

5. Adequate bone marrow function, defined as:

   a. ANC ≥1.5 x 10^9/L (≥1,500/μL);

   b. Platelets ≥100 x 10^9/L (≥100,000/μL);

   c. Hemoglobin ≥9 g/dL (>5.6 mmol/L).

      Patients must be transfusion independent (ie, no blood product transfusions for a period of at least 14 days prior to study entry).

6. Adequate renal function, including estimated creatinine clearance ≥50 mL/min (Phase 1b) or ≥30 mL/min (Phase 2) as calculated using the Cockcroft-Gault (CG) equation.

7. Adequate liver function, including:

   a. Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;

   b. AST and ALT ≤2.5 x ULN.

8. Resolved acute effects of any prior therapy to baseline severity or NCI CTCAE v.4.03 Grade ≤1 (except alopecia and Grade ≤2 sensory neuropathy are acceptable).

9. Negative serum/urine pregnancy test (for females of childbearing potential) at screening.

10. Sexually active male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use at least one highly effective method of contraception as detailed in Section 4.3, throughout the study and for at least 90 days after the last dose of assigned treatment or longer as required by local regulations.

Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

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

12. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Monoclonal antibody based anti-cancer therapy within 28 days prior to study entry or small-molecule based anti-cancer therapy (targeted therapy or chemotherapy) within 14 days prior to study entry. For Combination F: PD-1/PD-L1 agents within 14 days prior to study entry.

2. Current use of immunosuppressive medication at time of study entry. The following are exceptions to this exclusion criterion: intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent; steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

3. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Exceptions include: patients with controlled diabetes type 1, controlled hypo- or hyperthyroidism, resolved childhood asthma/atopy, vitiligo, or psoriasis not requiring immunosuppressive treatment.

4. Known prior or suspected hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to mAbs (NCI CTCAE v.4.03 Grade ≥3).

5. Major surgery within 4 weeks or radiation therapy within 14 days prior to study entry. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to study entry and there is at least 1 measurable lesion that has not been irradiated. Patients must have recovered from any of the acute adverse effects of radiation.

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

7. Previous high-dose chemotherapy requiring stem cell rescue.

8. Prior allogeneic stem cell transplant or organ graft.

9. Clinically significant (ie, 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 Class ≥II), or serious cardiac arrhythmia requiring medication.

10. Symptomatic pulmonary embolism within 6 months prior to study entry.

11. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) related illness.

12. Combination C only: Existing periorbital edema.

13. Combination C only: Hypocalcemia (serum albumin adjusted calcium <7.5 mg/dL), clinically significant bone disease that may affect safe study participation at the discretion of the investigator, or recent bone fracture (within 12 weeks prior to study entry).

14. Active infection requiring systemic therapy.

15. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening tests positive).

16. Vaccination within 4 weeks of the first dose of investigational product and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines).

17. Diagnosis of any other malignancy within 2 years prior to study entry, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason ≤6) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation or castration).

18. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

19. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry and/or during study participation.

20. Persisting toxicity related to prior therapy NCI CTCAE v.4.03 Grade >1 (alopecia and Grade ≤2 sensory neuropathy, or other Grade ≤2 AEs not constituting a safety risk based on Investigator judgment are acceptable); previous Grade ≥3 irAE within 3 months prior to study entry; or unresolved irAEs prior to study entry.

21. Other severe acute or chronic medical conditions, psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational products 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.

22. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use at least 1 highly effective method of contraception, as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of investigational product or longer as required by local regulations.

4.3. Lifestyle Guidelines

Patients enrolled in this study will receive avelumab in combination with other investigational products (ie, utomilumab, PF-04518600, PD 0360324, or CMP-001) for which the teratogenic risk is currently unknown. Male patients who are able to father children and female patients who are of childbearing potential, if sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of the selected method of contraception throughout the study and continue for at least 90 days after the last dose or longer as required by local regulations. The investigator or his or her designee, in consultation with the patient, will select an appropriate method of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and instruct the patient in its consistent and correct use. Patients need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method, preferably with low user dependency consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
- Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
- Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

1. Female patients of non-childbearing potential must meet at least one of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum FSH level within the laboratory's reference range for postmenopausal women.

     All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). This is a study of avelumab in combination with other immune modulators. The investigational products to be evaluated in this study are described in Table 19.

Table 19. Study B9991004 Investigational Products

Investigational Product	Dose(s)	Regimen	Combination(s)
Avelumab	10 mg/kg	1-hr IV Q2W	All
Utomilumab (4-1BB agonist mAb)	20, 100, 500 mg	1-hr IV Q4W	A
	20, 50 mg	1-hr IV Q4W	D
	100 mg	1-hr IV Q4W	F
PF-04518600 (OX40 agonist mAb)	0.1, 0.3, 1, 3 mg/kg	1-hr IV Q2W	B
	0.1, 0.3, 1 mg/kg	1-hr IV Q2W	D
	0.3 mg/kg	1-hr IV Q2W	F
PD 0360324 (M-CSF mAb)	50, 100, 150 mg	30-min IV Q2W	C
CMP-001	10 mg	SC/IT	F

IT = intratumoral; mAb = monoclonal antibody; M-CSF = macrophage colony stimulating factor; SC = subcutaneous.

5.1. Allocation to Treatment

Each combination will be evaluated in 2 study parts, Phase 1b and Phase 2. During Phase 1b and Phase 2 for all combinations, allocation of patients to specific dose levels or cohorts will be performed by an interactive response technology (IRT) system after patients have given their written informed consent and have completed the necessary baseline assessments.

The IRT system will also be used to assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient.

No patient shall receive study treatments until the investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level cohort for that patient, and
- Permission to proceed with dosing the patient.

The Sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

Study treatment in randomized cohorts must be initiated preferably on the day of randomization, but no later than 7 days after randomization.

5.2. Patient Compliance

5.2.1. Parenterally Administered Investigational Products

For avelumab, utomilumab, PF-04518600, PD 0360324, and CMP-001, the site will complete required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

5.3. Investigational Product Supplies

5.3.1. Avelumab (MSB0010718C)

Avelumab (MSB0010718C) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

5.3.2. Other Immune Modulators

PF-05092566, PF-04518600, PD 0360324 and CMP-001 investigational products and CMP-001 diluent will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. See details above for avelumab (Section 5.3.1).

5.3.3. Formulation/Dosage Forms and Packaging

5.3.3.1. Avelumab (MSB0010718C)

Avelumab (MSB0010718C) is a sterile, clear, and colorless solution intended for IV administration. It is presented with a nominal volume of 10 mL at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip off seal. The vial is intended for single use only.

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

5.3.3.2. Other Investigational Products

5.3.3.2.1. Utomilumab (Combinations A, D and F)

Utomilumab is a sterile, colorless solution intended for IV administration. It is presented at a concentration of 10 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum overseal. The vial is intended for single use only.

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

5.3.3.2.2. PF-04518600 (Combinations B, D and F)

PF-04518600 10 mg/mL injection is presented as a sterile solution for IV 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°C to 8°C) that are monitored with temperature control monitoring devices.

5.3.3.2.3. PD 0360324 Combination C

PD 0360324 is provided 75 mg/vial as a powder for solution for injection for IV administration. The drug product is supplied in a clear glass vial with an appropriate stopper and an aluminum overseal. The formulation consists of the active drug substance containing the precedented excipients. The vial is intended for single use only.

PD 0360324 will be shipped under refrigerated conditions (2°C to 8°C) that are monitored with temperature monitoring devices.

5.3.3.2.4. CMP-001 Combination F

The CMP-001 drug product will be supplied at a concentration of 5 mg/mL. CMP-001 is a colorless to pale yellow/brown opalescent liquid. Each single-use vial contains an extractable volume of 1 mL (with an overfill of 0.1 mL). Please refer to the Pharmacy Manual for dose preparation. CMP-001 will be shipped under refrigerated conditions (2°C to 8°C) that will be monitored with temperature monitoring devices.

5.3.3.2.5. CMP-001 Diluent

The CMP-001 diluent product will also be supplied by Pfizer Inc. CMP-001 diluent is a colorless to pale yellow/brown opalescent liquid. Each single-use vial contains an extractable volume of 10 mL. Please refer to the dosage and administration (DAI) section of the Investigational Product (IP) manual for dose preparation. CMP-001 diluent will be shipped under refrigerated conditions (2°C to 8°C) that are monitored with temperature monitoring devices.

5.3.4. Preparation and Dispensing

Investigational products must not be used for any purpose other than the trial.

5.3.4.1. Parenterally Administered Investigational Products

For avelumab, utomilumab, PF-04518600, PD 0360324, and CMP-001, please see the dosage and administration instructions (DAI) section of the Investigational Product (IP) Manual for instructions on how to prepare the investigational products for administration. The IV investigational products should be prepared and dispensed by an appropriately qualified and

experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of hazardous agents.

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

Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration(s) for each investigational product will be provided in the DAI section of the IP Manual.

5.3.5. Administration

5.3.5.1. Parenterally Administered Investigational Products

Avelumab, utomilumab, PF-04518600, and PD 0360324 investigational products will be administered IV at the investigational site on an outpatient basis. After Cycle 1, IV investigational products may be administered up to 2 days before or after the scheduled treatment day of each cycle for administrative reasons. However, if the IV administration is given 2 days before or after the scheduled treatment day, and multiple IV investigational products are to be administered, all scheduled IV investigational products should be given on the same day. Patients will be observed in the clinic for at least 2 hours after the last infusion of investigational product. If, following the 4th infusion of avelumab, no infusion reaction is observed, the post-infusion observation period may be discontinued thereafter.

Avelumab (all combinations) will be administered at 10 mg/kg as a 1-hour IV infusion Q2W on Day 1 and Day 15 of each cycle. Note: for all patients except those in Cohort A9, avelumab administration will start on Cycle 1 Day 1. For patients randomized to Cohort A9, avelumab administration will begin on Cycle 2 Day 1.

Utomilumab (Combination A, Combination D and Combination F) will be administered as a 1-hour IV infusion Q4W on Day 1 of each cycle. Note: for all patients except those in Cohort A10, utomilumab administration will start on Cycle 1 Day 1. For patients randomized to Cohort A10, utomilumab administration will begin on Cycle 2 Day 1.

PF-04518600 (Combination B, Combination D and Combination F) will be administered as a 1-hour IV infusion, Q2W on Day 1 and Day 15 of each cycle.

PD 0360324 (Combination C) will be administered as a 30-minute IV infusion Q2W on Day 1 and Day 15 of each cycle.

Avelumab, utomilumab, and PF-04518600 are to be administered as a 1-hour IV infusions; PD 0360324 is to be administered as a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to the duration specified for the investigational product as possible. However, the 1–hour infusion(s) administered over 50-80 minutes will be considered protocol compliant. The accepted window for a 30 min infusion is ±10 minutes. The exact duration of infusion should be recorded in both source documents and CRFs. Dose reduction for toxicity management for any of the investigational products is not permitted, however next cycle administration may be omitted due to persisting toxicity as described in Table 21 and Section 5.3.7.2.

The dose amount required to prepare the dose for weight-based infusion solutions (ie, avelumab and PF-04518600) will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle. If the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of investigational product required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. If weight change is ≤10% compared to the weight used to calculate the prior dose, dose recalculation is optional and the site should follow their standard practice.

CMP-001 will be administered initially as 2 weekly SC doses followed by IT dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 will be administered IT every 2 weeks (Q2W) (all cohorts). From C2D1, if IT administration is not feasible then CMP-001 should be administered in the peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh, or anterior abdominal wall) administration should be implemented. CMP-001 administration and requirements are summarized in Table 20.

Table 20. CMP-001 Administration and Requirements

Visit/Dose	CMP-001 Administration[a]		Premedications	Post injection Observation Period
C1D1 and C1D8	SC (either arm, thigh or anterior abdominal wall)	Weekly	Mandated	Required (4 hrs)
C1D15, C1D22, C2D1, C2D8	IT[b]	Weekly	Mandated	Required (4 hrs)
C2D15 onwards	IT[b]	Every 2 weeks	Recommended	Required (can be reduced up to 1 hr based on reactions to prior injections and clinical judgement).

C=cycle; D=day; hr=hour; IT=intratumoral; SC=subcutaneous.
a. CMP-001 will be administered initially as 2 weekly SC doses, followed by IT dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 will be administered IT every 2 weeks (Q2W) (all cohorts).
b. From C2D1, if IT is not feasible then CMP-001 should be administered in peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh or anterior abdominal wall) should be implemented.

Detailed instructions for CMP-001 administration, including tumor lesion selection and dose splitting, are provided in Appendix 4 and in the Injection Manual.

5.3.5.2. Timing of Investigational Product Administration

For Combinations A, B, and C, the avelumab infusion is to be administered at least 30 minutes (+20-minute time window, if needed) after the end of the infusion of the other investigational product.

For Combination D, on days when three investigational products are to be administered, utomilumab will be administered first, followed at least 30 minutes (+20-minute time window, if needed) later by the PF-04518600 infusion (second), followed at least 30 minutes (+20-minute time window, if needed) later by the avelumab infusion (third). On days when only avelumab and PF-04518600 are administered, PF-04518600 will be administered first followed by the avelumab infusion at least 30 minutes (+20-minute time window, if needed) after the end of the PF-04518600 infusion.

For Combination F, on days when two investigational products are to be administered (CMP-001 and avelumab), avelumab will be administered first followed by CMP-001. On days when three investigational products are to be administered, either utomilumab (Cohort F2) or PF-04518600 (Cohort F3) will be administered first, followed by avelumab and then followed by CMP-001. A 30 to 50 minute window is recommended between administration of the individual drugs to conduct end of infusion/injection procedures (eg, sample collections) and accommodate any logistical arrangements (eg, drug preparation, moving patient from one location to another for treatment administration etc.). The drug administration visits can be spread over two consecutive days eg, avelumab alone or avelumab and utomilumab or avelumab and PF-04518600 to be administered on 1 day (eg, C1D1) and CMP-001 to be administered on the next day (eg, C1D2).

For Combination F, during the Phase 2 part of the study, the order of drug administration can be changed for individual patients to address any logistical issues to accommodate IT injections. Such changes should be discussed with the medical monitor of the study before implementation.

On days when PK samples are taken, samples will be taken relative to dosing as described in the Schedule of Activity tables.

Premedication for avelumab in Combinations A, B, C, D, and F:

Avelumab premedication: in order to mitigate infusion-related reactions, patients must be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first four infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence and severity of prior infusion reactions. In Combinations A, B, C, and D, when two or three investigational products are to be administered on the same day, premedication should be given prior to the first investigational

product administration. This may be modified based on local treatment standards and guidelines.

Premedication in Combination F:

To reduce the severity of symptoms associated with CMP-001 induced cytokines, prophylaxis is mandated prior to the initial two SC (C1D1 and C1D8) and four IT **(**C1D15, C1D22, C2D1, C2D8**)** doses.

The following premedication regimen is mandated in prevention of CMP-001 induced reactions unless clinically contraindicated:

- Fluids (ie, 1000 mL IV normal saline);
- NSAIDS (ie, 1000 mg acetaminophen and 50 mg indomethacin);
- Anti-emetics (ie, 8 mg Zofran orally [per os (PO)]).

It is also highly recommended to continue to administer additional fluids **immediately following** the CMP-001 injection, rather than waiting to initiate fluids when hypotension is detected.

If some of these premedications are administered prior to avelumab infusion, they may not need to be repeated before CMP-001 administration. If the drug administration visit is spread over two consecutive days, appropriate premedication should be administered on both days, according to the study drug being administered on each day. Premedication for subsequent CMP-001 doses (C2D15 onwards) is recommended and should be administered based upon clinical judgment and presence and severity of prior infusion reactions. The CMP-001 premedication requirements are summarized in Table 20.

Stress Dose Steroids

Prophylaxis with stress dose steroids is recommended for patients who have experienced CMP-001-related Grade 3 CRS lasting ≤24 hours (ie, a minimum dose of corticosteroids of 25 mg prednisone or equivalent [eg, hydrocortisone, methylprednisone, and dexamethasone]) for subsequent CMP-001 doses. The selection and dose of corticosteroid should be determined by the Investigator based on clinical parameters.

Patients with a history of adrenal insufficiency are at increased risk for moderate to severe AEs such as hypotension which may occur with 1 to 4 hours after injection. It is strongly recommended that these patients receive stress dose steroids (eg, 50 to 100 mg hydrocortisone administered orally [PO] every 8 hours [Q8]) prior to and for 24 to 48 hours following CMP-001 injection.

Post Administration Observation Period

Combinations A, B, C, D

Patients will be observed in the clinic for at least 2 hours after the last infusion of investigational product. If, following the fourth infusion of avelumab, no infusion reaction is observed, the post-infusion observation period may be discontinued thereafter.

Combination F

CMP-001 post-injection observation period: the observation period is mandated after the initial two SC (C1D1 and C1D8) and four IT **(**C1D15, C1D22, C2D1, and C2D8) doses. Patients must be observed for a period of at least 4 hours following each of the CMP-001 injections for signs and symptoms of reactions to the injection and other AEs. Vital signs including measurement of blood pressure (systolic and diastolic blood pressure [mmHg]), respiratory rate, heart rate (bpm), and body temperature (°C) are to be collected prior to CMP-001 injection, and at 30 (±15) minute intervals during the post-infusion observation period. Starting on C2D15, the observation period can be reduced to 1 hour based on the investigators assessment of AE profile associated with prior injections.

5.3.5.3. Treatment after Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents such as avelumab and the other immune modulators to be evaluated in this study may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, tumor assessment should be repeated ≥4 weeks later in order to confirm the observation. Assigned study treatments may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression.

Patients may receive study treatments while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging no longer shows PD but rather CR, PR or SD compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target as well as non-target lesions (refer to the Study Manual). Before continuation of treatment after initial PD, the patient must be re-consented via an informed consent addendum and informed that by continuing to receive investigational products, the patient may be foregoing available therapy with possible clinical benefit(s).

If repeat imaging does not confirm PD, treatment with investigational products may be continued.

If the repeat imaging confirms PD, patients should be considered for discontinuation from all investigational products. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the investigational products. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events, and laboratory data.

Patients who stop treatment for reasons other than toxicity with any of the investigational products and then experience radiologic disease progression shortly thereafter will be eligible for re-treatment with the investigational products at the discretion of the Investigator and after discussion with the Sponsor.

5.3.5.4. Treatment after Confirmed Complete Response

Patients who have experienced a confirmed CR may continue treatment under the discretion of the investigator and upon agreement with the Sponsor for up to 2 years from the first dose of investigational product (Cycle 1 Day 1).

5.3.6. Food Requirements

The IV, SC, and IT investigational products may be administered without regard to food.

5.3.7. Recommended Dose Modifications

Every effort should be made to administer each of the investigational products at the planned dose and schedule. No dose modifications are permitted in this study, but the next administration of investigational product may be omitted based on persisting toxicity, as outlined in the next sections.

5.3.7.1. Dose Delays

In the event of significant toxicity, dosing for investigational products may be delayed as described below. In the event of multiple toxicities, dose delays should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. In addition to dose delays, investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

5.3.7.2. Study Treatment Modifications for Investigational Products Drug-Related Toxicity

Recommended treatment modifications for the investigational product attributable to drug-related toxicity are shown in Table 21.

Table 21. Avelumab, Utomilumab, PF-04518600, PD 0360324, and CMP-001 Treatment Modifications for Drug-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Treatment Modification
Drug-related adverse reactions (excluding infusion-related reaction/hypersensitivity and immune-related AEs)	Grade 1	• Continue per schedule.
	Grade 2	• Continue per schedule. • Consider withholding treatment for intolerable adverse reaction based on medical judgment.
	Grade 3	• Withhold until recovery to Grade 1 or better. • If toxicity does not resolve to Grade 1 or better within 12 weeks of last administration or if based on medical judgment the event is considered critical, consider permanent discontinuation after consultation with the sponsor. • Upon the second occurrence of the same Grade 3 toxicity that does not resolve to Grade ≤1 by the next administration, treatment must be permanently discontinued. **Exceptions are:** Laboratory values out of normal range that do not have any clinical correlation.
	Grade 4	• Permanent discontinuation. **Exceptions are:** Laboratory values out of normal range that do not have any clinical correlation.
Infusion-related Reaction	Grade 1-4	• See Section 5.3.7.3.1 and Table 22.
Hypersensitivity reactions	Grade 3-4	• See Section 5.3.7.3.2.
Immune-related AE (irAE)	Grade 1-4	• See Section 5.3.7.3.4 and Table 25.

5.3.7.3. Special Precautions for Avelumab, Utomilumab, PF-04518600, PD 0360324, and CMP-001 Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Investigational products (biologics) 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.

Premedications to mitigate infusion-related reactions associated with investigational product administration are described in Section 5.3.5.

Treatment recommendations for the management of infusion-related reactions, severe hypersensitivity reactions, and CRS are outlined in Section 5.3.7.3.1, Section 5.3.7.3.2 and Section 5.3.7.3.3, respectively.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at the earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like antinuclear antibodies (ANAs) or antineutrophil cytoplasmic antibodies (ANCAs). Treatment recommendations for the management of irAEs are outlined in Section 5.3.7.3.4.

5.3.7.3.1. Management of Infusion-Related Reactions

Since some of the investigational products (mAbs) are administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of the infusion(s) are mainly dependent upon severity, as indicated in Table 22.

Table 22. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modifications
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the investigational product infusion rate by 50% and monitor closely for any worsening.[a]
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Stop investigational product infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.[a]
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, 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 investigational product infusion immediately and disconnect bag infusion tubing from the patient. Investigational product treatment must be permanently discontinued.

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

a. The total infusion time for each investigational product should not exceed 120 minutes.

Once the investigational product infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 22 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that infusion. At the next infusion, the Investigator may consider

the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.3.7.3.2. Management of Investigational Product-related Severe Hypersensitivity Reactions and Flu-like Symptoms

Many mAb therapies can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis. In addition, given the CMP-001 mechanism of action resulting in secretion of large amounts of type 1 intereferons, flu-like symptoms similar to that seen after administration of interferons (eg, fever, rigors, nausea, and vomiting) may be associated with IT injection of CMP-001.

Investigational products (mAbs) should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment if required. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

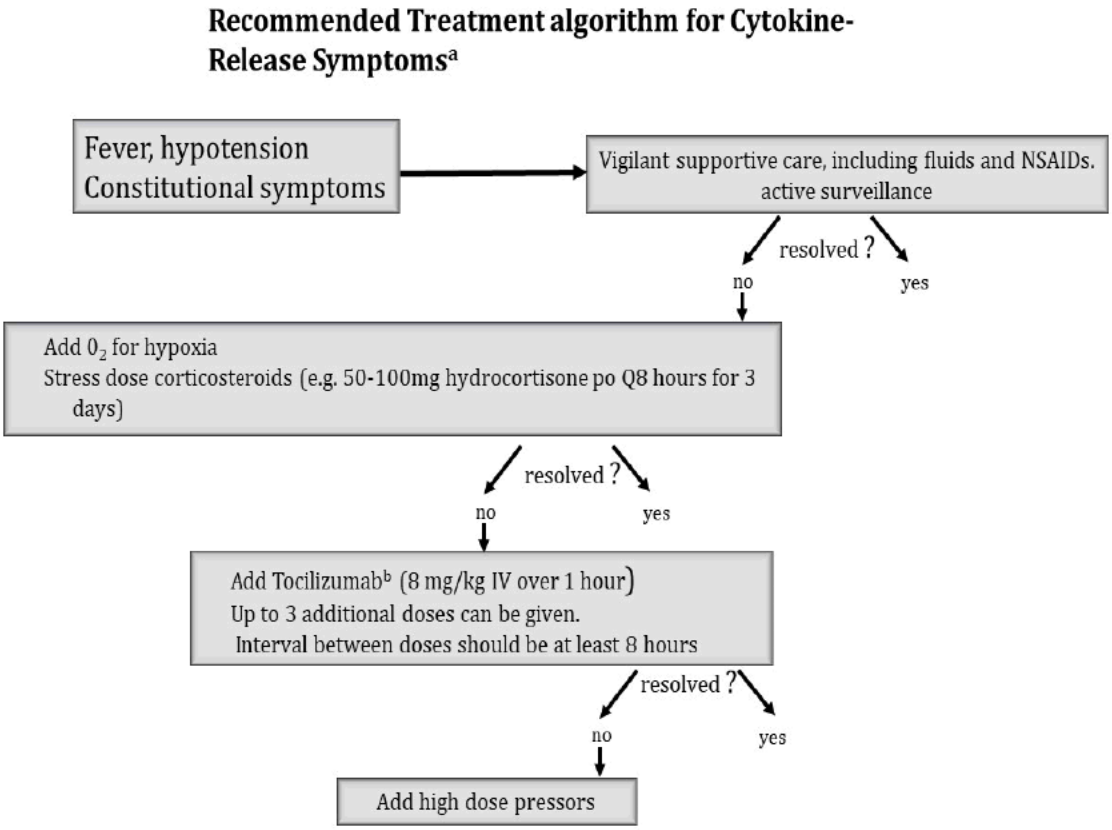
For prophylaxis of flu-like symptoms, and for patients treated with CMP-001, 25 mg indomethacin or comparable nonsteroidal anti- inflammatory drugs (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of investigational product(s) thought to be related to symptoms. Alternative treatments for fever (eg, paracetamol or ibuprofen) and rigors (eg, meperidine) may be given to patients at the discretion of the Investigator.

5.3.7.3.3. Management of Symptoms Associated with Cytokine Release

CMP-001 is designed to specifically bind to TLR9 expressed in the endosomes of pDCs. Upon activation through TLR9, pDCs will secrete large amounts of type 1 interferons and associated Th1-promoting cytokines. Therefore it is expected that symptoms associated with IFN-inducible chemokines and cytokines release, such as chills/rigors, fever, nausea/vomiting and hypotension, may occur within hours of a CMP-001 IT injection.

The recommended algorithm for the treatment of symptoms associated with cytokine release below has been adapted for the treatment of CRS resulting from other immunotherapies such as CAR-T cell therapy.[101] Its effectiveness in treating symptoms associated with cytokine release resulting from CMP-001 has not been previously studied. The first line of treatment for hypotension unresponsive to supportive care such as fluids, is stress dose steroids as outlined below. Additional treatment measures include the use of drugs targeting specific cytokines believed to be involved in the development of CRS-induced hypotension.

Figure 22 Recommended Treatment Algorithm for Cytokine Release Symptoms



IV=intravenously; NSAIDs=non-steroidal anti-inflammatory drugs; po=per os (orally); Q8=every 8 hours.
a. Lee et al.[101]
b. ACTEMRA US Prescribing Information.[102]

Table 23. Cytokine Release Syndrome Revised Grading system

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Table 24. High-Dose Vasopressors (All Doses Are Required for ≥3 hours)

Pressor	Dose
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min*

*VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10].
Adapted from Lee et al.[101]

5.3.7.3.4. Management of Injection Site-Reactions

If a patient develops inflammation at the injection site, this may be managed using cold compresses and/or acetaminophen or NSAIDs.

5.3.7.3.5. Management of Immune-Related Adverse Events

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v.4.03):

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

Management of irAEs for utomilumab, PF-04518600, and PD 0360324, is consistent with the management of irAEs for avelumab. Treatment of irAEs should follow guidelines set forth in Table 25.

Table 25. Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Diarrhea / Colitis **(NCI CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Continue investigational product therapy. Symptomatic treatment (eg, loperamide).	Close monitoring for worsening symptoms. Educate patient to report worsening immediately. If worsens: Treat as Grade 2 or ¾.
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold investigational product therapy. Symptomatic treatment.	If improves to Grade 1: Resume investigational product therapy. If persists >5-7 days or recur: 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	Withhold investigational product for Grade 3. Permanently discontinue investigational product for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume investigational product following steroids taper (for initial Grade 3). If persists >3 to 5 days, or recur after improvement: Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Rash **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids). Continue investigational product therapy.	If Grade 2 persists >1 to 2 weeks or recurs: Consider skin biopsy. Withhold investigational product therapy. Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy following steroids taper. If worsens:

Table 25. Management of Immune-Related Adverse Events

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

Table 25. Management of Immune-Related Adverse Events

	biopsy	
Grade 3 to 4 Severe new symptoms; New/worsening hypoxia; life-threatening	Permanently discontinue investigational product therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improves to baseline: Taper steroids over at least 6 weeks. If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Liver Function Tests (LFT) Increase **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue investigational product therapy.	Continue liver function monitoring. If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold investigational product therapy. Increase frequency of monitoring to every 3 days.	If returns to baseline: Resume routine monitoring, resume investigational product therapy. If elevations persist >5 to 7 days or worsen: Treat as Grade 3 or Grade 4.
Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	Permanently discontinue investigational product therapy. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤1: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Table 25. Management of Immune-Related Adverse Events

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN–1.5 x ULN	Continue investigational product therapy.	Continue renal function monitoring. If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 – 6 x ULN	Withhold investigational product therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤1: Taper steroids over at least 1 month and resume investigational product therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue investigational product therapy. Monitor creatinine daily. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold investigational product 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-related myocarditis.	If symptoms improve and immune-related etiology is ruled out, re-start investigational product therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis

Table 25. Management of Immune-Related Adverse Events

	Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	
Immune-related myocarditis	Permanently discontinue investigational product therapy. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg, European Society of Cardiology or American Heart Association guidelines. European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue investigational product therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (eg, hypopituitarism/hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold investigational product therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for	Resume investigational product once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate.

Table 25. Management of Immune-Related Adverse Events

	hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (eg, hypopituitarism/hypophysitis).	
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (eg, subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). • Hormone replacement/ suppressive therapy as appropriate. • Perform pituitary MRI and visual field examination as indicated. **If hypophysitis confirmed:** • Continue investigational product if mild or moderate symptoms with normal MRI. Repeat the MRI in 1 month. • Withhold investigational product if severe symptoms or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate high-dose corticosteroids (1 to 2 mg/kg/day methylprednisolone IV or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume investigational product once symptoms and hormone tests improve (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume investigational product only once shrinkage of the pituitary gland on MRI scan is documented. Continue hormone replacement/ suppression therapy as appropriate.

Table 25. Management of Immune-Related Adverse Events

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold investigational product therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider resuming investigational product therapy. If irAE is confirmed, treated as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold investigational product therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month and resume investigational product therapy following steroids taper.
Recurrence of same Grade 3 irAE	Permanently discontinue investigational product therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4 irAE	Permanently discontinue investigational product therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressants as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Requirement for ≥10 mg prednisone per day or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting ≥12 weeks	Permanently discontinue investigational product therapy. Specialty consult as appropriate.	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, irAE=immune-related adverse event, IV=intravenous, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.4. Investigational Product Storage

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the Sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

5.5. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all investigational product supplies.

5.5.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational products (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.6. Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of the inactivated influenza vaccine. Because multiple novel combinations will be explored during this study, live vaccines are not allowed during the active treatment period and for 90 days after the last dose of study treatment.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

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

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatments and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant treatments will not be collected for patients who initiate subsequent anticancer therapy.

Concurrent anticancer therapy with agents other than study treatments is not allowed. Medications intended solely for supportive care (eg, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat infusion-related reactions, hypersensitivity reactions and flu-like symptoms, tumor lysis syndrome and immune-related events are reported in Section 5.3.7.3.1, Section 5.3.7.3.2, Section 5.3.7.3.3, and Section 5.3.7.3.4, respectively.

5.6.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1 of treatment, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[22]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.6.2. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. In case of a surgical procedure, investigational products should be delayed. Postoperatively, the decision to reinitiate investigational products should be discussed with the Sponsor.

5.6.3. Concomitant Radiotherapy

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. Study treatment should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion.

5.6.4. Other Prohibited Concomitant Medicines and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than investigational products.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.6.3).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Table 25. below Clarification Regarding Steroid Use).
- Other experimental pharmaceutical products.
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactivated vaccines (eg, influenza vaccine).
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).

Combination F:

- Agents known to have TLR9 antagonist activity are prohibited throughout the study. The known antagonists are chloroquine, hydroxychloroquine, and quinacrine.

Clarifications Regarding Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[23,24] Furthermore, as with all immunotherapies intended to augment T-cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA-4 compounds indicate that short term use of steroids can be employed without compromising clinical outcomes.[25] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 25.

- Therapeutic use for treatment of CRS as specified in Section 5.3.7.3.3 is permitted.

- Stress dose steroids to prevent severe CRS in patients enrolled in Combination F as specified in Section 5.3.5.2.

- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily are acceptable. Higher doses of corticosteroids may be allowed for patients with a previous diagnosis of adrenal insufficiency. Sponsor consultation is required prior to enrollment to Combination F of a patient with adrenal insufficiency.

- Prophylactic use: prophylactic use, eg, for the prevention of acute infusion-related reactions, constitutes concomitant use and is prohibited except stress steroids to prevent severe CRS reactions in patients enrolled into Combination F as specified in Section 5.3.5.2.

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) are permitted.

- There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7. Rescue Medications and Supportive Care

5.7.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 25.

- Anti-inflammatory or narcotic analgesics may be offered as needed.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the Schedule of Activities and Assessments section (Section 7).

6.1.1. Tumor Biospecimens

6.1.1.1. Combination A, B, C and D

For Phase 1b: Archival formalin-fixed paraffin-embedded (FFPE) tissue is required if available for the first 3 patients enrolled in a cohort, including replacement patients. For additional patients enrolled in each Phase 1b cohort and Phase 2, FFPE tissue must be available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy, taken within 1 year prior to enrollment/randomization, with no intervening systemic anti-cancer therapy. This tissue may be obtained from a de novo biopsy performed prior to study entry.

A biopsy is required between Cycle 1 Day 21 (±4 days) and Cycle 2 Day 1 (prior to dosing) and then as clinically indicated during treatment. These on-treatment biopsies are required except in instances where the procedure poses unacceptable risks per investigator documentation.

A de novo tumor sample at End of Treatment if a patient discontinues due to disease progression is required except in instances where the procedure poses unacceptable risks per investigator documentation. The de novo tumor sample collected at the End of Treatment should be performed BEFORE initiation of subsequent anticancer therapy, preferably no later than 7 days after the End of Treatment visit.

6.1.1.2. Combination F

Baseline biopsy samples are required for all patients in Combination F.

1. Archival: Required for all patients when available.

2. De novo before first SC dose on C1D1. This is not required if an archival specimen is available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy, with no intervening systemic anticancer therapy.

Tissue is also required to be provided if tumor biopsies are taken during the study period as standard of care. If possible, the following tissues are preferable (a) at initial diagnosis, (b) between second SC dose (C1D8) and first IT dose on C1D15, (c) between C1D22 and

C2D1 before the IT dose on C2D1, and (d) within 30 days of disease progression confirmation and before initiation of subsequent anticancer therapy.

In rare circumstances, if a patient is motivated to participate and the investigator judges that the risk associated with the baseline biopsy is not appropriate for a research setting, after consultation with the Sponsor's medical monitor, the patient may be allowed on study without a biopsy prior to start of therapy.

6.1.1.3. Sample Processing and Submission Requirements

The biopsy sample(s) should be FFPE per routine pathology practice, and the resulting FFPE tissue should be submitted to the central laboratory. FFPE tissue blocks should be provided if available and permitted by local laws and policies. If blocks cannot be provided for these reasons, then sections must be freshly cut (cut no more than 30 days prior to shipment to the central laboratory), 5 μm thick, and mounted on positively-charged microscope slides (SuperFrost Plus glass slides are recommended). A minimum of 15 (preferably 25) slides should be provided. Core needle, excisional biopsies, or resection specimens are strongly preferred since intact tumor architecture is required for adequate assessment of CD8 and PD-L1 proximity. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) should only be submitted for patients for whom excisional or core needle biopsy methods are contraindicated. Additional information on tumor biospecimen collection procedures is included in the study laboratory manual.

Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), should only be submitted for patients for whom excisional or core needle biopsy methods are contraindicated.

6.1.1.4. Selection of Lesion for Biopsy

For each biopsy, a suitable tumor lesion will be designated for biopsy by the investigator. This designation will take into account: 1) the likelihood that the lesion is representative of the tumor, 2) the likelihood that the biopsy can be accessed safely, and 3) the lesion is distinct from the target lesions being followed for measurable disease. First preference is superficial (skin, subcutaneous, lymph node), palpable lesions. For other non-superficial locations, image guided biopsies are highly preferred. Second preference is abdominal lesions. Intrathoracic lesions should not be biopsied unless the potential for pneumothorax is judged to be minimal. Biopsies from bone lesions should not be submitted.

6.2. Treatment Period

For treatment period procedures, see the Schedule of Activities and Assessments section (Section 7). For all combinations, patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment up to a maximum of 2 years from the first dose of study drugs. After 2 years of treatment, patients without other options for treatment may continue on treatment with the combination to which they have been assigned or single agent avelumab upon agreement with the Sponsor.

For the treatment period, 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:

- Pharmacokinetic blood specimens – obtain at the scheduled time. When multiple investigational products are administered on the same day, the pre-dose PK samples for all investigational products may be obtained at any time BEFORE an infusion of the first investigational product on the given infusion day. The acceptable window for the post-dose sample(s) is ±10 minutes of an infusion completion.

- Electrocardiograms (ECGs) – obtain as close as possible to the scheduled time, but prior to blood specimen collection (eg, PK). In exceptional circumstances when blood sampling is not feasible before ECG measurement, the ECG measurement may be performed after the blood draws. The pre-dose ECG may be obtained any time before investigational product infusion. The acceptable window for the post-dose ECG is +30 minutes of an infusion completion.

- Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to blood specimen collection. The pre-dose blood pressure/pulse rate may be obtained any time before infusion of the first investigational product.

- Clinical safety laboratory tests – obtain as close as possible to the scheduled time.

- 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.

6.3. Follow-up

For follow-up procedures see the Schedule of Activities and Assessments section (Section 7).

Patients should be evaluated up to 90 days (30 days, 60 days, and 90 days) after last dose of investigational product(s) for safety. Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anticancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Follow-up beyond 30 days after last dose of investigational products product(s) may be performed either via a clinic visit or by remote contact (eg, telephone), with subsequent clinic visits requested if any concerns are noted during the telephone call.

Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anticancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required for all patients who enter Follow-up regardless of initiation of subsequent anticancer therapy. Patients whose disease has not progressed at the time of treatment discontinuation will enter into disease follow-up (for tumor assessment).

Patients will be followed for survival, independently of time of disease progression or initiation of subsequent anticancer therapy, for at least 2 years after randomization of the last patient in the randomized cohorts and for at least 2 years after first dose of the last patient for the non-randomized cohorts unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. Patients will be contacted every 3 months for survival status and subsequent anticancer treatment.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression by RECIST v1.1 assessment. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.3.5.3 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to 1 or more of the investigational products, the Investigator (in discussion with the Sponsor) may discontinue only the causal investigational product(s) and continue treatment with the other investigational product(s);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;

- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. 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 that 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 that he or 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.

7.1. Safety Assessments

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concomitant treatments. The results of safety assessments potentially requiring dose modifications must be reviewed prior to dosing as specified in Section 7.1.4.

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, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatments; once at the start of screening and once at the baseline visit, immediately before study drugs administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational products. Additional pregnancy tests (serum or urine) will also be routinely repeated at every cycle, prior to dosing, during the active treatment period, at the end of treatment, during follow-up (up to 90 days after last study treatment), and

additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive human chorionic gonadotropin (hCG) test, the patient will be withdrawn from study drugs but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by institutional review boards/ethics committees (IRB/ECs) or if required by local regulations.

7.1.2. Contraceptive Check

Male patients who are able to father children and female patients who are of childbearing potential, if sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of the selected method of contraception. The investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

7.1.3. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.4. Laboratory Safety Assessments

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. The hematology, blood chemistry, and pregnancy test (if applicable) results must be available and reviewed by the treating physician prior to study treatment administration. Further details are presented in Section 5.3.7. The required laboratory tests are listed in Table 26.

Table 26. Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Other
Hemoglobin	ALT	INR	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine (to be specified in the protocol)	HBV surface antigen Anti-HCV antibody If Anti-HCV antibody positive, then HCV RNA testing
Platelets	AST	aPTT			
WBC	Alk Phos				
Absolute Neutrophils	Sodium				
Absolute Lymphocytes	Potassium				
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic		
Absolute Eosinophils	Chloride				

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Other
Absolute Basophils	Total Calcium		(Reflex Testing)		
	Total Bilirubin[a]				Thyroid Function Tests: TSH, free T4
	BUN or Urea				
	Creatinine				Other Tests: ACTH
	Glucose (non-fasted)				Morning, cortisol[b]
	Albumin				Corticotropin (ACTH) stimulation test [c]
	Phosphorous or Phosphate				
	Amylase				
	Gamma glutamyl transferase				
	Creatine kinase				
	Lipase				

Note:
a. For potential Hy's Law cases, In addition to repeating measurements of AST and ALT and total bilirubin, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels.
b. Morning, cortisol required at Screening and when clinically indicated (adrenal insufficiency suspected) for Combination F patients. Blood sample should be drawn with ACTH.
c. Serum cortisol response to acute ACTH stimulation with a 250 µg dose should be performed to establish the diagnosis of adrenal insufficiency if basal morning ACTH and cortisol results are suggestive of adrenal insufficiency (eg, cortisol level is low) at Screening and when clinically indicated for Combination F patients. Institutional standards should apply.
Abbreviations: ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT = activated partial thromboplastin time; AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, HBV= hepatitis B Virus, HCV= hepatitis C Virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PT=prothrombin time; TSH=thyroid-stimulating hormone, WBC=white blood cell.

7.1.5. Vital Signs and Physical Examination

Patients will have a physical examination to include major body systems, supine or sitting blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the Schedule of Activities.

Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment.

7.1.6. (12-Lead) Electrocardiogram

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

All patients require a single ECG measurement at screening and End of Treatment (EoT) visit. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2, before and at the end of study treatment administration. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood sample draws for PK, the ECG

assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.

To ensure safety, if there is finding of QTc >500 msec (ie, > CTCAE Grade 2), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If manual reading verifies a rate corrected QTc of >500 msec, repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to conclusion that an episode of prolongation of the QTc interval is due to study treatment, 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 QTc interval reverts to less than 500 msec, and in the judgment of investigator and sponsor is determined to be due to a cause other than study treatment, then treatment may be continued with regular ECG monitoring.

7.2. Pharmacokinetics Assessments

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the post-dose samples obtained within ±10 min window relative to the end of infusion (eg, between 50-70 min of infusion start for 60 minute sample) will be considered Protocol compliant. The exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). The pre-dose samples can be taken at any time before infusion start. When multiple investigational products are administered on the same day, the pre-dose PK samples for all investigational products may be obtained at any time BEFORE the infusion of first investigational product on the given infusion day. If the infusion of avelumab is interrupted due to AE, the PK sample associated with that dose is not required. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation. CCI

CCI [redacted]

7.2.1. All Combinations: Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood at each time point) will be collected from all patients for PK analysis of avelumab as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion(s).

7.2.2. Combination A: Blood for PK Analysis of Utomilumab

Blood samples (3.5 mL whole blood at each time point) will be collected from all patients for PK analysis of utomilumab as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion (s).

7.2.3. Combination B: Blood for PK Analysis of PF-04518600

Blood samples (5 mL whole blood at each time point) will be collected from all patients for PK analysis of PF-04518600 as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion(s).

7.2.4. Combination C: Blood for PK Analysis of PD 0360324

Blood samples (3 mL whole blood at each time point) will be collected from all patients for PK analysis of PD 0360324 as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion(s).

7.2.5. Combination D: Blood for PK Analysis of Utomilumab and PF-04518600

Blood samples (3.5 mL whole blood for utomilumab and 5.0 mL whole blood for PF-04518600 at each time point) will be collected from all patients for PK analysis of utomilumab and PF-04518600 as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion(s).

7.2.6. Combination F: Blood for PK Analysis of CMP-001, Utomilumab and PF-04518600

Blood samples for CMP-001 PK will not be collected.

Blood samples (3.5 mL whole blood for utomilumab and 5 mL whole blood for PF-04518600 at each time point) will be collected from all patients for PK analysis of utomilumab (Cohort F2) and PF-04518600 (Cohort F3) as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion(s).

7.3. Immunogenicity Assessments

Immunogenicity blood samples will be assayed for ADA using a validated assay in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA will be further analyzed for Nab using a validated assay in compliance with Pfizer standard operating procedures. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

CCI [redacted]

For all patients, blood for ADA samples will be drawn from the contralateral arm of the drug infusion(s).

7.3.1. All Combinations: Immunogenicity Assessment of Avelumab

Blood samples (3.5 mL whole blood at each time point) for evaluation of immunogenicity (ADA) of avelumab will be collected from all patients at the following time points as outlined in the Schedule of Activities.

7.3.2. Combination A: Immunogenicity Assessment of Utomilumab

Blood samples (3.5 mL whole blood at each time point) for evaluation of immunogenicity (ADA) of utomilumab will be collected from all patients at the following time points as outlined in the Schedule of Activities.

7.3.3. Combination B: Immunogenicity Assessment of PF-04518600

Blood samples (5 mL whole blood at each time point) for evaluation of immunogenicity (ADA) of PF-04518600 will be collected from all patients at the following time points as outlined in the Schedule of Activities.

7.3.4. Combination C: Immunogenicity Assessment of PD 0360324

Blood samples (approximately 5 mL whole blood) to provide at least 2 mL serum for detection of ADA and neutralizing antibodies (Nab) against PD 0360324 will be collected at each sampling point from all patients according to the Schedule of Activities.

7.3.5. Combination D: Immunogenicity Assessment of Utomilumab and PF-04518600

Blood samples (3.5 mL whole blood for utolimumab and 5.0 mL whole blood for PF-04518600 at each time point) for evaluation of immunogenicity (ADA) of utomilumab and PF-04518600 will be collected at each sampling point from all patients as outlined in the Schedule of Activities.

7.3.6. Combination F: Immunogenicity Assessment of CMP-001, Utomilumab and PF-04518600

Blood samples (3.5 mL whole blood for utomilumab and 5.0 mL whole blood for PF-04518600 at each time point) for evaluation of immunogenicity (ADAs) of utomilumab (Cohort F2) and PF-04518600 (Cohort F3) will be collected at each sampling point from all patients as outlined in the Schedule of Activities.

Blood samples (5.0 mL whole blood for Anti-Qb10 at each time point) for evaluation of immunogenic response will be collected at each sampling point from all patients as outlined in the Schedule of Activities.

7.4. Biomarker and Pharmacodynamic Assessments

Information about tumor biomarkers of known prognostic significance will be collected at Screening. These include but are not limited to:

- NSCLC: EGFR, ALK, ROS1 (required for non-squamous NSCLC); PD-L1 (required for 1st line NSCLC); KRAS (if available);
- SSCHN: HPV(required); EBV, PD-L1 (if available);
- Melanoma: BRAF, NRAS, KIT, PD-L1 (if available);
- TNBC: estrogen receptor, progesterone receptor, HER2, BRCA1, BRCA2, PD-L1 (if available);
- Ovarian cancer: BRAF, BRACA, KRAS, PD-L1 (if available);
- Gastric cancer: HER 2, PD-L1 (if available).

Availability of PD-L1 status is required for NSCLC patients in Cohorts A8, A9, A10.

Biospecimens may be used to analyze candidate cellular, DNA, RNA, protein, or metabolic biomarkers, or relevant signatures of biomarkers, for (a) confirming appropriate target engagement, (b) determining pharmacodynamic effects of the study combinations and (c) identifying those patients who are most likely to benefit from treatment. Biospecimens collected at the End of Treatment visit may also help understand potential mechanisms of resistance.

As noted earlier, avelumab is expected to increase the effectiveness of anti-tumor T cells by preventing inhibition of T cell activation by PD-L1. This effect is expected to be enhanced by agents that promote anti-tumor immunity by complementary mechanisms such as extension of T cell survival or removal of other inhibitory factors such as myeloid cell activity. In order to test this hypothesis consistently across combinations in this study, PD-L1 expression and presence of CD8+ lymphocytes will be evaluated in tumors of all patients. Both PD-L1 and CD8 have been considered biomarkers of tumor responsiveness to immunotherapy. Levels of these biomarkers at baseline and on therapy will be correlated

with clinical endpoints in order to understand better the proportion of patients that respond to the combinations as well as the robustness of response. Further correlations between other biomarkers such as IFNγ-associated genes and TCR sequence diversity will be conducted as enabled by specimen availability.

Additional biomarker assessments may be performed to address questions related to specific combinations. Examples of biomarker specimen collections and analyses are described in Table 27. Details of biospecimen collections and potential analyses are included in the Schedule of Activities for each combination.

These analyses will be conducted using technical platforms that the Sponsor has confirmed to be fit for purpose. Examples are cited in Table 27. To enable these analyses, whole blood, serum, plasma, and tissue biospecimens will be retained in the central laboratory during study conduct until transfer to a qualified assay laboratory under Sponsor oversight. Biospecimens remaining at the close of the study may be transferred to long-term storage under Sponsor oversight and be assessed in accordance with the uses set forth in the informed consent document, unless prohibited by local regulation or by decision of the IRB or EC. Biospecimens not transferred to long-term storage will be destroyed.

Table 27. Examples of Biomarker Analyses and Intended Uses

Intended Use	Sample Type	Analysis (example of technical platform)
Confirm adequate target coverage at selected doses of study drug	Whole Blood	Target occupancy (flow cytometry)
Identify and/or confirm candidate biomarkers associated with pharmacodynamic effect and/or patient response	Tissue (FFPE)	Immune cell phenotype and location (immunohistochemistry and/or immunofluorescence)
		Gene expression profiling (next-generation sequencing or nanostring)
		T Cell Receptor profiling (next-generation sequencing)
		Mutation analysis (next generation sequencing)
	Whole Blood	Immune cell phenotyping (flow cytometry)
		Gene expression profiling (next-generation sequencing)
		T Cell Receptor profiling (next-generation sequencing)
	Serum and Plasma	Soluble factors associated with immune activation and regulation (using methods such as next-generation sequencing, immunoassay and mass spectrophotometry)
	Ascitic fluid (ovarian cancer only)	Immune cell phenotyping (flow cytometry)

Table 27. Examples of Biomarker Analyses and Intended Uses

Intended Use	Sample Type	Analysis (example of technical platform)
		Soluble factors associated with immune activation and regulation (immunoassay or mass spectrophotometry)

7.4.1. Combination A: Avelumab plus Utomilumab (4-1BB/CD136 Agonist mAb)\

Additional biomarkers to be assessed include 4-1BB expression by tumor-infiltrating lymphocytes, distribution of 4-1BB+ lymphocytes within the tumor, and association of 4-1BB with biomarkers linked to T cell exhaustion such as PD-1.

7.4.2. Combination B: Avelumab plus PF-04518600 (OX40/CD134 Agonist mAb)

Additional biomarkers to be assessed include expression of Ki67 and HLA-DR/CD38 on peripheral blood T cell subsets, OX40 expression by tumor-infiltrating lymphocytes, and distribution of OX40+ lymphocytes within the tumor.

7.4.3. Combination C: Avelumab plus PD 0360324 (Anti-M-CSF)

Additional biomarkers to be assessed include levels of CD14+ monocytes and CD68+ macrophages at baseline and on treatment.

7.4.4. Combination D: Avelumab plus Utomilumab plus PF-04518600

Additional biomarkers to be assessed include levels of OX40 and 4-1BB on tumor-infiltrating lymphocytes with specific attention given to differences between the triple combination and the double Combinations A and B respecting the baseline target expression needed for clinical benefit.

7.4.5. Combination F: Avelumab and CMP-001 with Utomilumab or PF-04518600

Serum will be collected for assessment of soluble proteins such as IP-10 that are expected to be released by pDCs after treatment with CMP-001. Lineage markers of the pDCs that are expected to respond to CMP-001 may be assessed in tissue.

7.4.6. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Tumor biospecimens from archived tissue samples and metastatic lesions and *de novo* biopsies (see Section 6.1.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signatures of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs. Markers that may be analyzed include, but may not necessarily be limited to, PD-L1 expression, tumor-infiltrating CD8+ T lymphocytes, and interferon-gamma-regulated genes. In addition, the quantity, target expression (eg, OX40, 4-1BB), phenotype and tissue localization of tumor associated macrophages (TAMs) may be evaluated. Optional tumor biopsies obtained upon disease progression may be used to investigate acquired mechanisms of resistance, such as the

presence of regulatory T-cells or myeloid-derived suppressor cells. Additional information on tissue collection procedures can be found in Section 6.1.1 and the Study Manual.

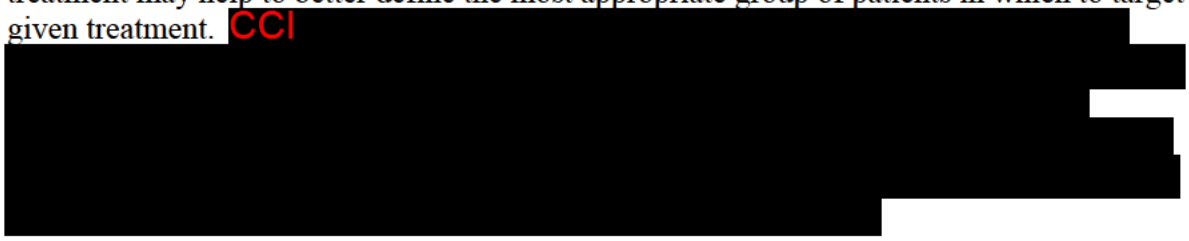
7.4.7. Peripheral Blood

Analyses in addition to those described in Table 27. may be warranted based on emerging data. These analyses may include identification or characterization of cells, DNA, RNA, or protein biomarkers known or suspected to be of relevance to the mechanisms of action of, or the development of resistance to, the combination of avelumab and immunomodulators. Such biomarkers may aid in the identification of those patients who might preferentially benefit from treatment with the combination of avelumab and a given immunomodulator, including but not limited to biomarkers related to anti-tumor immune response or target modulation, or epigenetic alterations for immune cell monitoring.

7.5. Banked Biospecimens

7.5.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. CCI



To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless

required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A 4 mL blood sample (K_2 edetic acid [ethylenediaminetetraacetic acid (EDTA)] whole blood collection optimized for DNA analysis) will be collected at the Cycle 1 Day 1 visit prior to dosing to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or by decision of the institutional review board or ethics committee. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimens will be collected from all patients unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage, and shipment instructions are provided in the laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response Section will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.6. Tumor Response Assessments

The decision for body areas to be scanned will depend on disease under study and extent of disease. Tumor assessments must include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for patients with known or suspected brain metastases. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Bone imaging using bone scan (bone scintigraphy) or 18-fluorodeoxyglucose positron emission tomography (^{18}F- FDG-PET) or

CT or MRI is required at baseline only if bone metastases are known or suspected outside the body areas scanned using other techniques, then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of CR for patients who have bone metastases. The minimum recommended body areas to be scanned depending upon malignancy are detailed in the Imaging Manual.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, every 8 weeks during treatment, at end of treatment, and until disease progression, as specified in the Schedule of Activities. Baseline tumor assessment must be performed within 28 days prior randomization (for randomized cohorts) or first dose (non-randomized cohorts). On treatment tumor assessments should be performed every 8 weeks (±7 days) starting from randomization (randomized cohorts) or first dose (non-randomized cohorts). In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks and prior response is other than confirmed PD). In case PR, CR, or PD is observed according to RECIST v1.1, tumor assessments should be confirmed on repeated imaging at least 4 weeks after initial documentation. After 1 year from randomization in the study (randomized cohorts) or first dose (non-randomized cohorts), tumor assessments will be conducted less frequently, ie, at 12-week (after 1 year) and 16-week (after 2 years) intervals, respectively. See the Schedule of Activities and Section 5.3.5.3 for treatment after initial evidence of disease progression.

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

Assessment of response will be made using RECIST version 1.1 (Appendix 1).

All patients' files and radiologic images must be available for source verification and for potential peer review.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an 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 Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. 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.

8.1.1. Avelumab Adverse Events of Special Interest

Any AE that is suspected to be a potential immune-related AE (irAE) will be considered an AE of special interest (AESI). Specific guidance for the management of immune-related AEs is provided in Section 5.3.7.3.4. AESIs are reported according to the general AE reporting rules specified in this section (Section 8).

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 study treatment are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of study treatment through 90 calendar days after the last administration of the study treatment.

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 and SAE must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;

- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the study drugs;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

The guidance on reporting of medication errors also applies to the reporting of overdose.

In this study, overdose of avelumab is defined as any dose ≥5% over the calculated dose for that particular administration as described in this protocol. For utomilumab and for PF-04518600, overdose is defined as any dose exceeding the prescribed dose by 20% over the prescribed dose for the dosing cohort under study.

Medication errors should be reported to the sponsor within 24 hours on a SAE Report Form only when associated with an SAE.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section 8.8 on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury (DILI) depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin (Tbili) baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above;

- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with:

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over the counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization;

however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the Common Terminology Criteria (CTC) term for Adverse Events (Version 4.03, Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html) listed in the Cancer Therapy Evaluation Program.

The investigator may use the following definitions of Severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements. If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product(s); or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product(s);

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product(s) prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product(s), the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational products.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See also Section 6.4 on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

This section describes the data analysis and statistical methods for each of the combinations of avelumab evaluated in this study.

9.1. Analysis Sets

9.1.1. Full Analysis Set

For **Combination A**, the full analysis set includes all randomized patients for Cohorts A1, A2, A3, A9, and A10 and all enrolled patients for Cohorts A4, A5, A6, A7, and A8 who receive at least 1 dose of study treatment. For the randomized cohorts, patients will be assigned to the randomized treatment assigned at randomization regardless of the treatment received.

For **Combination B**, the full analysis set includes all enrolled patients who receive at least 1 dose of study treatment.

For **Combination C**, the full analysis set includes all enrolled patients who receive at least 1 dose of study treatment.

For **Combination D**, the full analysis set includes all enrolled patients who receive at least 1 dose of study treatment.

For **Combination F**, the full analysis set includes all randomized patients. Patients will be assigned to the randomized treatment assigned at randomization regardless of the treatment received.

9.1.2. Safety Analysis Set

The safety analysis set includes all patients who receive at least 1 dose of study treatment. Patients will be classified according to the treatment assigned at randomization (for the randomized cohorts) unless the incorrect treatment(s) was/were received throughout the dosing period in which case patients will be classified according to the first treatment received.

9.1.3. Evaluable for DLT Analysis Set

This is the primary analysis set for the Phase 1 lead-in parts for all Combinations and includes all enrolled patients in Phase 1b who are eligible for the study, receive at least 1 dose of study treatment, and either experience DLT during the DLT observation period, or complete the DLT observation period. For Combinations A, B, C, and D, the DLT observation period is the first 2 cycles (8 weeks) of treatment. For Combination F, the DLT observation period will be 4 weeks including the first two weekly SC injections and the subsequent two weekly IT administrations.

Patients without DLTs who withdraw from study treatment before receiving at least 75% of the prescribed doses for all investigational products in the combination for reasons other than treatment-related toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

9.1.4. PK/Immunogenicity Analysis Sets

The PK/ADA concentration population is a subset of the safety analysis set including all patients who have at least one post-dose concentration measurement of either avelumab or other study drugs.

9.1.5. Biomarker Analysis Set

For all combinations, the biomarker analysis set is a subset of the safety analysis set including all patients who have at least one screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

If mutational profiling is performed on samples derived from the biomarker analysis set, the analysis may be limited to screening samples only.

9.2. Statistical Methods and Properties

9.2.1. Combination A

Phase 1b: Before expanding NSCLC Cohorts A1, A2, and/or A3 after the lead-in phase, the safety must be confirmed in the first 6 patients evaluable for DLT in those cohorts. The dose level is considered as safe and a cohort can be expanded when there are not more than 1 of 6 patients with DLTs within the first 2 cycles of treatment.

Table 28. shows the probability of confirming the safety in the first 6 patients for a range of underlying true DLT rates. For example, for a DLT that occurs in 10% of patients, there is a greater than 89% probability of confirming safety and expanding the corresponding cohort. Conversely, for a DLT that occurs with a rate of 60%, the probability of expanding is 4%.

Table 28. Combination A: Probability of Expanding Dose Level

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of expanding dose level	0.89	0.66	0.42	0.23	0.11	0.04	0.01	<0.01	<0.01

9.2.2. Combinations B, C, and D

Phase 1b: Dose escalation to identify a safe dose and RP2D of the other immune modulator(s) used in combination with avelumab (all solid tumor types):

A safe dose will be determined using the adaptive mTPI design. The mTPI design is flexible and allows dose reduction to doses in between the planned doses.

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (pT) rate (pT=0.25). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior

probabilities calculated under a coherent probability model. As shown by Ji and Wang, mTPI design is more efficient and safer thanthe 3+3 design.[49] They considered 42 scenarios to cover a wide range of practical dose-response shapes, and concluded that the 3 + 3 design was more likely to treat patients at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3 + 3 design exhibited a lower overall toxicity percentage than the mTPI design in only 1 of 42 scenarios.

Being a model-based design, mTPI automatically and appropriately tailors dose re-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a 2-way table. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as (0, pT-e1), the overdosing interval (pT+e2, 1), and the proper-dosing interval (pT- e1, pT+ e2), where e1 and e2 are small fractions. Based on the safety profile of PF-04518600, and PD 0360324, and avelumab, e1 is selected as 0.09, and e2 is selected as 0.08. Therefore, the target interval for the DLT rate is (0.16, 0.33).

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose re-escalation (RE), overdosing corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Simulations have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

Phase 2 can be initiated if not more than 3 in 10 (Combination C which has a maximum sample size of 10 patients for a dose level) or 12 (Combinations B, and D which have a maximum sample size of 12 patients for a dose level) DLT-evaluable patients have experienced a DLT at the recommended Phase 2 dose level since it meets the criterion associated with the target interval for the DLT rate of (0.16, 0.33) as described above.

For each of Combinations B, and C, it is estimated that up to approximately 30 to 36 DLT-evaluable patients will need to be enrolled to estimate MTD for the combinations under evaluation. For Combination D, it is estimated that approximately 72 DLT-evaluable patients will need to be enrolled to estimate the MTD for the utomilumab plus PF-04518600 plus avelumab combination.

9.2.3. Combination F

Phase 1b: Before expanding cohorts F1, F2, and F3 into the Phase 2 cohort expansion, the safety of the combination in that cohort must be confirmed in DLT-evaluable patients in the Phase 1b lead-in.

Up to 12 patients will be randomized into each cohort in the Phase 1b lead-in and evaluated for DLT during the first treatment cycle (4 weeks) as follows:

- If ≤1 of 6 patients experience DLT, the cohort will be expanded to enroll up to 14 additional patients in the Phase 2 cohort expansion.
- If 2 of 6 patients experience DLT, the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b lead-in part of the study:
  - If ≤3 of 12 patients experience DLT, the cohort will be expanded to enroll up to 8 additional patients in the Phase 2 cohort expansion;
  - If ≥4 of up to 12 patients experience DLT, enrollment in the specific cohort will be discontinued.
- If ≥3 of up to 6 patients experience DLT, enrollment in the specific cohort will be discontinued.

Table 29 shows the probability of expanding enrollment of a cohort into Phase 2 based on the DLT rates observed for 6 or 12 DLT-evaluable patients in Phase 1b and a range of underlying true DLT rates. For example, for a DLT that occurs in 10% of patients, there is a 97% probability of confirming safety and expanding the corresponding cohort.

Table 29. Combination F: Probability of Expanding Dose Level

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of expanding dose level	0.97	0.82	0.56	0.31	0.14	0.05	0.01	0.002	<0.0001

DLT = dose limiting toxicity.

9.3. Sample Size Determination

9.3.1. Combination A

The number of patients to be enrolled in Combination A may depend upon the observed safety profile, which will determine the number of patients at each dose level and the number of dose levels explored. The total number of patients treated in Combination A (Phase 1b and Phase 2 combined) is expected to be approximately 253.

9.3.1.1. Sample Size Determination for Utomilumab and Avelumab for NSCLC Cohorts A1, A2, and A3

There will be up to 3 dose level cohorts of patients with NSCLC that will be assessed for efficacy independently. The null hypothesis that the objective response rate does not exceed 15% (H0: ORR≤15%) will be tested against the alternative (H1: ORR>15%) for each cohort using the binomial distribution at one-sided level of significance α=0.05. For each cohort, data from the Phase 1b lead-in and Phase 2 will be combined for this assessment.

Within each cohort, 28 patients will provide at least 80% power to reject the null hypothesis if the true ORR is at least 35% (ORR≥35%).

At the end of the study, if there are ≤7 objective responders of 28 patients treated in a given cohort (6 +22 patients), then it will be declared that for that cohort, the null hypothesis cannot be rejected, or that clinically meaningful activity has not been demonstrated. If there are ≥8 objective responders of 28 patients treated in a given cohort, the null hypothesis will be rejected for that cohort and clinically meaningful activity has been demonstrated.

9.3.1.2. Sample Size Determination for Utomilumab and Avelumab for Melanoma Cohort A4

The primary objective for Cohort A4 is to test null hypothesis that the ORR in melanoma patients treated with combination of utomilumab and avelumab does not exceed 15% (H0: ORR≤15%). The null hypothesis will be tested against the alternative (H1: ORR>15%) at one-sided level of significance α=0.05 using the binomial distribution.

Twenty-eight patients will provide at least 80% power to reject the null hypothesis if the true ORR is at least 35% (ORR≥35%).

At the end of the study, if there are ≤7 objective responders of 28 patients in this cohort, then it will be declared that the null hypothesis cannot be rejected, or that clinically meaningful activity has not been demonstrated. If there are ≥8 objective responders of 28 patients treated in the cohort, the null hypothesis will be rejected and clinically meaningful activity has been demonstrated.

9.3.1.3. Sample Size Determination for Utomilumab and Avelumab for SCCHN Cohort A5

The primary objective for Cohort A5 is to test null hypothesis that the ORR in SCCHN patients treated with combination of utomilumab and avelumab does not exceed 20% (H0: ORR≤20%). The null hypothesis will be tested against the alternative (H1: ORR>20%) at one-sided level of significance α=0.05 using the binomial distribution.

Thirty-five patients will provide at least 80% power to reject the null hypothesis if the true objective response rate is at least 40% (ORR≥40%).

At the end of the study, if there are ≤11 objective responders of 35 patients in this cohort, then it will be declared that the null hypothesis cannot be rejected, or that clinically meaningful activity has not been demonstrated. If there are ≥12 objective responders of 35 patients treated in the cohort, the null hypothesis will be rejected and clinically meaningful activity has been demonstrated.

9.3.1.4. Sample Size Determination for Utomilumab and Avelumab for TNBC Cohort A6, SCLC Cohort A7, and First-Line NSCLC Cohorts A8, A9 and A10

Based on the emerging data, PD-L1 expression status shows prognostic significance for NSCLC patients. Thus, inclusion criteria for Cohort A8 are updated to add the requirement of having positive PD-L1 expression status. To reflect this change, at least 20 PD-L1 positive patients will be enrolled in the Cohort A8. Overall sample size for Cohort A8 may be larger (N= up to 26, based primarily on internal data that 6 patients [~30%] will need replacement) and can include PD-L1 negative patients that were enrolled prior to Protocol Amendment #6.

Twenty (20) patients each will be enrolled in Cohorts A6, A7, A9 and A10.

With 20 patients in each of the TNBC, SCLC cohorts, and 20 PD-L1 positive patients in first-line (1L) NSCLC cohorts, ORR can be estimated with a maximum standard error of 11.2%. Table 30. provides the exact binomial 90% confidence intervals for ORR based on different observed responses in a cohort.

Table 30. Sample Size and Exact 90% CI for ORR in Combination A, Cohort A6-A10.

N per cohort	Number of responses	Observed ORR	90% CI for ORR
20	1	5%	(0.3% - 21.6%)
	2	10%	(1.8% - 28.3%)
	3	15%	(4.2% - 34.4%)
	4	20%	(7.1% - 40.1%)
	5	25%	(10.4% - 45.6%)
	6	30%	(14.0% - 50.8%)
	7	35%	(17.7% - 55.8%)
	8	40%	(21.7% - 60.6%)
	9	45%	(25.9% - 65.3%)
	10	50%	(30.2% - 69.8%)
	11	55%	(34.7% -74.1%)
	12	60%	(39.4% -78.3%)
	13	65%	(44.2% -82.3%)
	14	70%	(49.2% - 86.0%)
	15	75%	(54.4% - 89.6%)

9.3.2. Combination B: Sample Size Determination for PF-04518600 and Avelumab

Up to 105 patients (Phase 1b and Phase 2 combined) may be enrolled for Combination B treatment.

For Phase 1b of Combination B, due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI approach cannot be determined in advance. It is expected that up to 30 patients will need to be enrolled in Phase 1b using the mTPI approach.

For Phase 2 of this combination, 25 patients will be enrolled from each of 3 tumor types: NSCLC, melanoma, and SCCHN. Thus up to 75 patients will be enrolled in Phase 2 for Combination B.

With 25 patients, ORR can be estimated with a maximum standard error of 10%.

Table 31 provides the exact binomial 90% confidence intervals for ORR based on different observed responses in a cohort.

Table 31 Sample Size and Exact 90% CI for ORR in Combinations B, C, and D

N per cohort	Number of responses	Observed ORR	90% CI for ORR
25	1	4%	(0.2% - 17.6%)
	2	8%	(1.4% - 23.1%)
	3	12%	(3.4% – 28.2%)
	4	16%	(5.7% – 33.0%)
	5	20%	(8.2% – 37.5%)
	6	24%	(11.0% – 42.0%)
	7	28%	(13.9% – 46.2%)
	8	32%	(17.0% – 50.4%)
	9	36%	(20.2% – 54.4%)
	10	40%	(23.6% – 58.3%)
	11	44%	(27.0% – 62.1%)
	12	48%	(30.5% – 65.9%)
	13	52%	(34.1% – 69.5%)
	14	56%	(37.9% – 73.0%)
	15	60%	(41.7% – 76.4%)
	20	80%	(62.5% - 91.8%)

9.3.3. Combination C: Sample Size Determination for PD 0360324 and Avelumab

Up to 80 patients (Phase 1b and Phase 2 combined) may be enrolled for Combination C treatment. For the Phase 1b part of Combination C, due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI approach cannot be determined in advance. It is expected that up to 30 patients will need to be enrolled in the Phase 1b part using the mTPI approach and backfill.

For the Phase 2 part of this combination, 2 tumor-specific cohorts of 25 patients each with the selected tumor types chosen for evaluation will be enrolled. The selected tumor types will be selected following completion of Phase 1b for the combination.

With 25 patients in each cohort, ORR can be estimated with a maximum standard error of 10%. Table 31 provides the exact binomial 90% confidence intervals for ORR based on different observed responses in a cohort.

9.3.4. Combination D: Sample Size Determination for Utomilumab and PF-04518600 and Avelumab

Up to 122 patients (Phase 1b and Phase 2 combined) may be enrolled for Combination D treatment.

For the Phase 1b part of Combination D, due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI approach cannot be determined in advance. It is expected up to 72 patients may be enrolled in the Phase 1b part using the mTPI approach and backfill.

For the Phase 2 part of this combination, 2 tumor-specific cohorts of 25 patients each with the selected tumor types chosen for evaluation may be enrolled. The selected tumor types will be selected following completion of Phase 1b for the combination.

The level of clinical activity observed in the Phase 1b part of Combination D, did not support further development. Therefore, Phase 2 is not planned.

With 25 patients in each cohort, ORR can be estimated with a maximum standard error of 10% within each tumor-specific cohort. Table 31 provides the exact binomial 90% confidence intervals for ORR based on different observed responses in a cohort.

9.3.5. Combination F: Sample Size Determination for CMP-001 and Avelumab and Utomilumab or PF-04518600

Up to 20 patients will be randomized in each of the Cohorts F1, F2 and F3 at the selected dose level.

With 20 patients in each cohort, ORR can be estimated with a maximum standard error of 0.112. The exact binomial 90% CIs for ORR based on different observed responses for each of the cohorts F1, F2 and F3 are as presented in Table 32.

Table 32 Sample Size and Exact 90% Confidence Intervals for Objective Response Rate in Combination F (Cohorts F1 to F3)

Number per cohort	Number of responses	Observed ORR	90% CI for ORR
20	1	5%	(0.3% - 21.6%)
	2	10%	(1.8% - 28.3%)
	3	15%	(4.2% - 34.4%)
	4	20%	(7.1% - 40.1%)
	5	25%	(10.4% - 45.6%)
	6	30%	(14.0% - 50.8%)
	7	35%	(17.7% - 55.8%)
	8	40%	(21.7% - 60.6%)
	9	45%	(25.9% - 65.3%)
	10	50%	(30.2% - 69.8%)
	11	55%	(34.7% -74.1%)
	12	60%	(39.4% -78.3%)
	13	65%	(44.2% -82.3%)
	14	70%	(49.2% - 86.0%)
	15	75%	(54.4% - 89.6%)

CI=confidence interval; ORR=objective response rate.

9.4. Efficacy Analysis

All efficacy analyses will be performed for each cohort and combination separately including Phase 1b lead-in and Phase 2 patients in the full analysis set.

In the definitions below, start date refers to the date of randomization for the NSCLC cohorts in Combination A, for all the cohorts in Combination F, and to the date of first dose of study treatment for all other cohorts in the other Combinations. For Cohort A8, A9 and A10, analysis will be performed for PD-L1 positive patients as assessed by central lab.

OR is defined as a CR or PR per RECIST v1.1 from the start date until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Objective response rate (ORR) is defined as the proportion of patients with a confirmed CR or PR per Investigator's assessment according to RECIST v.1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow up assessments) will be considered as non-responders in the assessment of ORR. The two-sided exact 90% CIs for ORR will be calculated.

Progression-Free Survival (PFS) is defined as the time from the start date to the date of disease progression by RECIST v1.1 or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after 2 or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor

assessments will be censored on the start date unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

Time to Tumor Response (TTR) is defined for patients with confirmed objective response (CR or PR) as the time from the start date to the first documentation of objective tumor response.

Duration of Response (DR) is defined for patients with confirmed objective response (CR or PR) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Overall Survival (OS) is defined as the time from the start date to the date of death. Patients without an event (death) will be censored at the date of last contact.

TTR will be summarized using simple descriptive statistics (eg median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods and descriptive statistics. Point estimates will be presented with their 90% and 95% confidence intervals. In addition, progression date, death date, date of first response, and last tumor assessment date will be listed, together with best overall response (BOR), TTR, DR, and PFS.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics of Study Drugs

C_{trough} and C_{max} for avelumab (all Combinations), utomilumab (Combination A and Combination D), PF-04518600 (Combination B and Combination D), and PD 0360324 (Combination C) will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose, cycle, and day.

Dose normalized parameters (eg, CDN- C_{max}, CDN- C_{trough}) will be reported as appropriate. The trough concentrations for avelumab, utomilumab, PF-04518600 and PD 0360324 will be plotted for each dose using a box whisker plot by cycle and day in order to assess the attainment of steady state. These plots will be used to help understand the relationship between PK parameters and dose.

The observed accumulation ratio and the linearity will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose. Individual and median profiles will be presented on both linear-linear and log-linear scales.

9.5.2. Analysis of Biomarker Endpoints

For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be determined at baseline and on-treatment/end of treatment time points, as appropriate.

Appropriate change from baseline measurements will be provided. For discrete measurement biomarkers, frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/post-treatment time points, as appropriate; shift tables may also be provided.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Wilcoxon signed-rank test, Wilcoxon rank-sum test, correlation/linear regression, box-and-whisker plots, etc. The statistical approaches will examine correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

9.5.3. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic Modeling

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab plus utomilumab (Combination A), avelumab and PF-04518600 (Combination B), avelumab plus PD 0360324 (Combination C), or avelumab plus utomilumab plus PF-04518600 (Combination D), exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.5.4. Analysis of Immunogenicity Data of Avelumab and Other Study Drugs

ADA/neutralizing antibody (Nab) data will be listed and summarized for each dosing interval for avelumab (all Combinations), utomilumab (Combination A, Combination D, and Combination F), PF-04518600 (Combination B, Combination D, and Combination F), PD 0360324 (Combination C), and Anti-Qb10 (Combination F). The percentage of patients with positive ADA and Nabs each will be summarized by dose. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab, utomilumab, PF-04518600, and PD 0360324 concentrations will be evaluated if data permit.

9.6. Safety Analysis

9.6.1. Analysis of the Primary Endpoint in the Phase 1b Lead-in

DLT is the primary endpoint of the Phase 1b lead-in part of the study for all Combinations evaluated.

Analyses of DLT are based on the DLT-evaluable set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed per cohort for patients in the Phase 1b lead-in (Combination A and Combination F) and summarized and listed for all patients in the Phase 1b lead-in (Combinations B, C, and D).

9.6.2. Analysis of Secondary Safety Endpoints

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be performed for each cohort and combination separately including Phase 1b lead-in and Phase 2 patients.

9.6.2.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE v.4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on TEAE, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles >1).

9.6.2.2. Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE v.4.03 severity grade whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test.

The analyses will summarize laboratory test results both on the entire study period and by cycle (Cycle 1 and Cycles >1).

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory toxicities.

9.6.2.3. Electrocardiograms

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, and QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post baseline corrected QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment. Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.7. Analysis of Other Endpoints

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

9.8. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

Surveillance for serious adverse events (SAEs) according to regulatory guidelines;

Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level will be performed in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

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

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

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

The informed consent document(s) used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/Independent Ethics Committee (IEC) before use, and available for inspection.

The Investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and Investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study drugs, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of Trial in all other participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab or other immune modulators at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Latchman Y, Wood CR, Chernova T, et al. PD-L1 is a second ligand for PD-1 and inhibits T-cell activation. Nat Immunol 2001;2(3):261-68.

2. Investigator's Brochure of avelumab (MSB0010718C), dated March 2017.

3. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011 May 12;364(19):1844-54.

4. Wang C, Lin GH, McPherson AJ, et al. Immune regulation by 4-1BB and 4-1BBL: complexities and challenges. Immunol Rev. 2009 May; 229(1):192-215.

5. Zhang X, Voskens CJ, Sallin M, et al. CD137 promotes proliferation and survival of human B cells. J Immunol. 2010 Jan 15; 184(2):787-95.

6. Broll K, Richter G, Pauly S, et al. CD137 expression in tumor vessel walls. High correlation with malignant tumors. Am J Clin Pathol. 2001 Apr; 115(4):543-9.

7. Seaman S, Stevens J, Yang MY, et al. Genes that distinguish physiological and pathological angiogenesis. Cancer Cell. 2007 Jun; 11(6):539-54.

8. Olofsson PS, Söderström LA, Wågsäter D, et al. CD137 is expressed in human atherosclerosis and promotes development of plaque inflammation in hypercholesterolemic mice. Circulation. 2008 Mar 11; 117(10):1292-301.

9. Chan FK. Three is better than one: pre-ligand receptor assembly in the regulation of TNF receptor signaling. Cytokine. 2007 Feb; 37(2):101-7.

10. Furtner M, Straub RH, Krüger S, Schwarz H. Levels of soluble CD137 are enhanced in sera of leukemia and lymphoma patients and are strongly associated with chronic lymphocytic leukemia. Leukemia. 2005 May;19(5):883-5.

11. Hentschel N, Krusch M, Kiener PA, et al. Serum levels of sCD137 (4-1BB) ligand are prognostic factors for progression in acute myeloid leukemia but not in non-Hodgkin's lymphoma. Eur J Haematol. 2006 Aug; 77(2):91-101.

12. Michel J, Langstein J, Hofstädter F, Schwarz H. A soluble form of CD137 (ILA/4-1BB), a member of the TNF receptor family, is released by activated lymphocytes and is detectable in sera of patients with rheumatoid arthritis. Eur J Immunol. 1998 Jan; 28(1):290-5.

13. Sabbagh L, Pulle G, Liu Y, et al. ERK-dependent Bim modulation downstream of the 4-1BB-TRAF1 signaling axis is a critical mediator of CD8 T-cell survival *in vivo*. J Immunol. 2008 Jun 15; 180(12):8093-101.

14. Croft M. The role of TNF superfamily members in T-cell function and diseases. Nat Rev Immunol. 2009 Apr; 9(4):271-85.

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

16. Vinay DS, Cha K, Kwon BS. Dual immunoregulatory pathways of 4-1BB signaling. J Mol Med. 2006 Sep; 84(9):726-36.

17. Houot R, Goldstein MJ, Kohrt HE. Therapeutic effect of CD137 immunomodulation in lymphoma and its enhancement by Treg depletion. Blood. 2009 Oct 15; 114(16):3431-8.

18. Kohrt HE, Houot R, Goldstein MJ.CD137 stimulation enhances the antilymphoma activity of anti-CD20 antibodies. Blood. 2011 Feb 24; 117(8):2423-32. Epub 2010 Dec 30.

19. Dong H, Strome SE, Salomao DR et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. Nature Medicine 2002;8:793-800.

20. Investigator's Brochure of PF-05082566, dated September 2016.

21. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials 1989; 10:1-10.

22. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28): 3199-3212.

23. Schleimer RP, Jacques A, Shin HS, et al. Inhibition of T-cell-mediated cytotoxicity by anti-inflammatory steroids. J Immunol. 1984; 132:266-71.

24. Khan MM, Immunosuppressive Agents. In: Immunopharmacology. New York: Springer; 2008.

25. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012 Jul 20; 30(21): 2691-7.

26. Wolchok JD, Hoos A, O'Day S et al., Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res. 2009; 12: 7412-7420.

27. Nishino M, Jagannathan JP, Krajewski KM, O'Regan K, Hatabu H, Shapiro G, Ramaiya NH. Personalized tumor response assessment in the era of molecular medicine: cancer-specific and therapy-specific response criteria to complement pitfalls of RECIST. Am J Roentgenol 2012;198(4):737–745.

28. Hoos A, Egermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst 2010; 102(18):1388-97.

29. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, and Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res 2004; 10: 5094-100.

30. Gadiot J, Hooijkaas AI, Kaiser AD, Tinteren HV, Boven HV, and Blank C. Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer 2011; 117: 2192-201.

31. Zandberg DP and Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. Oral Oncology 2014; 50:627-632.

32. Hodi FS, Bulter M, Oble DA, Seiden MV, haluska FG, Kruse A, et al. Immunologic and clinical effects of antibody blockade of cytotoic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. Proc Natl Acad Sci USA 2008; 105:3005-10.

33. Global Initiative for Asthma (GINA). The Global Strategy for Asthma Management and Prevention (http://www.ginasthma.org/uploads/users/files/GINA_Report2011_May4.pdf). Updated 2011.

34. Nishino M, Gargano M, Suda M, Ramaiya NH, Hodi FS. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer 2014;2:17.

35. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J of Cancer 2009; 45(2):228-47.

36. Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nat Rev Clin Oncol 2014;11(1):24-37.

37. Jensen SM, Maston LD, Gough MJ, et al. Signaling through OX40 enhances antitumor immunity. Semin Oncol 2010;37(5):524-32.

38. Vetto JT, Lum S, Morris A, et al. Presence of the T-cell activation marker OX40 on tumor infiltrating lymphocytes and draining lymph node cells from patients with melanoma and head and neck cancers. Am J Surg. 1997;174(3):258-6

39. Weinberg AD, Rivera MM, Prell R, et al. Engagement of the OX40 receptor in vivo enhances antitumor immunity. J Immunol 2000;164(4):2160-9.

40. Petty JK, He K, Corless CL, et al. Survival in human colorectal cancer correlates with expression of the T-cell costimulatory molecule OX40 (CD134). Am J Surg 2002; 183(5):512-8.

41. Ramstad T, Lawnicki L, Vetto J, et al. Immunohistochemical analysis of primary breast tumors and tumor-draining lymph nodes by means of the T-cell costimulatory molecule OX40. Am J Surg 2000; 179(5):400-6.

42. Redmond WL, Ruby CE, Weinberg AD. The role of OX40-mediated co-stimulation in T-cell activation and survival. Crit Rev Immunol 2009;29(3):187-201.

43. Bansal-Pakala P, Jember AG, Croft M. Signaling through OX40 (CD134) breaks peripheral T-cell tolerance. Nat Med 2001;7(8):907-12.

44. Bulliard Y, Jolicoeur R, Zhang J, et al. OX40 engagement depletes intratumoral Tregs via activating FcgammaRs, leading to antitumor efficacy. Immunol Cell Biol 2014; 92(6):475-80.

45. Kjaergaard J, Tanaka J, Kim JA, et al. Therapeutic efficacy of OX40 receptor antibody depends on tumor immunogenicity and anatomic site of tumor growth. Cancer Res 2000; 60(19):5514-21.

46. Curti BD, Kovacsovics-Bankowski M, Morris N, et al. OX40 is a potent immune-stimulating target in late-stage cancer patients. Cancer Res 2013; 73(24):7189-98.

47. Linch SN, McNamara MJ, Redmond WL. OX40 agonists and combination immunotherapy: putting the pedal to the metal. Frontiers in Oncology 2015; 5:1-14.

48. Ribas A, Robert C, Hodi FS, et al. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. J Clin Oncol 33, 2015 (suppl; abstr 3001).

49. Ji Y and Wang S-J. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design for Practical Phase I Trials. J Clin Oncol 2013;31(14):1785-1791.

50. Mittendorf EA, Philips AV, Meric-Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014:2(4);361-70.

51. Investigator's Brochure of PF-04518600, dated November 2018.

52. Piconese S, Valzasina B, Colombo MP. OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection. J Exp Med 2008;205(4):825-39.

53. Laoui D, Van Overmeire E, De Baetselier P, Van Ginderachter JA, Raes G. Functional Relationship between Tumor-Associated Macrophages and Macrophage Colony-Stimulating Factor as Contributors to Cancer Progression. Frontiers in immunology 2014;5:489.

54. Garceau V, Smith J, Paton IR, et al. Pivotal Advance: Avian colony-stimulating factor 1 (CSF-1), interleukin-34 (IL-34), and CSF-1 receptor genes and gene products. Journal of leukocyte biology 2010;87:753-64.

55. Hume DA, MacDonald KP. Therapeutic applications of macrophage colony-stimulating factor-1 (CSF-1) and antagonists of CSF-1 receptor (CSF-1R) signaling. Blood 2012;119:1810-20.

56. Pyonteck SM, Akkari L, Schuhmacher AJ, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nature medicine 2013;19:1264-72.

57. Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer cell 2014;25:846-59.

58. Tolcher AW, Sznol M, Hu-Lieskovan S, et al. Phase Ib study of utomilumab in combination with pembrolizumab in patients with advanced solid tumors. J Clin Oncol. 2016;34 (suppl; abstr 3002).

59. Bellovin D, Wondyfraw N, DeNardo DG, et al. cmFPA008, an anti-mouse CSF-1R antibody, combines with multiple immunotherapies to reduce tumor growth in nonclinical models. Journal for Immunotherapy of Cancer 2015, 3(Suppl 2):P351.

60. Hamid O, Thompson JA, Diab A, Ros W, Eskens F, Bermingham C, et al. First in human study of an OX40 agonist monoclonal antibody PF-04518600 (PF-8600) in adult patients with select advanced solid tumors: preliminary safety and pharmacokinetic/pharmacodynamic results. J Clin Oncol. 34, 2016 (suppl; abstr 3079).

61. Ott PA, Fernandez EE, Hiret S, Kim DW, Moss RA, Winser T, et al. Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. J Clin Oncol 33, 2015 (suppl; abstr 7502).

62. Antonia SJ, Lopez-Martin JA, Bendell JC, Ott PA, Taymol MH, Eder JP, et al. Checkmate 032: Nivolumab (N) alone or in combination with ipilimumab (I) for the treatment of recurrent small cell lung cancer (SCLC). J Clin Oncol 34, 2016 (suppl; abstr 100).

63. Tolcher, AW, Sznol M, Hu-Lieskovan S, Papadopoulos KP, Patnaik A, Rasco DW, et al. Phase 1b study of PF-05082566 in combination with pembrolizumab in patients with advanced solid tumors. J Clin Oncol 34, 2016 (suppl; abstr 3002).

64. Cassier PA, Gomez-Roca CA, Italiano A; Cannarile M; Ries C; Brillouet A, et al. Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS). J Clin Oncol 32:5s, 2014 (suppl; abstr 10504.

65. Lemke CD, Blackwell SE, Krieg AM, Salem A, Weiner GJ. Combination Lymphoma Immunotherapy Using Checkpoint Blockade and Intratumoral Virus-like Particles Containing CpG TLR9 Agonist. Blood 2016 128:3023.

66. Bichat F. et al. "The best therapeutic efficacy was obtained with the combination of all three immune modeulators, regardless of the responder model" Cancer Research Jul 2017 Suppl 13.

67. Investigator's Brochure of CMP-001, Edition 4. Dated December 2018.

68. Manolova, et al. Nanoparticles target distinct dendritic cell populations according to their size. Eur. J. Immunol. 2008. 38: 1404.

69. Mark J. Ernsting, Mami Murakami et al. Factors Controlling the Pharmacokinetics, Biodistribution and Intratumoral Penetration of Nanoparticles *J Control Release.* 2013 December 28; 172(3): 782-794.

70. Fourcade J, Sun Z, Pagliano O, Chauvin JM, Sander C, Janjic B, et al. PD-1 and Tim-3 regulate the expansion of tumor antigen-specific CD8+ T cells induced by melanoma vaccines. Cancer Res. 2014;74(4):1045-55.

71. Fourcade J, Kudela P, Andrade Filho PA, et al. Immunization with analog peptide in combination with CpG and montanide expands tumor antigen-specific CD8+ T cells in melanoma patients. J Immunother. 2008;31(8):781-91.

72. Speiser DE, Liénard D, Rufer N, et al. Rapid and strong human CD8+ T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909. J Clin Invest. 2005;115(3):739-46.

73. Mangsbo S.M. Enhanced Tumor Eradication by Combining CTLA-4 or PD-1 Blockage with CpG Therapy. J Immunother 2010;33:225–235.

74. 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 Res. 2013;73(23):6900-12.

75. Cohen E, Algazi A, Laux D, Wong D, Amin A, Nabell L, et al. Abstract 3560: Phase 1b/2, Open-Label, Multicenter Study of Intratumoral SD-101 in Combination With Pembrolizumab in Anti-PD-1 TreatmentNaïve Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (SYNERGY-001/KEYNOTE-184, NCT02521870).

76. Cooper D, Bansul-Pakala P, and Croft M. 4–1BB (CD137) controls the clonal expansion and survival of CD8 T cells in vivo but does not contribute to the development of cytotoxicity. Eur J Immunol 2002;32:521-9.

77. Gramaglia I, Jember A, Pippig SD, et al. The OX40 Costimulatory Receptor Determines the Development of CD4 Memory by Regulating Primary Clonal Expansion. J Immunol 2000;165:3043-50.

78. Gallotta M, Assi H, Degagne E, et al. Inhaled TLR9 Agonist Renders Lung Tumors Permissive to PD-1 Blockade by Promoting Optimal CD4+ and CD8+ T-cell Interplay. Cancer Res 2018;78:4943-56.

79. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.

80. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.

81. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015 May 21;372(21):2018-28.

82. Diab A, El-Khouerie A, Eskens F, Ros W, Thompson J, Konto C. et al. 1053PD – A first in human (FIH) study of PF-04518600 (PF-8600) OX40 agonist in adult patients (pts) with select advanced malignancies. Annal Oncol 27 (suppl 6) vi-vi14, 2016.

83. Verschraegen CF, Chen F, Spigel DR, Iannotti N, McClay EM, Redfern CH, et al. Avelumab (MSB0010718C; anti-PD-L1) as a first-line treatment for patients with advanced NSCLC from the JAVELIN Solid Tumor phase 1b trial: safety, clinical activity, and PD-L1 expression. J Clin Oncol 34, 2016 (suppl; abstr 9036).

84. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. Trends Immunol 2013; 34(3):137-43.

85. Van Baren N, Van den Eynde BJ. Tumoral immune resistance mediated by enzymes that degrade tryptophan. Cancer Immunol Res 2015; 3(9):978-85.

86. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol 2004; 4(10):762-74.

87. Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003; 9(10):1269-74.

88. Okamoto A, Nikaido T, Ochiai K, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. Clin Cancer Res 2005; 11(16):6030-9.

89. Brandacher G, Perathoner A, Ladurner R, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. Clin Cancer Res 2006; 12(4):1144-51.

90. Tzeng A, Kauke MJ, Zhu EF, et al. Temporally programmed CD8α^+ DC activation enhances combination cancer immunotherapy. Cell Reports 2016; 17:2503-11.

91. Parkhurst MR, Gros A, Pasetto A, et al. Isolation of T cell receptors specifically reactive with mutated tumor associated antigens from tumor infiltrating lymphocytes based on CD137 expression. Clinical Cancer Resarch 2016; DOI: 10.1158/1078-0432.CCR-16-2680.

92. Long AH, Haso WM, Shern JF, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nature Medicine 2015;21(6):581-90.

93. Keytruda® [package insert]. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ; 2016.

94. Optivo [package insert]. Bristol-Myers Squibb Company, Princeton, NJ; 2017.

95. Tencentriq® [package insert]. Genentech, Inc., South San Francisco, CA; 2016.

96. Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. N Engl J Med. 2015 Jul 30;373(5):428-37.

97. Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. Lancet Oncol. 2015 Aug;16(8):949-56.

98. Hartmann E, Wollenberg B, Rothenfusser S, et al. Identification and functional analysis of tumor-infiltrating plasmacytoid dendritic cells in head and neck cancer. Cancer Research 2003; 63: 6478-87.

99. Yanyan Lou at al. Antitumor activity mediated by CpG: the route of administration is critical J Immunother 2011; 24:279-288.

100. Shirota et al. Intra-tumoral injection of CpG oligonucleotides includes the differentiation and reduces the immunosuppressive activity of myeloid-derived suppressor cells. J Immunol 2012 February 15; 188(4): 1592-1599.

101. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014 July 10; 124(2): 188-195.

102. ACTEMRA® United States Prescribing Information. San Francisco, CA: Genetech Inc. 2018. https://www.gene.com/download/pdf/actemra_prescribing.pdf.

103. Marabelle A, et al. Starting the fight in the tumor: expert recommendations for the development of human intratumoral immunotherapy (HIT-IT). Ann Oncol 2018;29(11):2163–2174.

Appendix 1. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[35]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

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

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

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

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

Target Lesions

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

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

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

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

Non-target Disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Not evaluable (NE): Progression has not been documented, and
    - one or more target lesions have not been assessed; or
    - assessment methods used were inconsistent with those used at baseline; or
    - one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
    - one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Not evaluable (NE): Progression has not been determined, and:

  - one or more non-target lesion sites have not been assessed; or

  - assessment methods used were inconsistent with those used at baseline; or

  - one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images); or

  - one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

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

Supplemental Investigations

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

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

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

Determination of Tumor Response by RECIST

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

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

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

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

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment/randomization until disease progression/recurrence (taking as reference for PD the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment/randomization at a minimum interval of 6 weeks.

Appendix 2. ECOG Performance Status

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

From: Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.

Appendix 3. Abbreviations and Definitions of Terms

1L	First-line
4-1BBL	4-1BB Ligand
ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANA	AntinuclearAntibody
ANC	Absolute Neutrophil Count
ANCA	Antineutrophil Cytoplasmic Antibody
APC	Antigen Presenting Cell
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BA	Biomarker Analysis
BID	Twice-Daily
BMDC	Bone marrow-derived dendritic cell
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAR	Chimeric Antigen Receptor
CEA	Carcinoembryonic Antigen
CG	Cockroft-Gault
CI	Confidence Interval
CK-MB	Creatine Kinase – Muscle and Brain Subunits
CL	Clearance
CLE	Cutaneous Lupus Erythematosus
Cmax	Maximum Plasma Concentration
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
Ctrough	Lowest (trough) Concentration
CR	Complete Response
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CSA	Clinical Study Agreement
CSF-1	Colony-Stimulating Factor-1
CSF-1R	Colony-Stimulating Factor-1 Receptor
CT	Computerized Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events (US NCI)

CTL	Cytotoxic T cell
CTLA-4	Cytotoxic T Lymphocyte Associated Protein
CV	Coefficient of Variation
D	De-escalation
DAI	Dosage and Administration Instructions
DC	Dendritic Cell
DILI	Drug-Induced Liver Injury
DL	Dose Level
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure During Pregnancy
EDTA	Ethylene Diamene Tetra-acetic Acid
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FcγR	Fragment Crystallizable gamma Receptor
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin Fixed, Paraffin Embedded
FL	Follicular Lymphoma
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GITR	Glucocorticoid Induced TNF Receptor
GLP	Good Laboratory Practices
GVHD	Graft versus Host Disease
HA	Hyaluronic Acid
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
NIB	Investigator's Brochure
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
ICH	International Committee Harmonization
ID	Identification
IDO1	Indoleamine 2, 3-dioxygenase
IEC	Independent Ethics Committee

IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2
IL-12	Interleukin-12
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International Normalized Ratio
IP	Investigational Product
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
irRECIST	Immune Related RECIST
irSD	Immune-Related Stable Disease
IRT	Interactive Response Technology
IT	Intra Tumoral
IUD	Intra-Uterine Device
IUS	Intrauterine System
IV	Intravenous
KD	Dissociation Constant
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MAP	Mitogen Activated Protein
MCC	Merkel Cell Carcinoma
MCL	Mantle Cell Lymphoma
M-CSF	Macrophage-Colony Stimulating Factor
M-CSFR	Macrophage-Colony Stimulating Factor Receptor
MD	Multiple Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MSI^{high}	Microsatellite Instability High
MSS	Microsatellite Stable
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NA	North America
Nab	Neutralizing Antibody
NCI	National Cancer Institute
NHL	Non-Hodgkin’s Lymphoma
NK	Natural Killer
NKT	Natural Killer T-cell
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
ODN	Oligodeoxynucleotide

OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
pDC	Plasmocytoid Dendritic Cell
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PO	Per os (orally)
PR	Partial Response
PS	Performance Status
PT	Preferred Term
PT	Prothrombin Time
PVNS	Pigmented Villonodular Synovitis
Q3D	Every 3 Days
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q4W	Every 4 Weeks
QD	Once Daily
R	Rituximab
RA	Rheumatoid Arthritis
RCC	Renal Cell Carcinoma
RE	Re-escalation
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Reticuloendothelial System
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
ROA	Route of administration
RP2D	Recommended Phase 2 Dose
S	Stay (at current dose)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SCLC	Squamous cell lung cancer
SD	Stable Disease
SD	Standard Deviation
SoD	Sum of Diameter
SEM	Standard Error of the Mean
SIB	Suicidal Ideation and Behavior
SOC	Standard of Care

SOC	System Organ Class
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Plasma elimination half life
TAM	Tumor Associated Macrophage
TBili	Total Bilirubin
TCGA	The Cancer Genome Atlas
TCR	T-cell Receptor
TE	Target Engagement
TEAE	Treatment Emergent Adverse Event
TGCT	Tenosynovial Giant Cell Tumor
TGI	Tumor Growth Inhibition
Th1	T helper cell type 1
TID	Three-Times-Daily
TIL	Tumor Infiltrating Lymphocytes
TKI	Tyrosine Kinase Inhibitor
TLS	Tumor-Lysis Syndrome
TLR9	Toll- like receptor 9
Tmax	Time to Maximum Plasma Concentration
TNBC	Triple Negative Breast Cancer
TNF	Tumor Necrosis Factor
TNFRSF	Tumor Necrosis Factor Receptor Superfamily
TO	Target Occupancy
TPS	Tumor Proportion Score
TRAF	TNF Receptor Associated Factor
TSH	Thyroid Stimulating Hormone
TTR	Time to Tumor Response
UK	United Kingdom
ULN	Upper Limit of Normal
UPM	Unit Probability Mass
US	United States
VLP	Virus Like Particle
Vss	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

Appendix 4. CMP-001 Administration

Tumor Selection

It is recommended that the tumors selected at baseline for CMP-001 intratumoral injection be at least 1 cm in diameter and may be cutaneous, subcutaneous, and/or nodal or visceral tumors that are visible, palpable, or detectable by appropriate imagining guidance. The lesion must be safe to inject. The assessment for safety should consider following aspects:

- Proximity to major blood vessels: lesions in the vicinity of large vessels with a risk of vessel blow out (eg, the common, internal or external carotid arteries or their branches), or other situations with a risk of vascular catastrophe such as tumor-encased large vessels should be excluded. Special caution should be taken in patients with neck lesions that have been re-irradiated, especially if the second course of radiation was given at radical doses with curative intent and in whom the disease is ulcerated and/or connects to a skin or mucosal surface. Also, patients with tumor lesions with macroscopic intravascular tumor invasion (eg, liver lesions with tumor infiltration into the main portal vein, hepatic vein or vena cava) should not receive intratumoral therapy.[103]

- Potential for airway obstruction: lesions in close proximity to airway and potential to obstruct airway with slight increase in size should be avoided eg, hypopharynx, larynx, trachea.

The most preferred of these to be selected for injection is the most aggressively progressing tumor in the judgment of the Investigator. The tumor selected for injection does not need to be the largest lesion.

CMP-001 can be injected into target or non-target lesions, although target lesions are preferred. Preferably single large lesions should be injected with the entire dose of 10 mg. If the total dose of CMP-001 is to be split across lesions, a minimum of approximately 5 mg should be injected into each lesion. The same tumor(s) should be injected each week during therapy, if possible, except as outlined below to involuting tumors. If the full volume cannot be administered into the tumor, peritumoral injection of any remaining volume is acceptable.

If over time an injected tumor is clearly responding to therapy (regresses below the minimum size that can readily be injected with the required volume), or if in the judgment of the Investigator, the patient cannot tolerate continued injections in that lesion because of a local injection site reaction or other issues, then the injection may instead be administered intratumorally into a different progressing tumor lesion, or peritumorally at the original site or into a new tumor lesion site.

For patients who have a documented Complete Response (CR), the investigator has the option to continue study treatment given subcutaneously in an area of the draining lymph node where primary disease exists if this is determined to be in the best interest of the patient by the Investigator; or study therapy may be discontinued and the patient can continue in safety and long term survival follow up. Therapy for patients taken off-treatment for a

confirmed CR may be continued upon subsequent relapse, if there is no intervening anticancer therapy and if the relapse occurs within the maximum treatment period specified for the study.

Table 33. CMP-001 Injection Volumes

Dose	Size of lesion to be injected in greatest dimension (cm)	Volume of injection	Concentration Of Injection
10 mg	<5 cm	2 mL	5 mg/mL
10 mg	≥5 cm	5 mL	2 mg/mL

The CMP-001 drug product will be supplied at a concentration of 5 mg/mL. Detailed information regarding dilutions and injected volumes for multiple lesions can be found in the Pharmacy Manual.

Table 34. CMP-001 Administration and Requirements

Visit/Dose	CMP-001 Administration[a]		Premedications	Post injection Observation Period
C1D1 and C1D8	SC (either arm, thigh or anterior abdominal wall)	Weekly	Mandated	Required (4 hrs.)
C1D15, C1D22, C2D1, C2D8	IT[b]	Weekly	Mandated	Required (4 hrs.)
C2D15 onwards	IT[b]	Every 2 weeks	Recommended	Required (can be reduced up to 1 hr. based on reactions to prior injections and clinical judgement).

C=cycle; D=day; hr=hour; IT=intratumoral; SC=subcutaneous.
a. CMP-001 will be administered initially as 2 weekly SC doses, followed by IT dosing at weekly intervals for 5 additional doses. After the first 7 doses, CMP-001 will be administered IT every 2 weeks (Q2W) (all cohorts).
b. From C2D1, if IT is not feasible then CMP-001 should be administered in peritumoral region. If peritumoral administration is not feasible, then SC administration in an area of the draining lymph node where primary disease exists should be implemented. If any of the above is not feasible, then SC (either arm, thigh or anterior abdominal wall) should be implemented.

Method of CMP-001 Subcutaneous Administration

CMP-001 should be injected using aseptic technique. Use of topical and/or local anesthetic is permitted. The injection may be given into any SC site in the body. Using standard aseptic technique, the needle is inserted into the SC tissue. After using gentle backward

pressure on the syringe plunger to confirm extravascular location of the needle tip, the desired volume of CMP-001 is injected and the needle is withdrawn.

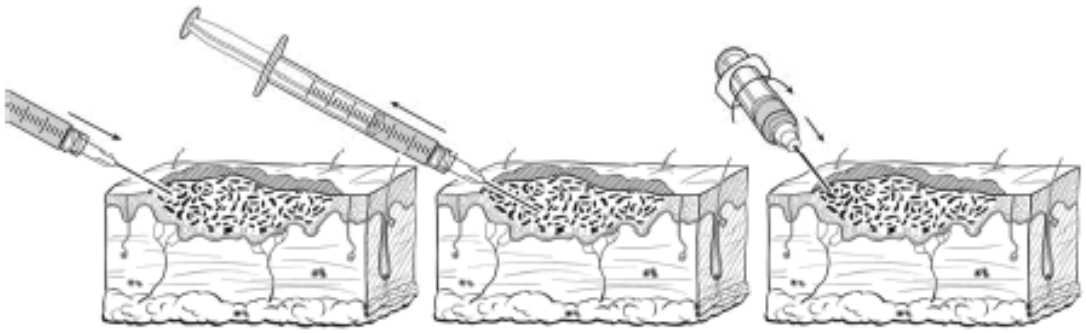
Initial 2 SC injections (C1D1 and C1D8) can be administered at any suitable subcutaneous site (arm, thigh, anterior abdominal wall etc.) as a single injection.

For **SC injections following initial IT injections**, in order to maximize the distribution and exposure to CMP-001, the full volume from a single dose should be distributed to as many SC sites as is practical. It is recommended that equal amounts of drug be injected at each SC site. Preferred sites of subcutaneous injection include: within the area of lymphatic drainage corresponding to the site of metastatic disease. For example, in a patient with a muscle or bone metastasis in the lower leg, preferred SC injection sites would be in the same leg, with the expectation that at least some of the CMP-001 will drain to lymph nodes that also contain tumor antigens. Likewise, in a patient with metastases in an upper lobe of the lung, a preferred SC injection site would be in the ipsilateral supraclavicular fossa, where the injection may activate pDC in the supraclavicular lymph nodes that also can drain the upper lung. Unsuitable sites for injection would include, for example, the palm of the hand or the sole of the foot.

Method of CMP-001 Intratumoral Administration

Topical, local, or general anesthesia may be given as appropriate in the Investigators' judgment. Using standard aseptic technique, the needle is inserted near the tumor periphery (Figure 23 left panel) and is advanced into the tumor to the desired depth (usually to the needle hub, if the tumor size permits) while maintaining gentle backward pressure on the syringe plunger to confirm extravascular location of the needle tip. The syringe and needle are then slowly withdrawn to within a few millimeters of the skin or tumor surface while maintaining gentle downward pressure on the plunger to inject the desired volume of CMP-001 along the needle track (Figure 23, middle panel). With the tip of the needle still within the skin, the syringe is then rotated by approximately 20 to 40^{o} and the process of insertion and injection during needle withdrawal is repeated (Figure 23, right panel). Using this process, CMP-001 is injected along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; two insertion points can be used if the tumor is larger than the radial reach of the needle and the intended CMP-001 volume cannot be delivered from a single insertion point. If gentle injection pressure along five needle tracks within the tumor has not succeeded in delivering the desired volume, then the remainder of the CMP-001 may be injected in the area of tumor location, around the same lesion.

Figure 23. Method for CMP-001 Intratumoral Injection



Essentially the same process is performed for subcutaneous, nodal and visceral injections, but for deeper injections, the tip of the needle may be kept within the tumor and a longer needle may be used.

For detailed guidance on tumor selection and method of CMP-001 administration refer to the Injection Manual.